CLINICAL REPORT

Strong Associations Between Inflammation, Pruritus and Mental Health in Dialysis Patients

Severin SCHRICKER[1], Thorsten HEIDER[2], Moritz SCHANZ[1], Jürgen DIPPON[3], Mark Dominik ALSCHER[1], Heinz WEISS[4], Thomas METTANG[5] and Martin KIMMEL[1]

[1]Department of Internal Medicine, Division of General Internal Medicine and Nephrology and [4]Department of Internal Medicine, Division of Psychosomatic Medicine, Robert-Bosch-Hospital, Stuttgart, [2]Clinic for Neurology, Klinikum St. Marien Amberg, Amberg, [3]Department of Mathematics, University of Stuttgart, Stuttgart, and [5]Department of Internal Medicine, Division of Nephrology, DKD Helios Klinik, Wiesbaden, Germany

Pruritus, impaired mental health and inflammation contribute to morbidity in end-stage renal disease. There are no studies on all 3 conditions. We therefore obtained inflammatory parameter data (C-reactive protein and interleukin-6), pruritus data and psychological test data (36-Item Short-Form Health Survey, "Allgemeine Depressionsskala" and Toronto Alexithymia Scale-20) for 19 dialysis patients with pruritus, 20 dialysis patients without pruritus and 15 healthy controls. Non-parametric hierarchical clustering revealed 3 clusters of parameters: one mainly driven by pruritus scores (chronic kidney disease-associated pruritus cluster), one by mental health scores (mental health cluster) and one by inflammatory parameters (inflammatory cluster). Factor analysis showed strong associations (mental health cluster/chronic kidney disease-associated pruritus cluster, r=−0.49; mental health cluster/inflammatory cluster, r=−0.52; inflammatory cluster/chronic kidney disease-associated pruritus cluster, r=0.48). For the first time, complete correlations between inflammation, mental health and pruritus in dialysis patients have been established. As all 3 conditions are associated with mortality, knowledge about their interdependence helps to understand end-stage renal disease pathophysiology.

Key words: inflammation; IL-6; pruritus; depression; quality of life (QoL); dialysis.

Accepted Jan 23, 2019; E-published Jan 23, 2019

Acta Derm Venereol 2019; 99: 524–529.

Corr: PD Dr. med. Martin Kimmel, Department of Internal Medicine, Division of General Internal Medicine and Nephrology, Robert-Bosch-Hospital, Auerbachstr. 110, DE-70376 Stuttgart, Germany. E-mail: vm.kimmel@t-online.de

SIGNIFICANCE

Itch, impaired mental health and inflammation contribute to morbidity in dialysis patients. We therefore analysed laboratory results, intensity of itch and psychological tests in dialysis patients with pruritus, without and healthy people. The data was analysed by different statistical tests. This revealed 3 independent groups. One was mainly driven by itch, one by mental health and another by inflammatory parameters. Additionally, all 3 showed strong associations. This means inflammation, mental health and itch are somehow interconnected in dialysis patients. Since all 3 comorbidities are associated with the risk of death, knowledge about the interdependence of these factors is important.

Patients with chronic kidney disease (CKD) exhibit many alterations and comorbidities including uremic pruritus (also called CKD-associated pruritus [CKD-aP]), impaired mental health (iMH) and chronically elevated levels of inflammatory parameters (e.g. C-reactive protein [CRP] and interleukin [IL]-6). CKD-aP is associated with reduced quality of life (1) and psychosocial alterations in patients who require renal replacement therapy (RRT) (2). Based on several observations and results from various trials on CKD-aP, there is evidence that CKD-aP is a systemic disease rather than an isolated skin disease (3). The involvement of alterations of the immune system and a pro-inflammatory pattern (pIP) in the pathogenesis of CKD-aP has been discussed in the past, but remains still unclear (3, 4). This was noted as one of the most important fields of research in CKD (5).

Additionally, the prevalence of iMH is high among patients with end-stage renal disease (ESRD) (6). It has been shown that iMH can also affect somatic outcomes (7). Of note, pIP – and especially elevation of IL-6 – was recently reported to be involved in the development of depression and other iMH conditions (8). Furthermore, pIP may be a major contributor to morbidity and mortality in ESRD (9).

Based on this, it can be assumed that a correlation exists at least between one pair of these factors (CKD-aP, pIP and iMH). However, a simultaneous analysis and characterization of the correlations between all 3 factors is still missing. Gaining knowledge about the interdependence of these factors may help to understand the pathophysiological mechanisms underlying all 3 aspects of morbidity in ESRD.

METHODS

Patients and controls

Data on hemodialysis (HD) patients (with and without CKD-aP) and controls, including inflammatory parameter data, were previously published (4). In this study, we included further data regarding 13 patients who were undergoing peritoneal dialysis (PD), and data on psychological test results, where available. This data-enriched *post-hoc* analysis therefore included 19 dialysis (RRT) patients with CKD-aP ("RRT-CKD-aP" subgroup: 6 PD patients and 13 HD patients) and 20 age-matched dialysis (RRT)

doi: 10.2340/00015555-3128
Acta Derm Venereol 2019; 99: 524–529

patients without pruritus ("RRT" subgroup: 7 PD patients and 13 HD patients). Another control group consisted of 15 healthy individuals ("control" subgroup), as confirmed by clinical history and basic laboratory parameters. Patients in the RRT-CKD-aP subgroup were included if they experienced substantial pruritus for >3 months (10). Substantial CKD-aP was defined as a visual analogue scale (VAS) score > 3 (0 = no pruritus to 10 = unbearable pruritus). Furthermore, patients in both dialysis groups had to be on RRT for ≥ 6 months and had to be well dialyzed, with a Kt/V ≥ 1.3 in HD patients and ≥ 2.1 (weekly) in PD patients at the time of laboratory testing.

A full data set of every variable in this retrospective analysis was available for 39 of the 54 individuals. Regarding the 9 variables included in the factor and clustering analyses, 40 of the 54 patients had complete data (with incomplete psychological data for the remaining 14 patients).

Exclusion criteria

Patients with infection, other active inflammatory disease, a history of skin diseases, liver disease, and systemic diseases such as malignancy and allergic diathesis, and patients on immunosuppressive therapy, were excluded.

Pruritus assessments

For screening, the dialysis patients were asked to estimate their itching intensity by marking a VAS (0 = no pruritus to 10 = unbearable pruritus). CKD-aP was assessed using the VAS during a 7-day period (marked daily in the week during which the blood samples were obtained) and the median value was calculated. Furthermore, a detailed questionnaire (to calculate the modified Duo pruritus score (11) was used to monitor the severity and distribution of pruritus, as well as the frequency of pruritus-related sleep disturbance. None of the healthy controls had pruritus. Both the VAS and Duo scores are regarded as pruritus scores throughout this paper.

Mental health assessments

Three tools were used to assess iMH: The Depression Scale ("Allgemeine Depressionsskala – Langform" [ADS-L]), the 36-Item Short-Form Health Survey (SF36) quality of life scale and the Toronto Alexithymia Scale 20 (tas-20), all validated in German. A full data set of psychological test results was obtained for 15 patients in the RRT group, 11 in the RRT-CKD-aP group and 14 in the control group. These parameters are regarded as iMH parameters throughout this paper.

"Allgemeine Depressionsskala – Langform". ADS-L is a validated German depression assessment tool based on the American Centre of Epidemiological Studies Depression Screening Index (CES-D) scale (12), which consists of 20 items that are summed up to a score of 0–60 points. A score >23 is considered to indicate a depressive condition.

36-Item Short-Form Health Survey. The generic norm-based SF36 was used to assess subjects' perceived quality of physical and mental health in general. The physical (SF36-psc) and mental (SF36-msc) subscale scores are computed by weighted averaging of the single questionnaire items following the manual for the original test and the "general current and chronic disease" normalization of the first German version of the SF36 by Bullinger & Kirchberger (13). Lower subscale scores indicate lower levels of perceived health.

Toronto Alexithymia Scale 20. Alexithymia is a state of altered psychological functioning and describes difficulties regarding verbalizing affect and imaginativeness. The term was first introduced in psychosomatic medicine, and alexithymia is observed in patients with a wide range of medical and psychiatric disorders (14). To assess alexithymia, we used the validated German version of the tas-20 (15), which consists of 20 items that sum up to a score of 20–100 points. Patients with scores >60 are considered to have alexithymia (16).

Laboratory investigations

In all HD patients, blood samples were obtained after a long dialysis-free weekend before starting HD. In the healthy control group and PD patients, blood was drawn after taking the subject's medical history and conducting a short physical examination. Samples were processed within 2 h of collection.

The following parameters were measured automatically in our routine clinical laboratory: leukocytes (g/l), hemoglobin (g/l), hematocrit (%), platelets (g/l), ferritin (µg/l), transferrin (mg/dl), albumin (g/dl), total protein (g/dl), creatinine (mg/dl), urea (mg/dl), glucose (mg/dl), sodium (mmol/l), potassium (mmol/l), calcium (mmol/l), phosphate (mmol/l), parathyroid hormone (PTH) (pmol/l), alanine aminotransferase (ALT) (U/l), aspartate aminotransferase (AST) (U/l), alkaline phosphatase (AP) (mg/dl), gamma-glutamyl transferase (GGT) (mg/dl), CRP (mg/dl) and IL-6 (pg/ml). CRP was measured to the nearest 0.1 mg/dl. For data management purposes, values < 0.5 mg/dl were set to 0.4 mg/dl. The laboratory assessments for each participant followed a previously published protocol (4). CRP and IL-6 are regarded as inflammatory parameters throughout this paper.

Statistical analysis

Kruskal–Wallis and Wilcoxon rank-sum tests were employed to compare medians between groups. To test correlations, Spearman's rho statistic was used.

In the non-parametric hierarchical clustering analysis, the homogeneity measure was based on the Pearson correlation. Initially, most similar variables were paired into (basic) clusters. These clusters were then repeatedly merged until a root cluster contained all variables.

In the exploratory factor analysis, we used an oblique factor rotation method for modeling correlated factors. To decide on the number of factors in our model, we used the chi-square statistic. To ensure a clear graphical depiction of the factor model, no arrows with factor loadings with absolute values <1/3 are shown.

Missing values were imputed using random forests (17). Findings were considered to be significant if p-values were < 0.05. Statistical analysis was performed with R (18), version 3.4.2, using the packages ClustOfVar (19) for clustering variables, Hmisc (20) for plotting correlation matrices, psych (21) for factor analysis, randomForestSRC (22) for imputation of missing values and qgraph (23) for displaying networks.

RESULTS

Patient characteristics

Causes of ESRD were equally distributed between those with pruritus (RRT-CKD-aP group) and those without (RRT group) (**Table I**). The controls had a younger median age (52 in the control group vs. 64 in both dialysis groups). Kruskal–Wallis and Wilcoxon rank-sum tests performed for all parameters revealed significantly altered values in the dialysis groups compared to the healthy controls regarding the mental health scores tas-20 and ADS-L (see Table I), inflammatory parameters (CRP and IL-6), hemoglobin, ferritin, transferrin, phosphate and PTH levels (see Table I).

Table I. Patient characteristics, psychological scores and laboratory results

Patient characteristics	RRT (dialysis, no pruritus)	RRT-CKD-aP (dialysis, pruritus)	Controls (healthy)	Significance
Number of patients per subgroup	*n* = 20 (HD *n* = 13, PD *n* = 7)	*n* = 19 (HD-CKD-aP *n* = 13, PD-CKD-aP *n* = 6)	*n* = 15	
Age, years (range), median (IQR)	63.5 (30–84)	64.0 (35–84)	52 (28–75)	
Female, *n*	10	6	3	
RRT vintage, months, median (IQR)	17.5 (9.00-51.50)	45.0 (29.50-82.00)	n.a. (=0)	
Cause of ESRD, *n*				
Glomerulonephritis	5	4	n.a.	
Polycystic kidney disease	2	1	n.a.	
Nephrosclerosis	6	3	n.a.	
Interstitial nephritis	1	3	n.a.	
Diabetic nephropathy	5	7	n.a.	
Unknown	1	2	n.a.	
Kt/V (range), median (IQR)	HD 1.5 (1.30–2.10) PD 2.2 (2.07–3.02)	HD 1.4 (1.31–2.60) PD 2.7 (2.31–4.4)	n.a.	
Pruritus scores, median (IQR)				
VAS	0	4.07 (3.55-5.8)	0	
Duo	0	12.0 (9.00-20.00)	0	
Psychological assessment, median (IQR)				
tas-20	47.0 (36.00-56.0) (m=3)	51.0 (44.50-58.50) (m=4)	37.00 (31.25–41.50) (m=1)	s_{123}, s_{13}, s_{23}
ADS-L	10.50 (6.75-19.20) (m=4)	16.0 (10.0-29.0) (m=8)	5.0 (0.5–11.75) (m=1)	s_{123}, s_{23}
SF36-msc	51.00 (44.7-55.70) (m=5)	42.06 (37.50-53.06) (m=4)	55.65 (53.97–58.41) (m=1)	s_{123}
SF36-psc	40.17 (33.77-47.61) (m=5)	28.55 (20.82-39.34) (m=4)	55.92 (53.32–58.43) (m=1)	s_{123}, s_{13}, s_{23}
Laboratory results, median (IQR)				
Haemoglobin (g/l)	118.5 (110.8-127.0)	111.0 (108.5-126.5)	152.0 (142–158.5)	s_{123}, s_{13}, s_{23}
Ferritin (µg/l)	335.0 (206.0-406.0) (m=1)	177.0 (150.0-420.0)	55.0 (41.50–102.50) (m=4)	s_{123}, s_{13}, s_{23}
Transferrin (mg/dl)	194.0 (164.0–216.0) (m=7)	190.0 (179.0–202.0)	252.0 (244.0–265.0) (m=2)	s_{123}, s_{13}, s_{23}
Albumin (g/dl)	3.55 (3.28–3.70)	3.3 (3.10–3.40)	3.9 (3.80–4.15)	s_{123}, s_{13}, s_{23}
Calcium (mmol/l)	2.35 (2.27–2.45)	2.23 (2.17–2.34)	2.32 (2.29–2.38)	
Phosphate (mmol/l)	1.57 (1.35–1.86)	1.74 (1.32–2.42)	0.93 (0.82–1.03) (m=1)	s_{123}, s_{13}, s_{23}
PTH (pmol/l)	8.4 (3.50–18)(m=3)	13.8 (4.9–37.6)	3.1 (2.65–3.8)	s_{123}, s_{13}, s_{23}
ALT (U/l)	8 (7–9.25)	8 (7.5–9)	11 (10–12)	s_{123}, s_{13}, s_{23}
AST (U/l)	12 (10–13.25)	10 (8.5–12)	14 (12–14.5)	s_{123}, s_{13}, s_{23}
GGT (mg/dl)	9 (7–12)	14 (11–28.50)	11 (8–11.50)	
AP (mg/dl)	88.5 (70.0–103.0)	128.0 (89.5–172.5)	83.0 (78.0–97.0)	s_{123}, s_{12}, s_{23}
Inflammatory parameters, median (IQR)				
CRP (mg/dl)	0.75 (0.4–1.03)	1.0 (0.75–2.30)	0.4 (0.40–0.40)	s_{123}, s_{12}, s_{13}, s_{23}
IL-6 (pg/ml)	7.13 (2.99–8.89)	11.50 (5.00–21.73)	1.34 (0.68–1.71)	s_{123}, s_{12}, s_{13}, s_{23}

C-reactive protein (CRP) levels < 0.5 mg/dl were set to 0.4 mg/dl. Significance was defined as $p < 0.05$. Values rounded to 2 decimal places.
S_{123} = significant overall differences in medians of all 3 groups (renal replacement therapy [RRT], RRT- chronic kidney disease (CKD)-associated pruritus [CKD-aP] and Control). S_{12}: medians of RRT and RRT-CKD-aP were significantly different. S_{13}: medians of RRT and controls were significantly different. S_{23}: medians of RRT-CKD-aP and controls were significantly different; m: Number of missing values for the respective parameter in that row per subgroup when shown; n.a: not applicable; ESRD: end-stage renal disease; VAS: visual analogue scale for pruritus severity; Duo: modified "Duo" pruritus score; tas-20: Toronto Alexithymia Scale 20; ADS-L: "Allgemeine Depressionsskala - Langform" depression score; SF36-msc: mental health subscale of the 36-item Short-Form Health Survey; SF36-psc: physical health subscale of the 36-item Short-Form Health Survey; IQR: interquartile range.

In pruritus patients (RRT-CKD-aP group), the medians of AP, CRP and IL-6 were significantly different to levels in the pruritus-free dialysis group (RRT group). Thus, these parameters were included in the further analyses. Of note, indicators of other diseases associated with pruritus (ALT, AST, GGT, PTH, phosphate transferrin and ferritin levels) did not differ significantly between the RRT-CKD-aP and RRT groups (for numbers, see Table I), although there was a non-significant trend of increased PTH levels in the pruritus patients.

Parameter correlations

Significant correlations were found between all variables, apart from AP, which was the only parameter not significantly correlated with the psychological parameters SF36-msc, ADS-L and tas-20 (**Table II**).

Correlations were, as expected, strongest within each group of associated measurements: mental health parameters, pruritus parameters and inflammatory parameters (mental health: SF36-msc with tas-20, r=–0.70; SF36-msc with ADS-L, r=–0.69; ADS–L with tas-20, r=0.66; pruritus parameters: VAS with Duo, r=0.98; inflammatory parameters: CRP with IL-6, r=0.79) (see Table II). Of note, SF36-psc deviated from this pattern and was most strongly correlated with IL-6 (r=–0.73) and the two pruritus parameters (r=–0.61 and –0.6) (also see Table II). Additionally, AP was most strongly correlated with the two pruritus parameters (both r=0.49).

Regarding cross-group correlations involving the 4 mental health parameters, they were all most strongly correlated with IL-6 (r range = –0.38 to –0.73; also see Table II). Regarding cross-group correlations involving the two inflammatory parameters, they were both most strongly correlated with S36-psc (r=–0.55 and –0.73 respectively; also see Table II) followed by the two pruritus parameters (r range = 0.48 to 0.58; also see Table II).

Non-parametric hierarchical clustering

To measure the heterogeneity within a cluster, the y-axis value (height) is used. For example, the VAS and Duo

Table II. Pairwise correlations

		Duo	VAS	AP	ADS-L	tas-20	SF36-msc	SF36-psc	CRP	IL-6
CKD-aP-C	Duo									
	VAS	**0.98 <0.0001**								
	AP	0.49 *0.0001*	0.49 *0.0002*							
MH-C	ADS-L	0.34 *0.0117*	0.35 *0.0100*	0.26 *0.0539*						
	tas-20	0.41 *0.0019*	0.39 *0.0036*	0.24 *0.0747*	**0.66 <0.0001**					
	SF36-msc	−0.36 *0.0075*	−0.35 *0.0102*	−0.22 *0.1174*	**−0.69 <0.0001**	**−0.70 <0.0001**				
I-C	SF36-psc	**−0.61 <0.0001**	**−0.60 <0.0001**	−0.36 *0.0073*	**−0.56 <0.0001**	**−0.56 <0.0001**	0.48 *0.0002*			
	CRP	0.48 0.0003	**0.50 0.0001**	0.31 *0.0220*	0.35 *0.0104*	0.37 *0.0059*	−0.35 *0.0094*	**−0.55 <0.0001**		
	IL-6	**0.55 <0.0001**	**0.58 <0.0001**	0.32 *0.0169*	0.43 *0.0010*	0.48 *0.0003*	−0.38 *0.0046*	**−0.73 <0.0001**	**0.79 <0.0001**	

Bold font indicates r-values > 0.5 and *p*-values < 0.05.
VAS: visual analogue scale for pruritus severity; Duo: modified "Duo" pruritus score; tas-20: Toronto Alexithymia Scale 20; ADS-L: "Allgemeine Depressionsskala - Langform" depression score; SF36-msc: mental health subscale of the 36-item Short-Form Health Survey; SF36-psc: physical health subscale of the 36-item Short-Form Health Survey; MH-C: mental health cluster; CKD-aP-C: chronic kidney disease-associated pruritus cluster; I-C: inflammatory cluster.

variables are much more homogeneous than for example ADS-L and SF36-msc (Fig. S1[1]). On the basic level, clusters consisted of pairs of variables that were more similar to each other than to any other variable. On the intermediate level, non-parametric hierarchical clustering of the observed variables revealed 3 clusters. Based on the dominant parameters, we designated the clusters the inflammatory cluster (I-C: log(CRP), log(IL-6) and additionally SF36-psc), the mental health cluster (MH-C:tas-20, SF36-msc and ADS-L) and the chronic kidney disease-associated pruritus cluster (CKD-aP-C: VAS, Duo and additionally log(AP)). Each of these clusters contained variables that were more similar to the variables within the cluster and more dissimilar to the variables outside the cluster. Overall, these 3 clusters formed the most homogenous clusters of any combination of clusters of the intermediate level. These findings are in perfect accordance with the results of the factor analysis discussed in the following section.

Factor analysis

All 9 single parameters were included in the exploratory factor analysis, along with 3 latent factors. Tests with only two factors were insufficient ($p < 0.001$, chi-square statistic = 45.06, df = 19) and adding a fourth factor did not provide substantial additional informational content ($p = 0.78$, chi-square statistic = 8.02, df = 12). The three-factor model was able to explain 65.7% of the variance in the data set.

Factor 1 of the model was highly loaded by the pruritus parameters (compare this with the CKD-aP-C hierarchical cluster) (loadings: VAS = 0.91 and Duo = 1) and to a lesser extent, AP (loading: log(AP) = 0.52), which was also a CKD-aP-C cluster variable. Factor 2 was mainly driven by the mental health variables (compare this with the MH-C hierarchical cluster) (loadings: tas-20 = 0.82, ADS-L = 0.77, SF36-msc = –0.84). Factor 3 was highly loaded by the inflammatory variables CRP and IL-6 (compare this with the I-C hierarchical cluster) (loadings: log(IL-6) = 0.96 and log(CRP) = 0.72) and to a lesser extent, SF36-psc (loading = –0.42) (Fig. S2[1]).

As these results are in perfect accordance with the 3 hierarchical clusters from the analysis above, we propose that Factor 1 mainly reflects pruritus, Factor 2 represents mental health and Factor 3 represents inflammation.

Of note, the exploratory factor analysis revealed pairwise associations between each of the established factors/clusters of the model (CKD-aP-C with MH-C, r=–0.49; CKD-aP-C with I-C, r=0.48; MH-C with I-C, r=–0.52, see the correlation structure of the factors in Fig. S2[1]).

DISCUSSION

Mortality and morbidity in CKD patients are high and treatment options remain limited. A better understanding of the associations between factors leading to unfavorable outcomes is therefore crucial to improve outcomes for our patients. The 3 investigated conditions in our study (pruritus [CKD-aP], impaired mental health [iMH], chronically elevated inflammatory parameters/pro-inflammatory state [pIP]) are all correlated with mortality in CKD (24–28). While there is evidence for correlations between individual pairs of the 3 conditions (4, 29–32), to the best of our knowledge, our study shows for the first time that there are relationships between each

[1]https://doi.org/10.2340/00015555-3128

of the 3 aspects of morbidity when analyzed together. We were able to establish a factor model involving diverse parameters that consistently formed clusters with high degrees of association, which resemble a pruritus cluster, an iMH and quality of life cluster and an inflammation cluster. In this model, higher inflammatory parameters were associated with worse iMH and pruritus symptoms, while worse pruritus symptoms were associated with worse iMH in dialysis patients. This adds to the growing body of evidence on the complex nature of morbidity in ESRD that is most probably of multifactorial origin.

As AP level was the only parameter that was significantly elevated in dialysis patients with pruritus compared to dialysis patients without pruritus, we included this parameter in our analysis. AP was most strongly correlated with the two pruritus parameters, an association so far undescribed in the literature. Of note, dialysis patients with pruritus did not have any signs of liver impairment (normal levels for GGT, AST and ALT) or high bone turnover (PTH levels did not significantly differ from those in the dialysis patients without pruritus, and they were within desired ranges for dialysis patients), although there was a non-significant trend towards increased PTH levels in pruritus patients. One limitation of the study is that AP was not differentiated by its origin. For example, in addition to the mostly well-known bone and biliary AP, there is also an intestinal AP that might have contributed to increased AP levels (33), with the potential role of nutrition as a confounding factor (34). Further studies can shed more light on the role of AP in pruritus.

Further, systematic bias in patient selection may have occurred (based on subjective, self-reported pruritus) and bias may also have occurred due to social desirability in the answers to questions used for data collection (including mental health questions). On the other hand, different standard psychological questionnaires were included, and they showed a high level of consistency, underlining the inter-test reliability and overall reliability of the mental health assessments. Furthermore, VAS for pruritus assessment is considered an appropriate and validated tool for the assessment of pruritus (35). Of note, the analysis showed a very high correlation between the VAS and Duo scores (r=0.98) – this indicates that there is no additive value of the Duo score and the simple VAS seems to be sufficient to test for uremic pruritus. Of course, the small sample size further limits interpretation. However, we did find highly significant results despite the small sample size, emphasizing the robustness of our findings.

It seems feasible to overcome the restrictions of pairwise analyses, which led to contradictory and heterogeneous results in the past, by using statistical models such as non-parametric cluster analyses on larger cohorts to validate our findings for a better understanding of cross-group interactions.

Due to the nature of our study, conclusions regarding causality cannot be drawn. However, the existence of causal associations is supported by recent observation regarding the inflammation lowering effects of antidepressive treatments (36, 37). Yet, it remains unclear whether this is a mere pleiotropic side effect of antidepressive medication, one of multiple modes of action of this medication or the result of an improved mental health status. Therefore, further investigations on the effects of treatment options for one condition on the severity of the other conditions, especially in CKD patients, are needed to assert possible causality.

Interestingly, a currently published observational study in a large, representative cohort in Germany (GEHIS cohort) was also focused on quality of life and mental health in pruritus patients on dialysis (1, 38, 39). This study found significant associations between pruritus severity and the 12-Item Short Form Health Survey (SF-12) and the Hospital Anxiety and Depression Scale (HADS) (1), but no significant associations between pruritus severity and laboratory parameters (39).

Other research focusing on CKD-aP and inflammation found associations supporting an involvement of pIP (30). Regarding the association between pIP and iMH, meta-analyses on the association between serum inflammatory markers (foremost, IL-6 and CRP) and depression showed positive associations in previous population-based studies (40, 41). Based on these observations in the general population, previous studies in patients with ESRD showed heterogeneous results (c.f. 42, 43).

Conclusion

Our results show that pIP, CKD-aP and iMH are contributors to ESRD-related morbidity. These 3 health conditions are moderately associated with each other while being defined by distinct parameters. These findings might influence the way we perceive different aspects of morbidity in RRT patients, which have been reviewed and investigated as separate entities in the past. We want to emphasize that we face a complex system of symptoms and conditions in dialysis patients and one should be aware that mutual influences between the different aspects of morbidity exist.

ACKNOWLEDGEMENT

This study was supported by the Robert-Bosch-Foundation. The study was approved by the Ethics Committee of the University of Tuebingen, Germany.

The authors have no conflicts of interest to declare.

REFERENCES

1. Weiss M, Mettang T, Tschulena U, Weisshaar E. Health-related quality of life in haemodialysis patients suffering from chronic itch: results from GEHIS (German Epidemiology Haemodia-

lysis Itch Study). Qual Life Res 2016; 25: 3097–3106.
2. Susel J, Batycka-Baran A, Reich A, Szepietowski JC. Uraemic pruritus markedly affects the quality of life and depressive symptoms in haemodialysis patients with end-stage renal disease. Acta Derm Venereol 2014; 94: 276–281.
3. Mettang T, Kremer AE. Uremic pruritus. Kidney Int 2015; 87: 685–691.
4. Kimmel M, Alscher DM, Dunst R, Braun N, Machleidt C, Kiefer T, et al. The role of micro-inflammation in the pathogenesis of uraemic pruritus in haemodialysis patients. Nephrol Dial Transplant 2006; 21: 749–755.
5. Manns B, Hemmelgarn B, Lillie E, Dip SC, Cyr A, Gladish M, et al. Setting research priorities for patients on or nearing dialysis. Clin J Am Soc Nephrol 2014; 9: 1813–1821.
6. Joshi VD. Quality of life in end stage renal disease patients. World J Nephrol 2014; 3: 308–316.
7. Farrokhi F, Abedi N, Beyene J, Kurdyak P, Jassal SV. Association between depression and mortality in patients receiving long-term dialysis: a systematic review and meta-analysis. Am J Kidney Dis 2014; 63: 623–635.
8. Taraz M, Taraz S, Dashti-Khavidaki S. Association between depression and inflammatory/anti-inflammatory cytokines in chronic kidney disease and end-stage renal disease patients: a review of literature. Hemodial Int 2015; 19: 11–22.
9. Akchurin OM, Kaskel F. Update on inflammation in chronic kidney disease. Blood Purif 2015; 39: 84–92.
10. Ständer S, Weisshaar E, Mettang T, Szepietowski JC, Carstens, Earl, Ikoma A, et al. Clinical classification of itch: a position paper of the International Forum for the Study of Itch. Acta Derm Venereol 2007; 87: 291–294.
11. Pauli-Magnus C, Mikus G, Alscher DM, Kirschner T, Nagel W, Gugeler N, et al. Naltrexone does not relieve uremic pruritus: results of a randomized, double-blind, placebo-controlled crossover study. J Am Soc Nephrol 2000; 11: 514–519.
12. Hautzinger M, Bailer M, Hofmeister D, Keller F. Allgemeine depressionsskala (ADS). Psychiatr Prax 2012; 39: 302–304.
13. Bullinger M, Kirchberger I. Der SF-36 Fragebogen zum Gesundheitszustand.(SF-36)-Handbuch für die deutschsprachige Fragebogenversion. Göttingen: Hogrefe; 1998.
14. Taylor GJ. Alexithymia: concept, measurement, and implications for treatment. Am J Psychiatry 1984; 141: 725–732.
15. Schafer R, Schneider C, Sitte W, Franz M. [Evidence of validity of the German version of the TAS-20. Contribution to the 52nd conference of the German Board of Psychosomatic Medicine in Bad Honnef (2001)]. Psychother Psychosom Med Psychol 2002; 52: 449–453.
16. Simson U, Martin K, Schafer R, Franz M, Janssen P. [Changes in alexithymia and emotional awareness during psychotherapeutic inpatient treatment]. Psychother Psychosom Med Psychol 2006; 56: 376–382.
17. Tang F, Ishwaran H. Random forest missing data algorithms. Stat Anal Data Min 2017; 10: 363–377.
18. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2017.
19. Chavent M, Kuentz V, Liquet B, Saracco J. ClustOfVar: Clustering of Variables. R package version 1.1 ed, 2017.
20. Harrell Jr FE, with contributions from Charles Dupont and many others. Hmisc: Harrell Miscellaneous. R package version 4.0-3 ed, 2017.
21. Revelle W. Procedures for Personality and Psychological Research. 1.7.8 ed. Northwestern University, Evanston, Illinois, USA, 2017.
22. Ishwaran H, Kogalur UB. Random Forests for Survival, Regression, and Classification (RF-SRC). R package version 2.5.0 ed, 2017.
23. Epskamp S, Cramer AOJ, Waldorp LJ, Schmittmann VD, Borsboom D. qgraph: Network Visualizations of Relationships in Psychometric Data. J Stat Softw 2012; 48: 1–18.
24. Cohen SD, Phillips TM, Khetpal P, Kimmel PL. Cytokine patterns and survival in haemodialysis patients. Nephrol Dial Transplant 2010; 25: 1239–1243.
25. Barreto DV, Barreto FC, Liabeuf S, Temmar M, Lemke HD, Tribouilloy C, et al. Plasma interleukin-6 is independently associated with mortality in both hemodialysis and predialysis patients with chronic kidney disease. Kidney Int 2010; 77: 550–556.
26. Chilcot J, Davenport A, Wellsted D, Firth J, Farrington K. An association between depressive symptoms and survival in incident dialysis patients. Nephrol Dial Transplant 2011; 26: 1628–1634.
27. Kimmel PL. Depression in patients with chronic renal disease: what we know and what we need to know. J Psychosom Res 2002; 53: 951–956.
28. Narita I, Alchi B, Omori K, Sato F, Ajiro J, Saga D, et al. Etiology and prognostic significance of severe uremic pruritus in chronic hemodialysis patients. Kidney Int 2006; 69: 1626–1632.
29. Chen HY, Chiu YL, Hsu SP, Pai MF, Lai CF, Yang JY, et al. Elevated C-reactive protein level in hemodialysis patients with moderate/severe uremic pruritus: a potential mediator of high overall mortality. QJM 2010; 103: 837–846.
30. Virga G, Visentin I, La Milia V, Bonadonna A. Inflammation and pruritus in haemodialysis patients. Nephrol Dial Transplant 2002; 17: 2164–2169.
31. Yamamoto Y, Hayashino Y, Yamazaki S, Akiba T, Akizawa T, Asano Y, et al. Depressive symptoms predict the future risk of severe pruritus in haemodialysis patients: Japan Dialysis Outcomes and Practice Patterns Study. Br J Dermatol 2009; 161: 384–389.
32. Taraz M, Khatami MR, Gharekhani A, Abdollahi A, Khalili H, Dashti-Khavidaki S. Relationship between a pro- and anti-inflammatory cytokine imbalance and depression in haemodialysis patients. Eur Cytokine Netw 2012; 23: 179–186.
33. Lalles JP. Intestinal alkaline phosphatase: novel functions and protective effects. Nutr Rev 2014; 72: 82–94.
34. Ghosh SS, Gehr TW, Ghosh S. Curcumin and chronic kidney disease (CKD): major mode of action through stimulating endogenous intestinal alkaline phosphatase. Molecules 2014; 19: 20139–20156.
35. Reich A, Heisig M, Phan NQ, Taneda K, Takamori K, Takeuchi S, et al. Visual analogue scale: evaluation of the instrument for the assessment of pruritus. Acta Derm Venereol 2012; 92: 497–501.
36. Hannestad J, DellaGioia N, Bloch M. The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. Neuropsychopharmacology 2011; 36: 2452.
37. Taraz M, Khatami M-R, Dashti-Khavidaki S, Akhonzadeh S, Noorbala A-A, Ghaeli P, et al. Sertraline decreases serum level of interleukin-6 (IL-6) in hemodialysis patients with depression: results of a randomized double-blind, placebo-controlled clinical trial. Int Immunopharmacol 2013; 17: 917–923.
38. Weiss M, Mettang T, Tschulena U, Passlick-Deetjen J, Weisshaar E. Prevalence of chronic itch and associated factors in haemodialysis patients: a representative cross-sectional study. Acta Derm Venereol 2015; 95: 816–821.
39. Weisshaar E, Weiss M, Passlick-Deetjen J, Tschulena U, Maleki K, Mettang T. Laboratory and dialysis characteristics in hemodialysis patients suffering from chronic itch – results from a representative cross-sectional study. BMC Nephrol 2015; 16: 184.
40. Liu Y, Ho RC-M, Mak A. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. J Affect Disord 2012; 139: 230–239.
41. Hiles SA, Baker AL, de Malmanche T, Attia J. A meta-analysis of differences in IL-6 and IL-10 between people with and without depression: exploring the causes of heterogeneity. Brain Behav Immun 2012; 26: 1180–1188.
42. Ogrizovic SS, Jovanovic D, Dopsaj V, Radovic M, Sumarac Z, Bogavac S, et al. Could depression be a new branch of MIA syndrome? Clin Nephrol 2009; 71: 164.
43. Nowak L, Adamczak M, Wiecek A. Is inflammation a new risk factor of depression in haemodialysis patients? Int Urol Nephrol 2013; 45: 1121–1128.