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Original Article

ORIGINAL ARTICLE

Influence of autonomic neuropathy, systemic inflammation and other clinical parameters on mortality in dialysis patients

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ABSTRACT

Background. Autonomic neuropathy (AN) is prevalent in diabetes and chronic kidney disease. The Composite Autonomic Symptom Score 31 (COMPASS 31) is a self-assessment test developed to determine not only cardiac AN but also AN of other organs, including the vasomotor, pupillomotor, secretomotor, and gastrointestinal systems. As yet there are no data on the effects of combined AN-scores of a variety of affected organ systems on mortality in dialysis patients.
Methods. In 119 patients undergoing hemodialysis therapy, symptoms of AN were documented using COMPASS 31. After 5 years, survival rates were calculated depending on AN scores and other parameters. After this 5-year period, AN scores were assessed for a second time and correlated with those obtained 5 years earlier.
Results. Survival rates for patients with lower AN scores were better than for those with higher AN scores. Patients with lower C-reactive protein levels showed better survival compared to those with higher values. Dialysis patients with diabetes had a lower survival rate compared to non-diabetic patients. In women, survival rates were better than in men. AN scores remained unchanged over the 5-year period.
Conclusion. AN is frequently observed in dialysis patients and can be identified through the COMPASS 31 questionnaire. Patients with higher AN scores exhibit poorer survival rates compared to those with lower scores. This observation is applicable not only for cardiac AN but also to AN scores reflecting changes in other organ systems. Therefore, AN scores can be used effectively to detect various AN symptoms in dialysis patients and identify their increased risk of mortality.

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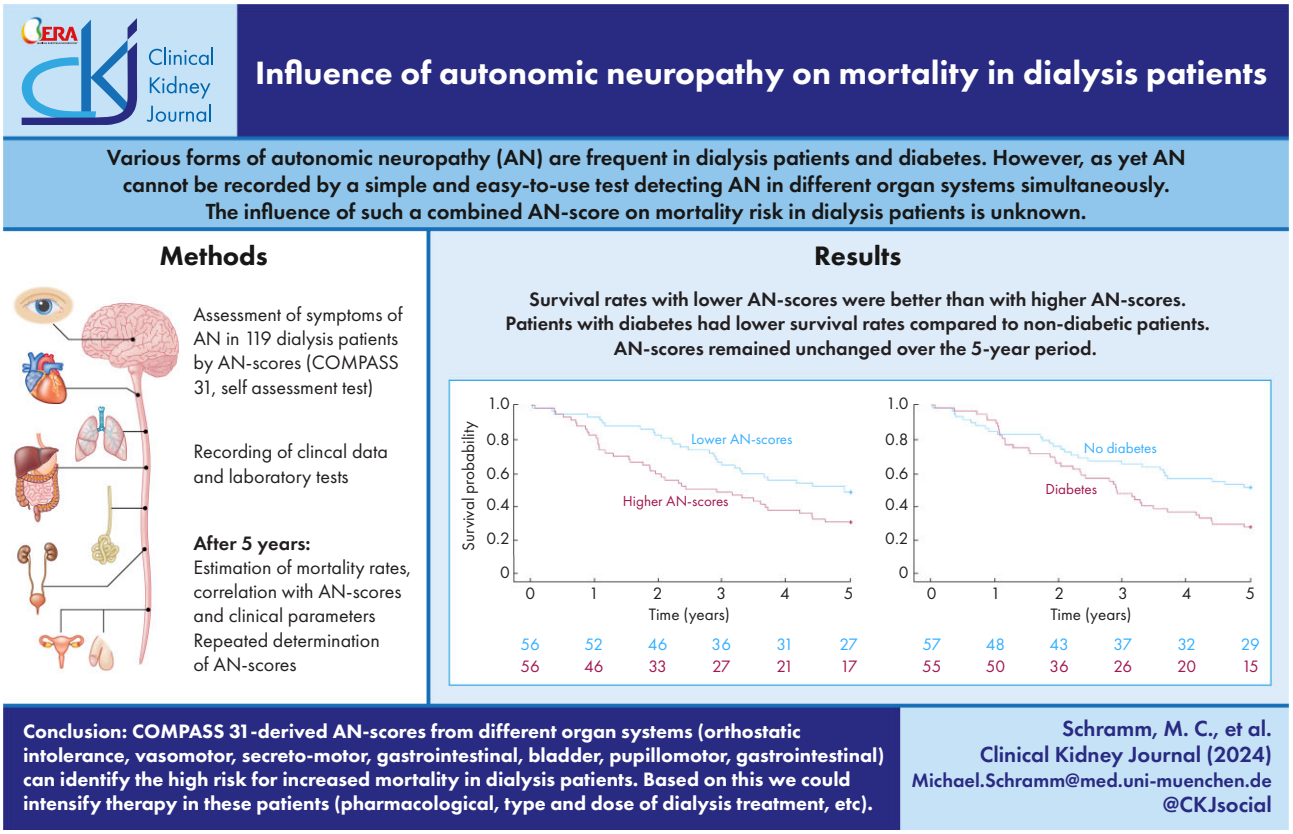
GRAPHICAL ABSTRACT



Keywords: autonomic neuropathy; COMPASS 31; dialysis; inflammation; mortality

KEY LEARNING POINTS

What was known:

- Autonomic neuropathy (AN) is frequent in dialysis patients and diabetes. As yet there is no instrument to identify and record autonomic neuropathic changes of different organ systems simultaneously. COMPASS 31, an easy-to-use self-assessment test with good reliability, can identify these autonomic neuropathic manifestation in different organ systems by AN scores. Up to now there are no data on the influence of combined registration of these autonomic changes in different organ systems on mortality in dialysis patients.

This study adds:

- Survival rates with lower AN scores were better than with higher AN scores. Patients with diabetes had lower survival rates compared to non-diabetic patients AN scores remained unchanged over the 5-year period.

Potential impact:

- Identification of symptoms of AN in a variety of organ systems (not only cardiac) results in AN scores, which can identify the high risk of mortality in hemodialysis patients. AN scores did not change over the 5-year observation period. In the future we could intensify treatment of patients with higher AN scores, for example by improving glycemic control, pharmacological therapy, or by using HDF therapy, and by that reduce their high mortality risk.

INTRODUCTION

Autonomic neuropathy (AN) is common in individuals with diabetes and chronic kidney disease, affecting heart function, blood pressure, temperature regulation, digestion, bladder function and more (Fig. 1) [1–5]. Cardiac AN is associated with cardiovascular complications and significantly increased mortality rates [1, 3, 6]. To date, most investigations were done in the field of cardiac AN, utilizing tilt-table testing, the Valsalva maneuver, heart rate variability, and other diagnostic tools. Additionally, more invasive diagnostic methods are available, such

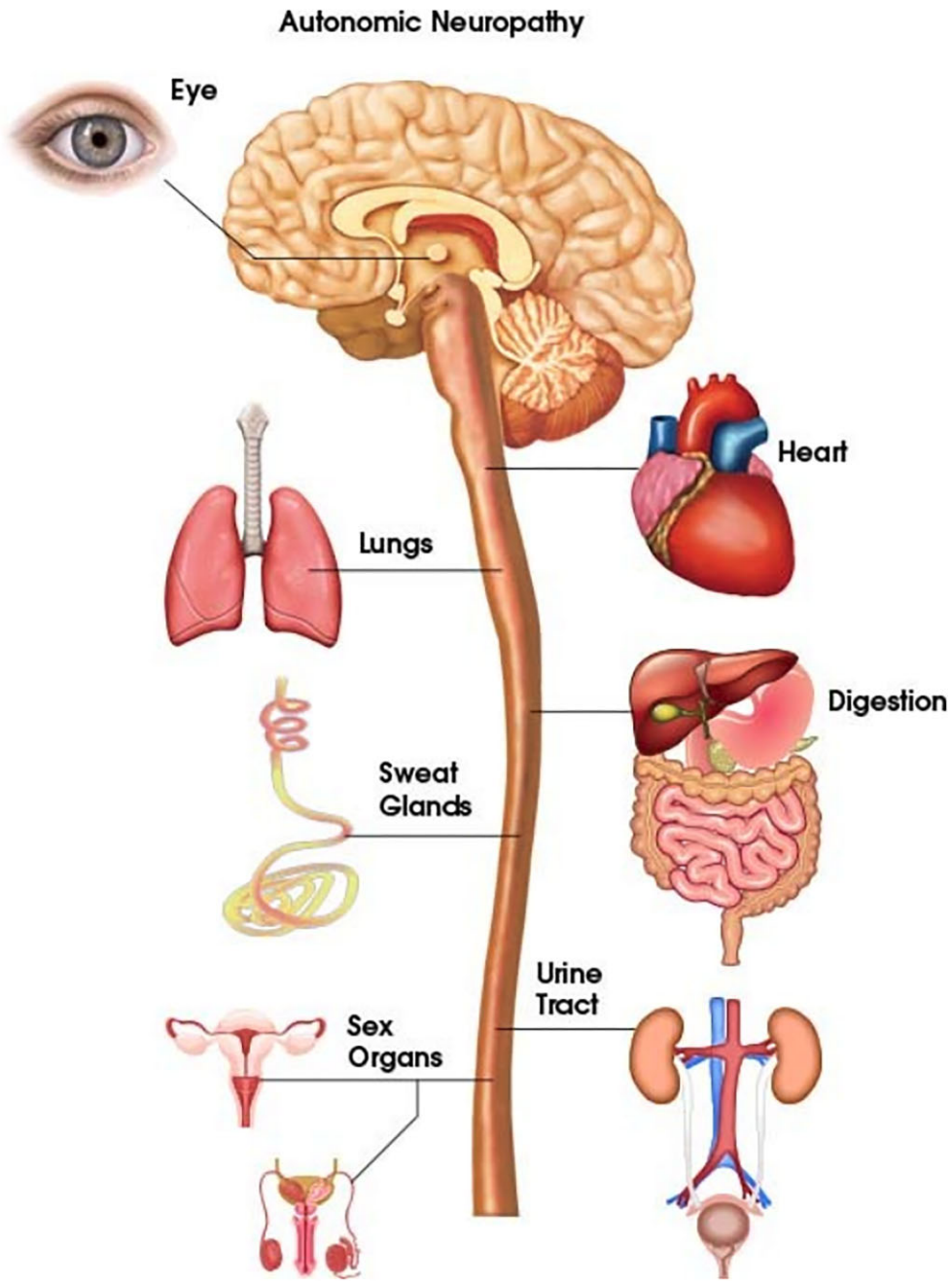


Figure 1: Autonomic neuropathy and possibly affected organ systems (with permission from www.intolife.in).

as nerve biopsies and electrophysiological techniques [7]. These methods are generally based in hospitals or research facilities, being more invasive, time-consuming, and less accepted by patients.

More recently, the Composite Autonomic Symptom Score 31 (COMPASS 31), a self-assessment test, has been developed to detect changes not only in cardiac AN but also in other organ manifestations (such as vasomotor, pupillomotor, secretomotor, gastrointestinal) [8, 9]. COMPASS 31 is based on the well-established Autonomic Symptom Profile [10] and is considered a concise and statistically robust tool for both research and clinical testing of AN [9]. Different degrees and extents of AN symptoms are expressed by AN scores. However, the impact of different AN subtypes on mortality rates in dialysis patients is poorly understood, and there is a lack of data on whether frequency and extent of changes in different organ systems are important parameters affecting mortality. In addition to examining the effects of AN on mortality in dialysis patients, we also investigated the impact of inflammation, indicated by C-reactive protein levels (CRP), as well as other epidemiological and clinical parameters on survival, including the diagnosis of diabetes, gender, body mass index (BMI), and others.

Moreover, we determined whether AN symptoms changed over a 5-year observation period during ongoing dialysis therapy, both individually and collectively for the whole cohort.

Table 1: Epidemiological data, laboratory values and AN scores of the dialysis patient cohort ($n = 119$; mean ± standard deviation) and the control group of a preceding study (see ref. 5) ($n = 64$; mean ± standard deviation; n.s. means not significant).

	Control group ($n = 64$)	Dialysis patients ($n = 119$)	
Age (years)	65 ± 12.9	68.4 ± 14.1	n.s.
Sex (male)	51%	59%	n.s.
Diabetes diagnosis	67%	47%	$p < 0.01$
Diabetes duration (years)	12.5 ± 10.1	23.4 ± 12.7	$p < 0.01$
Hypertension	75%	88%	$p = 0.03$
Body weight (kg)	84.5 ± 15.2	76.6 ± 16.1	$p < 0.01$
Height (cm)	169.3 ± 9.1	169.5 ± 9.0	n.s.
GFR (ml/min/1.73 m^2)	78.2 ± 19.6	7.4 ± 3.8	$p < 0.01$
Creatinine (µmol/l)	85.0 ± 20.4	650.8 ± 228.0	$p < 0.01$
Urea (mmol/l)	6.1 ± 2.7	20.5 ± 6.5	$p < 0.01$
Hemoglobin (mmol/l)	8.7 ± 0.8	6.8 ± 0.9	$p < 0.01$
CRP (mg/dl)	3.2 ± 3.3	9.3 ± 12.4	$p < 0.01$
Sodium (mmol/l)	139.7 ± 2.3	137.8 ± 3.4	$p < 0.01$
Potassium (mmol/l)	3.8 ± 0.5	5.2 ± 0.7	$p < 0.01$
HbA1c (%)	6.8 ± 1.3	5.9 ± 1.1	$p < 0.01$
AN score domains			
Orthostatic	4.63 ± 7.6	12 ± 12.2	$p < 0.01$
Vasomotor	0.05 ± 0.4	0.58 ± 1.2	$p < 0.01$
Secretory	1.81 ± 2.6	6.17 ± 4.3	$p < 0.01$
Gastrointestinal	2.29 ± 2.3	6.34 ± 4.2	$p < 0.01$
Bladder	0.64 ± 1.0	1.05 ± 1.6	$p < 0.05$
Pupillomotor	0.59 ± 0.8	1.35 ± 1.2	$p < 0.01$
AN score total	10 ± 10.3	27.5 ± 15.6	$p < 0.01$

MATERIALS AND METHODS

After obtaining written consent, 119 patients undergoing chronic hemodialysis therapy (no hemodiafiltration), both with and without diabetes mellitus, were enrolled in our study, which was approved by the Ethics Committee of the University of Rostock (No. A2015-0176). Only dialysis patients aged over 18 years were included. Those undergoing temporary renal replacement therapy, with primarily neurological diseases (ischemia or inflammatory diseases, which might influence autonomic symptoms), a history of alcohol abuse, or with intoxications were excluded. By that restriction we tried to reduce possible negative effects of possible confounders when regarding the effects of AN scores on survival rates. Also, patients with cognitive impairments or linguistic barriers were not allowed to participate in our study.

In a preceding cross-sectional investigation of 119 chronic dialysis patients, symptoms of AN were recorded using the COMPASS 31 questionnaire. Responses from 31 questions were transformed into raw values based on the extent and severity of symptoms, which were finally converted into weighted values. The obtained values indicated varying degrees of neuropathic symptoms (AN scores), ranging from 0 to 100 (0 = no symptoms, 100 = maximum expression). Details on interpretation and performance of COMPASS 31 are described elsewhere [5, 8]. Blood samples were collected simultaneously with self-assessment tests, along with clinical and epidemiological parameters such as diagnosis of diabetes or hypertension, age, gender, weight, height, sex, and BMI. Data regarding the presence of diabetes and hypertension, duration of dialysis therapy, and duration of diabetes disease were obtained from medical records and direct patient questioning. Subsequently, the calculated AN scores were correlated with clinical and laboratory parameters.

After a 5-year observation period, survival rates were calculated using the Kaplan–Meier method and analyzed based on initial AN scores and laboratory/clinical parameters. At that time (after 5 years), patients were reassessed with COMPASS 31, and AN scores were correlated with those obtained 5 years earlier.

During the study, seven patients received kidney transplants and were subsequently excluded from further observation.

For metric variables, the mean, median, standard deviation and interquartile range were calculated. Nominal and ordinal variables were described with absolute and relative frequencies using the statistic program SPSS 'Statistical Package for the Social Sciences'. Correlations between two parameters were calculated according to Pearson's method. Cox regression was used to investigate the influence of different variables, such as AN score, CRP, age, sex, BMI, and other, on survival. Survival rates were determined using the Kaplan–Meier method. Multiple Cox regression was applied to adjust the effects on mortality of the predictor variables for each other (sex, age, CRP, BMI, AN score, diabetes disease). This means that a relationship of one variable with mortality is not solely a consequence of confounding with other variables if the relationship is still significant in the simple cox regression model (as it was the case for AN score, CRP, age, and sex).

RESULTS

At the beginning of the 5-year observation period, the percentage of patients with diabetes was 49%, reflecting the global increase in diabetic dialysis patients. Of dialysis patients, 88% had hypertension, CRP levels were slightly above the upper normal limit. Both findings are common in dialysis patients. The initial AN scores were significantly elevated in dialysis patients compared to controls ($n = 64$) investigated in a preceding study (10.0 ± 10.3 versus 27.5 ± 15.6; $p < 0.01$). Symptoms of AN were not only more frequent but also more severe (Table 1) [5]. Patients

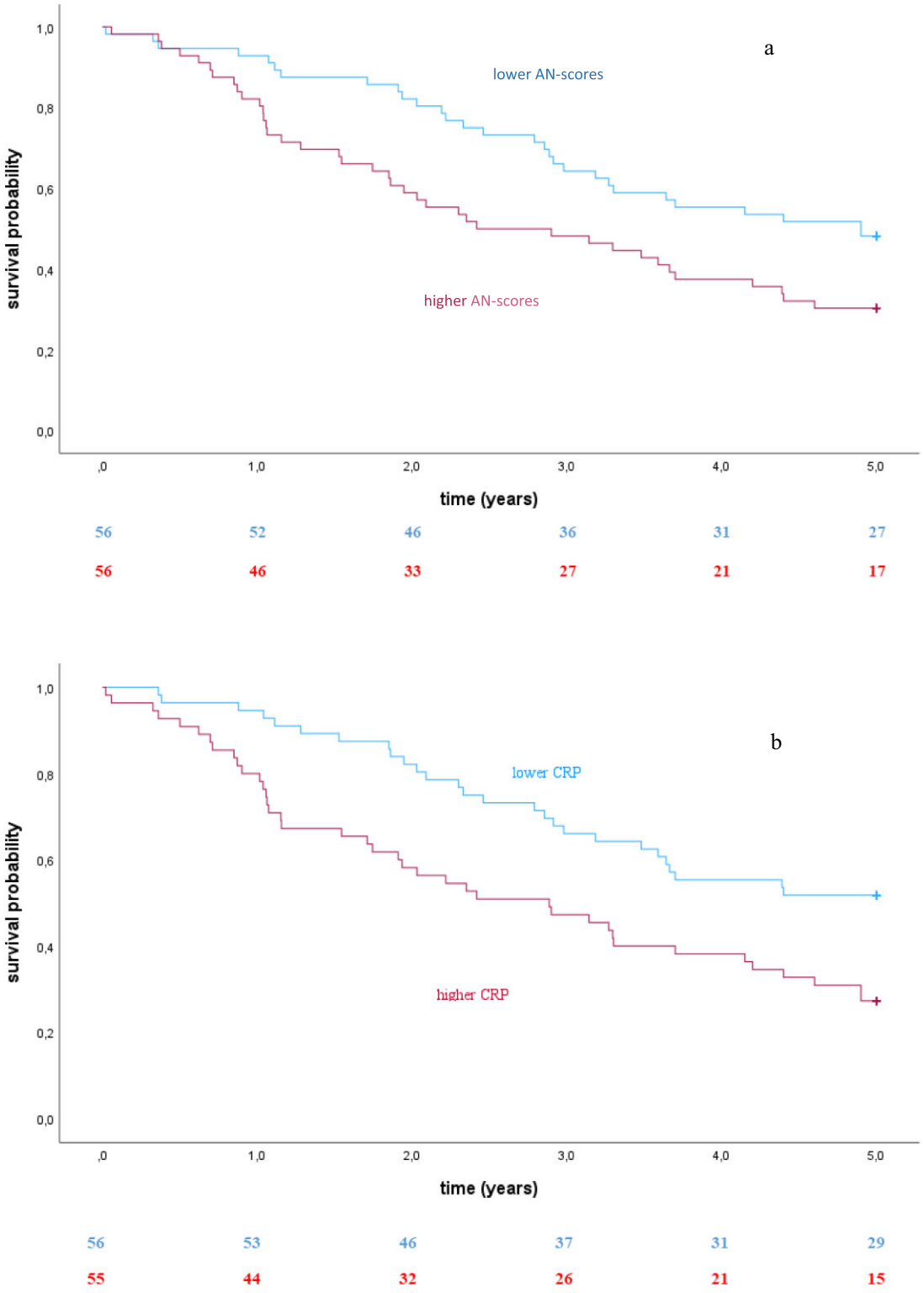


Figure 2: a: Kaplan–Meier survival curve for dialysis patients ($n = 112$) in dependence on AN scores during a 5-year interval; dichotomization of groups: red = group with the higher 50% of AN scores, blue = group with the lower 50% of AP scores. Under the curve: No. at risk for each group; survival after 5 years: 30% (95% CI 18 to 42) and 48% (95% CI 35 to 61), respectively ($p < 0.05$). b: Kaplan–Meier survival curve for dialysis patients ($n = 111$) in dependence on CRP levels during a 5-year interval; dichotomization of groups: red = group with the higher 50% of CRP, blue = group with the lower 50% of CRP. Under the curve: No. at risk for each group; survival after 5 years: 27% (95% CI 15 to 39) and 52% (95% CI 39 to 65), respectively ($p < 0.01$).

Table 2: Simple cox regression analysis (non-adjusted) and multiple cox regression analysis (adjusted) for AN-score sex, age, BMI, CRP and diabetes disease. Hazard ratios and 95% confidence intervals (CI) are shown with p-values for significant differences.

	Simple Cox regression (non-adjusted)		Multiple Cox regression (adjusted)	
Variable	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Sex (m = 1, or f = 0)	1.94 (1.15 to 3.28)	0.010	2.79 (1.46 to 5.33)	0.002
Age (years)	1.05 (1.03 to 1.07)	0.001	1.07 (1.04 to 1.10)	0.001
BMI (kg/m^2)	0.96 (0.91 to 1.01)	0.080	0.99 (0.94 to 1.05)	0.800
AN score	1.02 (1.002 to 1.03)	0.028	1.02 (1.003 to 1.033)	0.018
CRP (mg/l)	1.024 (1.01 to 1.04)	0.001	1.02 (1.003 to 1.030)	0.019
Diabetes (yes=1 versus no = 0)	1.78 (1.10 to 2.90)	0.02	1.37 (0.79 to 2.35)	0.260

with estimated glomerular filtration rate (eGFR) >60 ml/min/1.73 m^2 served as controls in this preceding study; eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation.

After 5 years, survival was determined using Kaplan–Meier curves based on AN scores. The cohort was divided evenly into two groups, with 50% having higher scores and 50% lower. Figure 2a shows the survival curve for patients with lower AN scores (blue curve), clearly indicating better survival compared to those with higher AN scores [hazard ratio (HR) 1.02; 95% confidence interval (CI) 1.002 to 1.03, $p = 0.028$]. By the end of the 5-year observation period, the mortality difference between the two groups was quite notable: 48% of those with lower AN scores survived, whereas only 30% of those with higher AN scores did. Differences in survival times in the higher and lower AN score groups remained significant after adjusting for age, sex, CRP, BMI, and diabetes (see below and also see Table 2 with HR, 95% CI, and *p*-values).

Differences in survival rates were also found with CRP levels as a marker of chronic systemic inflammation. Figure 2b shows a significant advantage for patients with lower CRP levels after 5 years: 52% survival in this group compared to 27% in those with higher CRP levels (HR 1.02; 95% CI 1.01 to 1.03, $p = 0.001$). Using correlation analysis, it could be shown that there is no correlation between AN score and CRP ($r = 0.067$; 95% CI –1.21 to 0.25, $p = 0.48$). Similarly no correlation could be detected for AN score with age ($r = 0.12$; 95% CI –0.07 to 0.29, $p = 0.21$), BMI ($r = –0.029$; 95% CI 0.76, to –0.22, $p = 0.76$), and sex ($r = –0.11$; 95% CI –0.28 to 0.09, $p = 0.29$).

Survival rates were higher in women than in men (55% versus 29%; HR 1.94; 95% CI 1.15 to 3.28, $p = 0.01$), and, as expected survival was better in younger patients compared to older ones (59% versus 20%; HR 1.05; 95% CI 1.028 to 1.072, $p = 0.01$; Fig. 3a and b).

Dialysis patients with diabetes had significantly lower survival rates after 5 years compared to those without diabetes (27% versus 51%; HR 1.78; 95% CI 1.096 to 2.895, $p = 0.02$; Fig. 4a). No significant differences in survival were observed between groups with higher and lower BMI (41% versus 39%; Fig. 4b; HR 0.96; 95% CI 0.91 to 1.007], $p = 0.08$).

Multiple Cox regression was applied to adjust the above-mentioned effects of the predictor variables on mortality for each other (sex, age, CRP, BMI, AN score, diabetes). This means that a relationship of one variable with mortality is not solely a consequence of confounding with other variables if the relationship is still significant in the simple Cox regression model. After mutual adjustment in multiple Cox regression this was the case for AN score, CRP, age, and sex. The effects of these variables remained significant, while significance for diabetes and a trend for BMI vanished. Results of simple Cox regression analysis (non-adjusted) and multiple Cox regression analysis (adjusted) are shown in Table 2 together with HR, 95% CI, and *p*-values.

AN scores remained unchanged over time, showing no significant differences between the beginning and end of the 5-year period (24.3 ± 15.2 and 25.7 ± 18.7; mean ± standard deviation). The highly significant correlation between AN scores at the beginning and end of the 5 years documents minimal or no intraindividual variation (Table 3; correlation coefficient $r = 0.54$, $p < 0.01$).

DISCUSSION

In dialysis patients, AN is observed more often than in healthy individuals or those with only mildly reduced renal function [11–14]. This observation was confirmed in our study, which demonstrated markedly increased AN scores in dialysis patients. We found symptoms of AN to be more pronounced and more frequent, affecting not only cardiac AN but also other areas such as vasomotor, pupillomotor, secretomotor, and gastrointestinal functions. The high values of AN scores in our study could be attributed to the prolonged duration of diabetes (23 years) and the extended period of chronic dialysis therapy (8 years) at the beginning of our 5-year observation period.

Our results showed that elevated AN scores not only map increased symptoms of AN but also significantly indicate higher mortality rates in patients with higher AN scores (70% versus 52% for the group with higher versus lower AN scores). Previous studies in dialysis patients identified cardiac AN qualitatively as a risk factor for higher mortality [12, 13]. For the first time, our study demonstrated that an increased mortality risk can be identified not only with regard to cardiac AN but also with other organ manifestations of AN, which can be easily detected using the COMPASS 31 questionnaire.

Our finding of a negative correlation between CRP levels and survival aligns with earlier studies that showed an association between higher CRP levels and increased mortality, not only in chronic kidney disease but also in dialysis patients [15–17]. In these studies patients were followed for only 2 years, whereas the observation period of our study was 5 years. Higher CRP levels are associated with left ventricular hypertrophy, accelerated atherosclerosis, augmented oxidative stress, and other factors [18–20]. With declining renal function, the elimination of mediators associated with CRP elevation, such as cytokines, is diminished, both due to reduced renal clearance and increased biosynthesis [20, 21].

Both in patients with higher CRP values and also patients with higher AN scores survival rate was significantly reduced, as shown in Fig. 2a and b. The missing correlation between

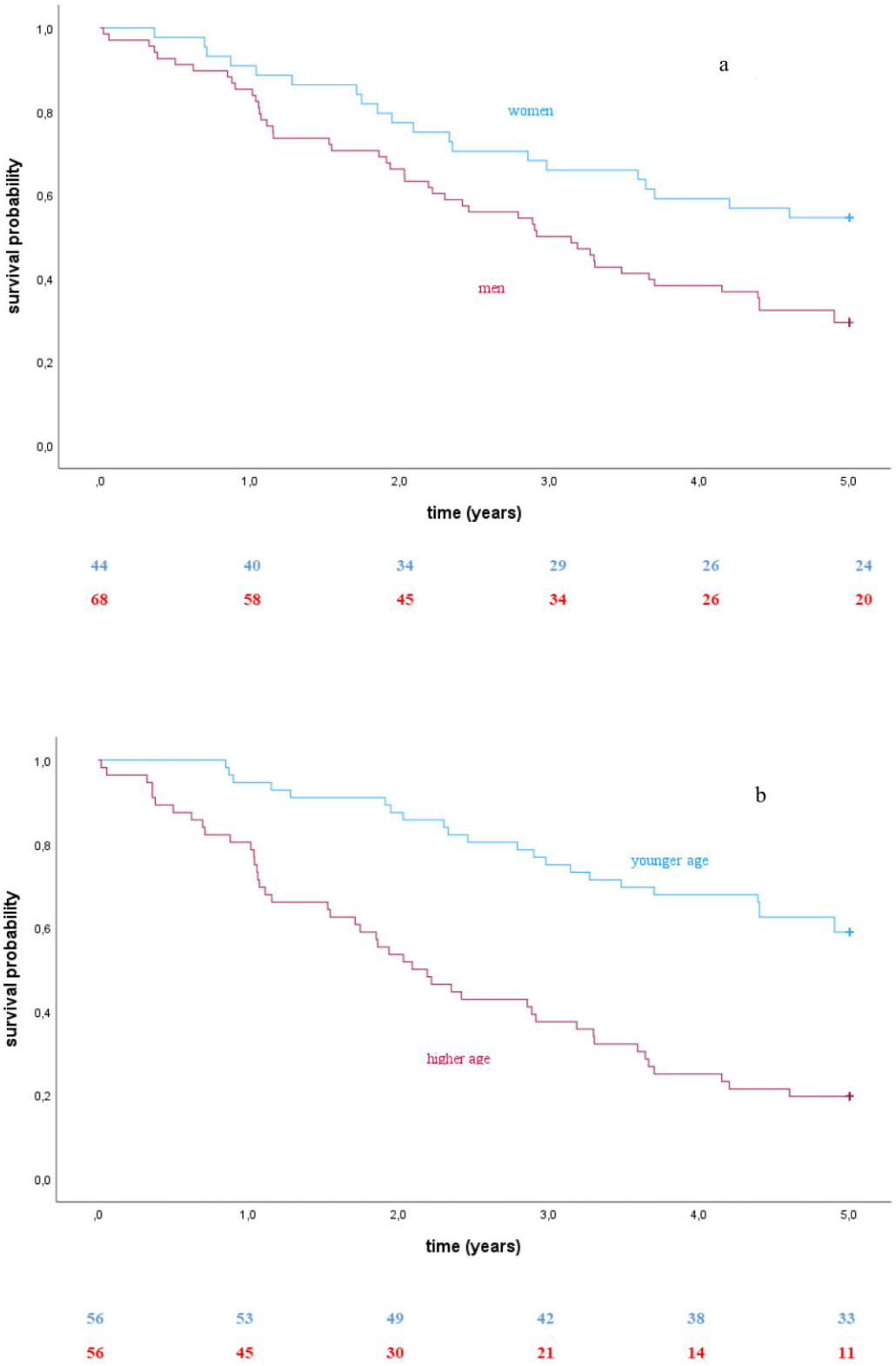


Figure 3: a: Kaplan–Meier survival curve for dialysis patients ($n = 112$) in dependence on sex during a 5-year interval; dichotomization of groups: red = men ($n = 68$), blue = women ($n = 44$). Under the curve: No. at risk in each group; survival after 5 years: 29% (95% CI 18 to 40) and 55% (95% CI 41 to 69), respectively ($p < 0.01$). b: Kaplan–Meier survival curve for dialysis patients ($n = 112$) in dependence on age during a 5-year intervall; dichotomization of groups: red = group with the older 50% of patients, blue = group with the younger 50% of patients (mean = 71.5 years). Under the curve: No. at risk for each group; survival after 5 years: 20% (95% CI 10 to 30) and 59% (95% CI 46 to 72), respectively ($p < 0001$).

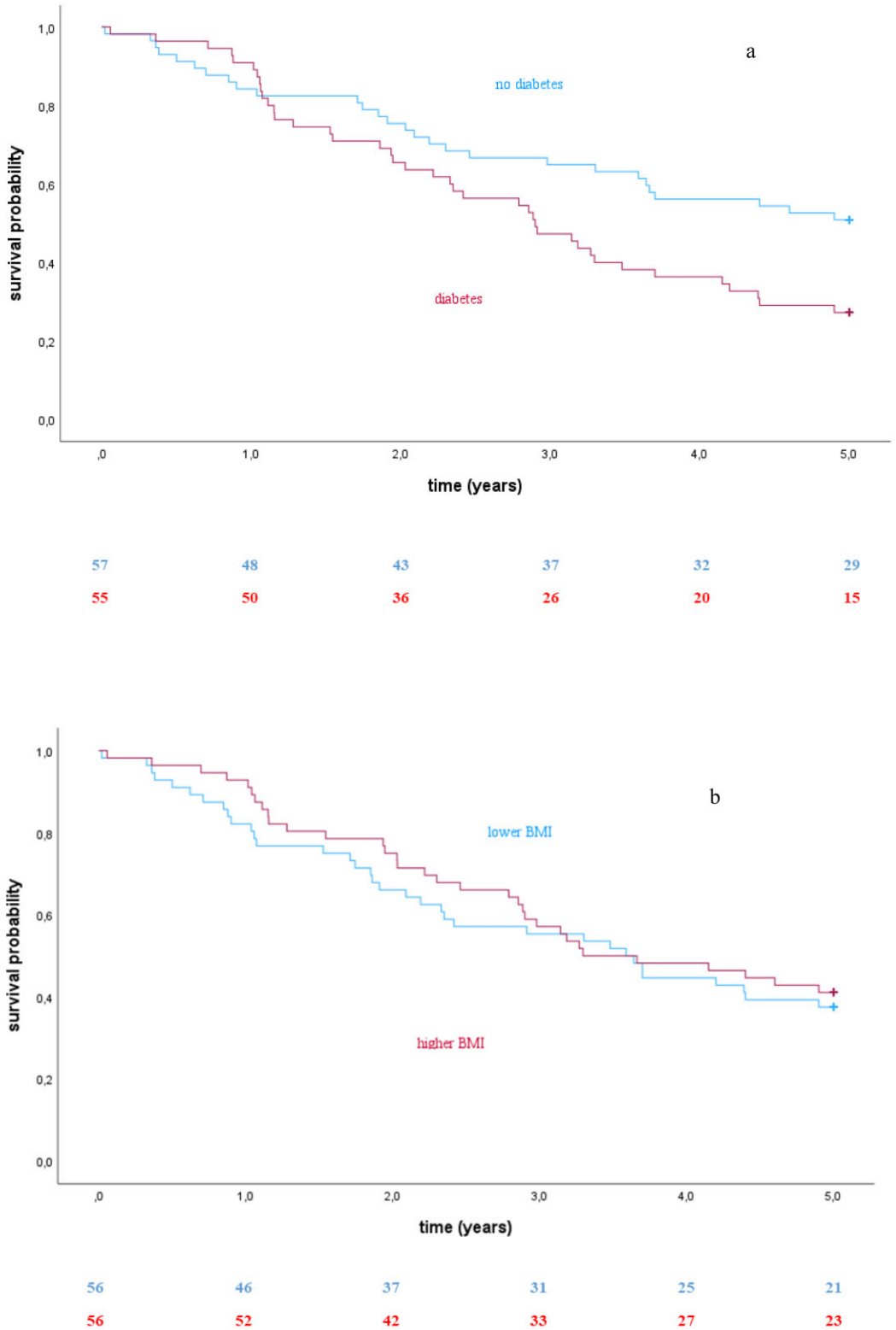


Figure 4: a: Kaplan–Meier survival curve for dialysis patients ($n = 112$) in dependence on diagnosis of diabetes during a 5-year interval; red = with diabetes ($n = 55$), blue = without diabetes ($n = 57$). Under the curve: No. at risk for each group; survival after 5 years: 27% (95% CI 16 to 38) and 51% (95% CI 38 to 64), respectively ($p < 0.05$). b: Kaplan–Meier survival curve for dialysis patients ($n = 112$) in dependence on BMI during a 5-year interval; dichotomization of groups: red = group with the higher 50% of BMI, blue = group with the lower 50% of patients. Under the curve: No. at risk for each group; survival after 5 years: 39% in both groups (n.s.). (95% CI 28 to 50 for higher BMI group and (95% CI 24 to 54 for lower BMI group).

Table 3: AN score at the beginning of the study (initial) and after 5 years (end); number of patients, mean and standard deviation are shown, significant correlation ($r = 0.537$, 95% CI 0.25 to 0.74, $p < 0.01$).

	N	Minimum	Maximum	Mean	Standard deviation
AN score initial	35	0	52.7	24.34	15.19
AN score end	35	0	60.2	25.71	18.66

the two parameters (see Results section) seems to indicate no direct association between CRP as a marker of inflammation and the intensity of symptoms of autonomic neuropathy. Some, but not all, studies in diabetic patients reported possible associations between inflammatory factors and peripheral neuropathy, especially in the early course of diabetes disease [22–24]. In a study looking simultaneously at inflammatory biomarkers and neuropathy longitudinal measurements of CRP were related with neuropathic symptoms [24]. However, not autonomic but only peripheral neuropathy was investigated. Another population-based investigation found no relationship between inflammatory biomarkers and neuropathy after adjusting for relevant clinical factors [25]. Separation between incident and prevalent dialysis patients, discrimination of traditional and non-traditional risk factors for mortality and other variables should be included in further studies to better understand the relationship between CRP and autonomic neuropathy in dialysis patients.

Mortality in dialysis patients is significantly increased in patients with diabetes. Our results show a high mortality rate of 73% in diabetic patients after 5 years, due to a prolonged preceding period of diabetes and chronic dialysis therapy. These findings align with other studies reporting 5-year mortality rates of 70% in diabetic patients, although some patients in these studies were incident dialysis patients without a prolonged preceding dialysis period [26–28]. Therefore, one might have expected even higher mortality rates in our cohort.

As expected, mortality increased with age in our study. BMI had no impact on survival in dialysis patients, while in the general population, obesity and high BMI are risk factors for cardiovascular disease and mortality [29]. In some, but not all, studies the seemingly unexpected associations between the traditional risk factors for cardiovascular disease (obesity, dyslipidemia, hypertension, and others) and paradoxically better survival in chronic kidney disease (CKD) have been documented. This paradox has been referred to as the 'reverse epidemiology' phenomenon, to indicate the associations which are contrasting with conventional findings in the general population [30–32]. On the other hand, no association of BMI and mortality risk was seen in older incident dialysis patients [33]. Different attempts to explain the obesity paradox in CKD were reported, amongst them protein energy wasting (PEW), frequently observed in patients with CKD [34, 35]. PEW in these patients is connected with induction of inflammatory processes, for example activation of inflammatory cytokines. Another study in dialysis patients showed a higher mortality risk in inflamed compared with non-inflamed patients [36]. Lower BMI could be the consequence of lower food intake due to appetite loss and dietary restrictions, both also known to be associated with worse outcome [37–39]. Our data are not able to identify higher or lower BMI as a risk factor for increased mortality and cannot remarkably elucidate the underlying mechanisms. To more accurately investigate these correlations in upcoming studies, it would be necessary to have a design that pays particular attention to the duration of diabetes disease and of chronic dialysis therapy and to the contribution of skeletal muscle and fat mass when calculating BMI. Moreover, whether incident or prevalent patients are included should be taken into account when proving the effects of BMI on mortality and other relevant factors.

Survival is better for women in the general population, mainly due to a lower prevalence of cardiovascular risk factors and diseases [40]. Similarly, a better survival rate was documented for our female dialysis patients, while other studies did not find such an advantage in survival for female dialysis patients [27]. These studies suggested that dialysis therapy itself might negate women's survival advantage. However, they did not consider whether women were in a pre- or postmenopausal status. This could be significant, as another study found a better survival among women who began dialysis therapy post menopause. Regarding gender-specific survival in dialysis patients, future studies should account for gender-specific differences in renal replacement therapy, womens' age at the start of dialysis, time of referring to dialysis therapy (early or late beginning), and dialysis access.

AN scores did not change during the 5-year observation period, with nearly the same mean at the beginning and the end. Individually, there was no marked change, as indicated by a strong positive correlation between both parameters. With increasing duration of diabetes, one might expect higher AN scores at the end of the 5-year observation period [41]. On the other hand, dialysis therapy itself could have a beneficial effect on neuropathic symptoms. Supporting this idea, other studies showed that neuropathy could be improved by long nightly dialysis sessions or renal transplantation [42, 43]. As we found no differences in AN scores at the beginning and end of the 5-year observation period, it is possible that positive and negative effects might have negated each other.

CONCLUSION

AN is frequently observed in dialysis patients and can be easily detected by scores derived from the self-assessment test COMPASS 31. Patients with higher AN scores have a worse survival rate compared to those with lower scores. This is true not only for autonomic cardiac neuropathy but also for AN scores reflecting changes in other organ systems. AN scores can easily detect not only cardiac autonomic changes but also those in various other organ systems in dialysis patients and identify their high risk for increased mortality. To identify patients with severe autonomic dysfunction, the COMPASS 31 questionnaire could be easily integrated into routine clinical assessments for dialysis patients. Clinicians could tailor interventions such as enhanced cardiovascular monitoring or targeted treatment of autonomic symptoms. A practical measure could be performance of COMPASS 31 in certain intervals, for instance every year. Patients with higher AN scores thereafter should undergo best possible treatment of all traditional and non-traditional cardiovascular risk factors.

AUTHORS' CONTRIBUTIONS

All authors contributed to the conception and design of the work, analysis, and interpretation of data, drafting the work and reviewing it critically. Final approval of the version to be published was within the responsibility of M.C.S. and C.V.S. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

The authors have no relevant financial or non-financial interests to disclose and did not receive support from any organization for the submitted work.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

ETHICAL APPROVAL

Ethical approval was granted by the 'Ethikkommission der Medizinische Fakultät der Universität Rostock' (A2015–0176,/Dr med. M. Hinz, Universitätsmedizin Rostock—ZIM III Nephrologie). Patients were enrolled in the study only after written informed consent was obtained.

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