High Cardiovascular Risk Profile in Young Patients on the Kidney Transplant Waiting List

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ABSTRACT

Background. Cardiovascular complications are the leading causes of morbidity and mortality in patients with end-stage renal disease. The risk profile very often contributes to their death while on the waiting list. Most studies have been carried out in older patients with end-stage renal disease, reflecting the general dialysis population. The aim of this study was to analyze the risk profile in young patients with advanced chronic kidney disease on the kidney transplant waiting list.

Methods. This was a retrospective, single-center study of 748 patients on the kidney transplant waiting list at the University Hospital Essen, Germany. Clinical and laboratory parameters were collected between 2015 and 2016.

Results. Of 748 patients (62% male), the median age was 48 years. Hypertension, coronary heart disease, and diabetes mellitus were the leading comorbidities, and their frequency rose significantly with age. Their median laboratory values did not differ significantly depending on age except for albumin. Hyperuricemia was quite common in our population with a prevalence of about 75% in women and 50% in men throughout all age groups. A total of 26.6% of the patients between 18 and 35 years of age had advanced anemia (hemoglobin < 10 g/dL), and thus they were affected most frequently. Elevated C-reactive protein serum levels were observed in 37.2% of the patients. Regarding the lipid profile, we observed that HDL cholesterol was within the normal range in only among 51.9% of men and 44.3% of women.

Conclusions. Cardiovascular risk factors are quite common in our cohort and affect young patients similarly.

PATIENTS with end-stage renal disease (ESRD) are 3 to 4 times more likely to die prematurely than the normal population [1]. The leading causes of morbidity and mortality in patients with ESRD are of cardiovascular origin [1–3]. There is a pronounced cardiovascular risk [3,4] even at early stages of chronic kidney disease (CKD). Various complications in patients with ESRD lead to increased risk profiles such as anemia, hypoalbuminemia, dyslipidemia, hyperuricemia, and chronic inflammation. Kidney transplant is the renal replacement therapy approach carrying the lowest risk of cardiovascular mortality compared with the general population [5]. However, because of a drop in

Data Availability: The data and analyses that support these study findings are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate: This study was approved by the University Hospital Essen Ethics Committee coordinator (reference: 17–7377-Bo) as a quality and service improvement initiative in accordance with the National Statement on Ethical Conduct in Human Research.

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organ availability, the waiting time on German transplant lists has risen [6]. The risk of dying on the waiting list or shortly after transplant will therefore continue to rise, affecting young patients with ESRD especially.

Anemia. The prevalence of anemia in CKD rises with a decreasing glomerular filtration rate (GFR) and affects nearly 100% at stage 5 [7]. Anemia is associated with advanced cardiovascular risk and mortality as well as hospitalization [7,8]. A correction of hemoglobin (Hb) levels to 11 to 13 g/dL with erythropoietin-stimulating agents (ESAs) reduces the cardiovascular mortality in predialysis patients [9], but there is no benefit of further rises in Hb levels; on the contrary, they raise the risk of cardiovascular events [10–12].

Hypoalbuminemia. Hypoalbuminemia is associated with increased mortality and hospitalization rates in patients requiring dialysis [13,14]. A strong predictor of decreased albumin levels is apparently elevated C-reactive protein (CRP) as the best marker of chronic inflammation [15].

Chronic inflammation. Elevated CRP levels as an inflammation marker are quite common in patients with ESRD on hemodialysis [16], on peritoneal dialysis [17], and not on dialysis [18]. Various reasons are discussed, such as the impaired renal excretion of proinflammatory cytokines, recurrent infections because of immunosuppression, metabolic acidosis, and dialysis-specific factors (punctures, catheter-insertion wounds, and contact with artificial surfaces) [19]. Chronic inflammation is associated with cardiovascular complications [20,21], anemia with advanced erythropoietin resistance [22–25], and hypoalbuminemia [15] in patients with CKD.

Hyperuricemia. The sex-independent prevalence of hyperuricemia in the general population differs among countries, that is, 9.9% in men and 7.0% in women in China [26] and 21% in the United States [27]. In patients with CKD, there is evidence of elevated uric acid levels in patients with decreased estimated glomerular filtration rate (eGFR) [28,29]. It remains questionable whether asymptomatic hyperuricemia is a causal risk factor for developing hypertension [30–32], elevated cardiovascular risk [33,34], and kidney damage [35–37].

Dyslipidemia. The lipid profile of patients with CKD typically changes with a decreasing GFR. Their total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol values are decreased, whereas triglycerides are elevated [38]. Excessive LDL cholesterol levels are a known risk factor for cardiovascular complications in the general population. In contrast, HDL cholesterol seems to be a protective factor. Recent study results seem to question the protective role of elevated HDL values [39,40]. There are certain factors that must be considered regarding patients with CKD. The HDL molecules transform with a decreasing GFR into modified particles with noxious characteristics [41–43]. Beyond that, the role of LDL cholesterol as a traditional risk factor in patients with ESRD remains uncertain as well, as studies report effective lipid-lowering therapy via statins but without reducing cardiovascular mortality [44,45].

The aim of our study was to analyze the risk profile of adults with advanced CKD on the kidney transplant waiting list, giving younger patients special consideration.

MATERIALS AND METHODS

Patients and Inclusion Criteria

In total we collected the data from 748 patients with advanced CKD older than 18 years at the date of registration at the Transplant Outpatient Clinic of the University Hospital Essen, Germany. All of these patients had been placed on the kidney transplant waiting list. To investigate the role of age in the prevalence of cardiovascular risk factors, we compared patients aged a minimum 50 years with those who were younger. In addition, we divided the whole sample into 4 age categories (18 to $<$ 35 years; 35 to $<$ 50 years; 50 to $<$ 65 years; $\geq$ 65 years) to obtain a more differentiated perspective.

Data Acquisition

We retrospectively analyzed the data from the registration date at the Transplant Outpatient Clinic. This entailed biochemical and clinical data and the patients' medication. Laboratory values were followed up during their time on the waiting list. Those data were collected between December 2015 and November 2016.

Clinical parameters. Basic information on sex, age, and body mass index was supplemented by data on the underlying kidney disease as well as documented comorbidities (hypertension, coronary heart disease, and diabetes mellitus), medications, and the type of dialysis (hemodialysis, peritoneal dialysis, or not on dialysis).

The underlying kidney diseases were, depending on the pathomechanism, divided into groups:

1 Diabetic nephropathy (diabetes mellitus)
2 Glomerulonephritis (acute and chronic glomerulonephritis)
3 Nephrosclerosis (hypertensive nephropathy)
4 Congenital diseases (autosomal dominant polycystic kidney disease, autosomal recessive polycystic kidney disease, atypical hemolytic uremic syndrome)
5 Interstitial nephropathy (toxic, reflux nephropathy)
6 Systemic autoimmune diseases (vasculitides, collagen vascular disorders)
7 Others (unknown course, perioperative, typical hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, retroperitoneal fibrosis, and status after bilateral nephrectomy)
8 Combined diseases

Medication. Medications at the date of the registration, documented in n = 737 (98.5%) patients, were analyzed.

Antihypertensive drugs: beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor type 1 receptor blockers, diuretics.

Metabolic drugs: lipid reducers (statins, fibrates), uric acid reducers (allopurinol, probenecid, benzbromarone).

Others: ESAs.

Laboratory values: The first laboratory values were collected at the registration date (median 1 month before registration). Acquired laboratory parameters were hemoglobin, GFR, uric acid, albumin, CRP (elevation: $\geq$ 5 mg/L), LDL cholesterol, HDL cholesterol, total cholesterol, and triglycerides.

Statistics

Statistical analysis was calculated with SPSS Statistics V 24 (IBM, Armonk, NY, United States). To check whether the data showed a normal distribution, the Kolmogorov-Smirnov test was run. For a descriptive data presentation, absolute and relative frequencies were used as well as median as measures of location and interquartile range was used as measure of variation. These results were tested for statistical significance with Kruskal-Wallis test, Mann-Whitney test, χ^2 test, and Wilcoxon signed rank test. Spearman ρ was used to calculate correlations. For all statistical procedures performed, the significance level was set at $\alpha = 0.05$.

RESULTS

Patient Characteristics and Underlying Kidney Diseases

Basic patient characteristics are summarized in Table 1. Regarding the entire population, the proportion of men (61.9%) was significantly higher ($\chi^2 = 42.358$; $P < .001$) than women (38.1%). Most patients were on hemodialysis (59.5%). There was no significant difference in time on dialysis until the date of registration between hemodialysis and peritoneal dialysis ($P = .22$). Table 1 divides the patients into 2 age categories. Our study age cutoff was set at 50 years. The 2 groups were balanced in terms of the dialysis modality ($\chi^2 = 0.587$; $P = .75$) and time on dialysis ($U = 36584.5$; $P = .39$), whereas the frequency of women was significantly higher in the younger group ($\chi^2 = 4.439$; $P = .04$).

The frequency of all patients' underlying kidney diseases is shown in Fig 1. The most common diseases were glomerulonephritis (29%) and congenital diseases (24%). The frequency of diabetic nephropathy was quite low (7%). The distribution between younger and older patients did not differ ($\chi^2 = 21.878$; $P = .41$). Table 2 illustrates the frequency of comorbidities and the median values of biochemical parameters depending on age.

Body Weight and Cardiovascular Risk Factors

The median body mass index (BMI) of all patients was 25.8 kg/m^2. Only 2.4% of the patients were underweight (BMI < 18.5), but 32.3% had a BMI between 25.0 and 29.9 kg/m^2 and 23.3% were overweight (BMI ≥ 30.0 kg/m^2). We noted a significant positive correlation between age and BMI ($\rho = 0.179$; $P < .001$), but as shown in Table 2, the median BMI decreases in the oldest patients (≥ 65 years) compared with the middle-aged ones. The prevalence of coronary heart disease, diabetes mellitus, and hypertension were lower in the youngest subgroup; the prevalence of coronary heart disease rose especially with age (Table 2). In patients 50 years or older, the prevalences of hypertension (97% vs 91%; $\chi^2 = 12.587$; $P < .001$), coronary heart disease (33% vs 13%; $\chi^2 = 44.304$; $P < .001$), and diabetes (21% vs 15%; $\chi^2 = 4.455$; $P = .04$) were significantly higher than those in patients younger than 50 years.

Biochemical Risk Factors

Figure 2 illustrates the distribution of the laboratory values. Patients were divided into 2 groups according to age and the cutoff was 50 years. There was no statistically significant difference between these groups except for albumin ($\chi^2 = 5.701$; $P = .02$). The separate values are described below.

Uric acid. We observed a significant difference in the median values of uric acid between male (m) and female (w) patients (m: 7.0 mg/dL, w: 6.6 mg/dL; $P < .001$), but considering the sex-specific normative values, there was higher prevalence of hyperuricemia in women (74.7%) than men (48.7%). The intake rate of uric acid–lowering medication was rather low (32.0%) in relation to that prevalence. Uric acid did not correlate significantly with age in either sex (m: $\rho = -0.99$, $P = .05$; w: $\rho = -0.53$, $P = .42$); thus, uric acid's median values (Table 1) and the frequencies of hyperuricemia (Fig 2C and D) did not vary significantly between the age-based groups. Even the prevalence in the youngest patients (< 35 years; m: 50.0%, w: 74.5%) was quite similar compared with the total population. Only 10% in that subgroup of men and 22% of the women diagnosed as having hyperuricemia took uric acid reducers in this subgroup. There were no significant differences in the prevalences of diabetes, coronary heart disease, and hypertension in men and women with elevated uric acid levels compared with the patients without hyperuricemia.

Hemoglobin, albumin, and CRP. A total of 111 of 694 (15.9%) patients had hemoglobin levels < 10.0 g/dL, whereas 82 of 694 (11.8%) patients had levels > 13.0 g/dL. Albumin reveals a similar distribution with a total of 74 of 388 (19.1%) patients who presented levels below the normal range. There was no significant difference in median hemoglobin values

Table 1. Patient Characteristics Depending on Age

Patient Characteristics	All Patients	Patients < 50 Years	Patients ≥ 50 Years
No.	748	391	357
Female, No. (%)	285 (38.1)	135 (34.5)	150 (42.0)
Male, No. (%)	463 (61.9)	256 (65.5)	207 (58.0)
Age, median (IQR), y	48	38.0 (29.0–44.0)	57.0 (53.0–62.0)
On hemodialysis, No. (%)	445 (59.5)	231 (59.1)	214 (59.9)
Time on dialysis, median (IQR), mo	11.0	10.0 (5.0–26.0)	11.0 (6.0–24.3)
On peritoneal dialysis, No. (%)	108 (14.4)	54 (13.8)	54 (15.1)
Time on dialysis, median (IQR), mo	9.5	8.5 (4.0–17.0)	11.0 (6.0-21.3)
Not on dialysis, No. (%)	195 (26.1)	106 (27.1)	89 (24.9)
GFR, median (IQR), mL/min	12.0	14.0 (10.0–17.0)	11.0 (8.0–13.5)

Table 1 gives the basic patient characteristics of our population. Two groups are divided. The cutoff age was set at 50 years.
Abbreviations: GFR, glomerular filtration rate; IQR, interquartile range.

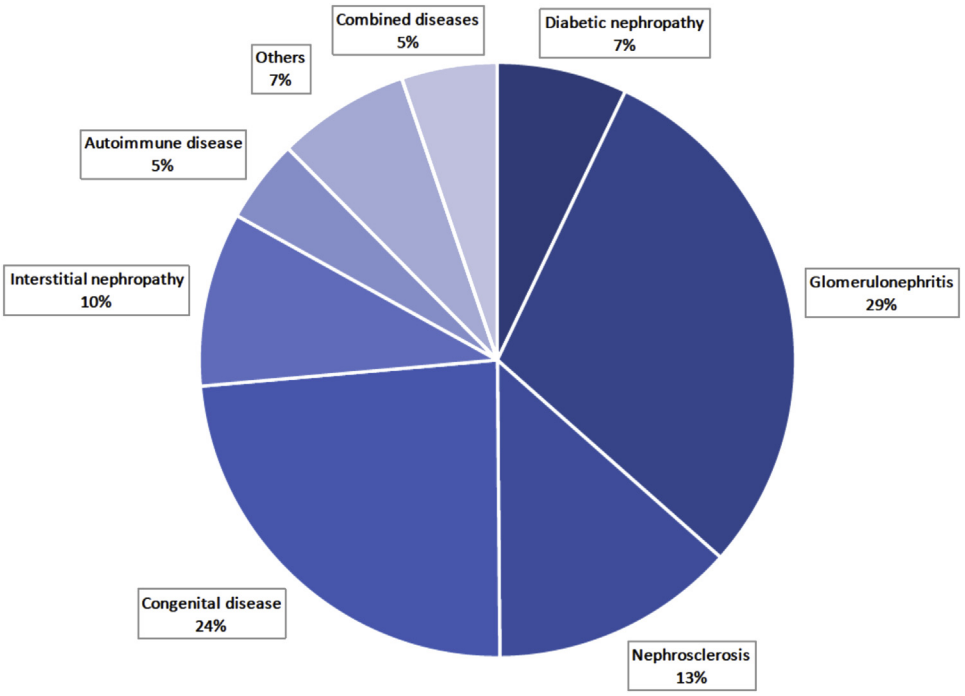

Fig 1. Illustration of the frequency of underlying kidney diseases of all patients (n = 748).

(m: 11.6 g/dL, w: 11.3 g/dL) and albumin values (m: 39.8 g/dL, w: 39.0 g/dL) between men and women. Elevated CRP levels were defined as values ≥ 5.0 mg/L. A total of 181 of 486 (37.2%) presented elevated CRP levels, and 20% had CRP rates > 10.0 mg/L. In relation to the entire sample, CRP values correlated positively with BMI ($\rho = 0.145$; $P = .001$), and its elevation was significantly associated with a diabetes diagnosis ($\chi^2 = 4.911$; $P = .03$). The aforementioned associations

Table 2. Comorbidities and Biochemical Parameters Depending on Age

Variable	All patients	Age, y				*P* Value
		18 to < 35	35 to < 50	50 to < 65	≥ 65	
No. (%)	748 (100)	162 (21.7)	229 (30.6)	300 (40.1)	57 (7.6)	
Hemoglobin, median (IQR), g/dL	11.3	11.2 (9.9–12.3)	11.3 (10.4–12.1)	11.4 10.6–12.2)	11.4 (10.4–12.4)	.46
Uric acid, median (IQR), mg/dL	6.8	7.00 (6.0–8.1)	6.85 (6.3–8.1)	6.80 (5.8–7.7)	6.65 (5.3–7.6)	.13
Total cholesterol, median (IQR), mg/dL	188.5	180.5 (142.0–211.8)	187.0 (158.0–214.0)	194.0 (164.0–224.0)	184.0 (156.0–236.5)	.06
HDL cholesterol, median (IQR), mg/dL	44.0	46.0 (33.0–54.0)	42.0 (36.0–54.0)	41.0 (33.0–52.5)	49.0 (43.5–62.0)	.09
LDL cholesterol, median (IQR), mg/dL	109.0	109.0 (80.0–132.0)	105.0 (84.0–133.0)	116.0 (82.8–143.0)	100.5 (86.0–147.5)	.80
Triglycerides, median (IQR), mg/dL	165.5	147.5 (94.5–227.0)	165.0 (116.0–247.7)	176.0 (122.0–245.5)	174.0 (115.0–220.0)	.10
Albumin, median (IQR), g/L	39.0	41.0 (38.0–34.0)	39.0 (36.9–42.0)	39.0 (35.0–42.0)	38.4 (34.5–42.0)	.04*
CRP elevation, %	37.2	41.0	35.0	41.0	20.0	.06
BMI, median (IQR), kg/m^2	25.8	23.80 (21.0–27.0)	26.25 (23.4–31.0)	26.71 (24.0–30.0)	25.72 (24.0–38.3)	<.001*
Coronary heart disease, %	22.5	4.0	19.0	31.0	46.0	<.001*
Hypertension, %	93.6	86.0	94.0	97.0	95.0	<.001*
Diabetes mellitus, %	18.0	8.0	20.0	20.0	25.0	.002*

Table 2 illustrates the median values of hemoglobin, albumin, the lipids, the percentage of elevated CRP values, and the frequencies (percentage) of comorbidities (coronary heart disease, diabetes mellitus and hypertension). The patients are divided into different age categories.

Abbreviations: BMI, body mass index; CRP, C-reactive protein; IQR, interquartile range.

*$P < .05$.

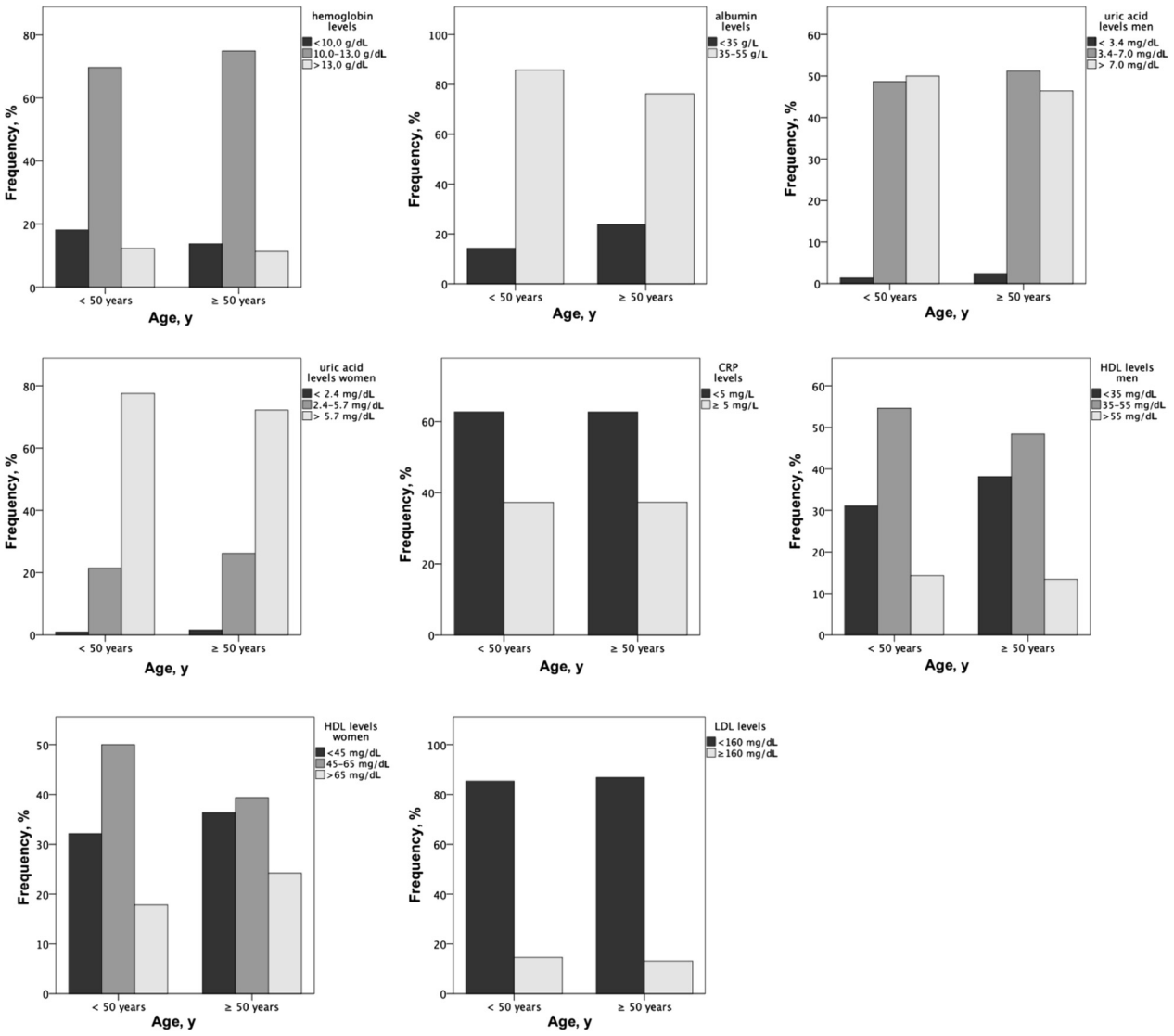

Fig 2. **(A-H)** Distribution of the laboratory values depending on age (cutoff: 50 years). CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

between CRP elevation and BMI ($\rho = -0.068$; $P = .51$) and diabetes ($\chi^2 = 0.11$; $P = .74$) were not observed in patients between 18 and 35 years of age.

About a quarter (25%) of the patients with anemia were not treated with ESAs, whereas 42% of the patients with hemoglobin levels > 13 g/dL received such a therapy.

Compared with our entire study cohort, younger patients presented equal frequencies of anemia and CRP elevation (Fig 2A and E); there was no significant correlation between hemoglobin ($\rho = 0.072$; $P = .06$) and CRP ($\rho = -0.017$; $P = .71$) with age. Table 2 shows that the youngest subgroup (< 35 years) had the lowest median hemoglobin values (without significance) highly prevalent inflammation (41%). The prevalence of anemia was 26.6% in the latter group, with 22% of anemic patients not receiving ESAs. Albumin reveals a different distribution pattern, as it correlated significantly negative with age ($\rho = -0.147$; $P = .004$); thus, the prevalence of hypoalbuminemia was lower ($\chi^2 = 5.701$; $P = .02$) in younger patients (Fig 2B).

Table 3 illustrates the relation between the dialysis procedure and the values of hemoglobin, albumin, and CRP. The median hemoglobin values were similar in each group, whereas there was a difference in albumin and CRP between groups, but only albumin was significant. If only 2 groups are differentiated (not shown in the table), patients on dialysis (hemodialysis and peritoneal dialysis together) and those not on dialysis, the CRP levels were significantly different ($P = .03$) as well.

Both hemoglobin and albumin correlated negatively with CRP serum levels (albumin and CRP: $\rho = -0.121$; $P = .04$;

Table 3. Hemoglobin, Albumin, and CRP Values Depending on the Dialysis Procedure in All Patients

Laboratory Value	Hemodialysis	Peritoneal Dialysis	Not on Dialysis	*P* Value
Hemoglobin, median (IQR), g/dL	11.3 (10.5–12.2)	11.5 (10.4–12.3)	11.4 (10.3–12.3)	.68
Albumin, median (IQR), g/L	39.0 (36.0–42.0)	37.8 (34.7–40.0)	41.0 (37.9–43.0)	.002
CRP $\geq$ 5.0 mg/L (%)	112 (39.0)	33 (43.0)	37 (29.0)	.07

Table 3 illustrates the median values of hemoglobin and albumin and the percentage of elevated CRP values depending on the kind of dialysis. Three groups of dialysis are distinguished: hemodialysis, peritoneal dialysis, and not on dialysis.
Abbreviations: CRP, C-reactive protein; IQR, interquartile range.

hemoglobin and CRP: $\rho = -0.134$; $P = .003$). We noted a significant difference in the distribution of hemoglobin ($\chi^2 = 33.276$; $P < .001$) and albumin ($\chi^2 = 5.421$; $P = .02$) levels depending on CRP values. In patients with CRP levels < 10 mg/L, the prevalences were about 36% (anemia) and 33% (hypoalbuminemia) vs 12% (anemia) and 19% (hypoalbuminemia) in patients with pronounced inflammation (CRP $\geq$ 10 mg/L).

Lipids. HDL cholesterol was within the normal range in only 51.9% of men and 44.3% of women (m: 35–55 mg/dL, w: 45–65 mg/dL). A total of 34% of both sexes presented insufficient HDL levels, whereas elevated levels were measured in 14% of men and 21% of women. Total cholesterol was elevated in 40.3%, triglycerides in 40%, and LDL levels in only 14% of the patients. A total of 34% of patients were taking lipid reducers, with no significant difference between groups (lipids within the normal range vs elevated).

Dyslipidemia was not prevalent in only elderly patients (Fig 2F-H). Even patients younger than 35 years revealed similar values (Table 2), yet only about a fifth (20.3%) of them were taking lipid reducers. None of the lipids we examined revealed any significant correlation with age: total cholesterol ($\rho = 0.086$; $P = .06$), LDL cholesterol ($\rho = 0.034$; $P = .54$), triglycerides ($\rho = 0.065$; $P = .16$). and HDL cholesterol (m: $\rho = -0.19$, $P = .78$; w: $\rho = 0.086$, $P = .35$).

DISCUSSION

This retrospective, single-center study aimed to analyze the prevalence and expression of clinical and biochemical risk factors and comorbidities in patients on the kidney transplant waiting list with special emphasis on younger ones. The patients enrolled included both sexes, patients with heterogeneous underlying kidney diseases, and patients undergoing different dialysis procedures. We divided the whole population in 2 groups depending on age to compare the cardiovascular risk profile of younger (< 50 years) patients with the older patients' profile. We chose the cutoff of 50 years because it nearly matched with the median age of 48 years, and we aimed to acquire well-comparable groups. The groups did not differ significantly in their distribution of underlying kidney diseases, type of dialysis, or median time on dialysis. In addition, we were interested in the cardiovascular risk profile of extremely young patients (< 35 years).

The leading causes of ESRD in general are diabetes mellitus and hypertension [46]. However, glomerulonephritis and congenital anomalies were the most frequent underlying kidney diseases in our population, while diabetic nephropathy had quite low prevalence. One reason for this might be the strong impact of comorbidities and complications in patients with advanced diabetes such as severe atherosclerosis that renders them disqualified for transplant. The distribution in our population was quite similar to Akolekar et al [47], who also mentioned glomerulonephritis and congenital diseases as the most common diseases in those on kidney transplant waiting lists.

The comorbidities we assessed, namely coronary heart disease, hypertension, and diabetes mellitus, were less prevalent in our young patients. Body mass index was lowest in patients younger than 35 years as well and correlated positively with age, but, after an increase in the middle-aged ones, dropped again in patients 65 years and older. A total of 74.2% of our entire patient cohort had a BMI between 18.5 and 29.9 kg/m^2. Panwar et al [48] reported a protective influence of having a slightly increased BMI (25.5 kg/m^2) in patients with ESRD. Our patients thus seem to have acceptable weight overall, especially compared with a study on BMI's influence on successful transplant, where just 59.3% of the listed patients had a BMI 18.5 and 29.9 kg/m^2 [49].

In 2 German studies on the general population, the prevalence of hypertension was 74.3% in men (median age, 64.9 years) and 70.2% in women (mean age, 63.8 years) [50] and 7.8% in men and 1.7% in women aged between 25 and 34 years [51]. In comparison with our results, patients younger than 35 years had a hypertension prevalence of 86.0%, whereas its prevalence was 94% to 97% in older patients. Thus, the difference between patients with and without kidney disease is much more pronounced in younger patients.

Akolekar et al also report a statistically significant increase in prevalence with age characteristic of coronary heart disease and diabetes [47]. They investigated the impact of patient characteristics and comorbidity profiles on being placed on the kidney transplant waiting list in the United Kingdom. However, compared with Akolekar et al, who reported a prevalence of 12.6% of coronary heart disease and 4.1% of diabetes in all patients currently on the waiting list, the prevalences in patients younger than 50 years in our population regarding coronary heart disease (13.0%) and diabetes (15.0%) were even higher.

The sex-independent prevalence of hyperuricemia in the general population differs among countries, with 9.9% in men and 7.0% in women in China [26] and 21% in the United States [27]. In patients with CKD, there is growing evidence that elevated uric acid levels are associated with

decreased GFR. Bellomo et al reported a significant negative correlation between uric acid and eGFR [28]. Suliman et al [52] studied a cohort of Swedish patients (mean age, 53 years) and detected a mean uric acid value of 7.5 mg/dL (men) and 6.7 mg/dL (women) in patients with CKD stage 5 at the time when renal replacement therapy was being planned. Those results are in accordance with ours: median values of 7.0 mg/dL (men) and 6.6 mg/dL (women). In the German CKD study of 5085 white patients, the prevalence of hyperuricemia rose up to 73% while eGFR decreased to 30 mL/min/1.73 m^2. Unfortunately, information on the sex-specific prevalence of hyperuricemia is lacking [29]. There is practically no data so far on sex differences in uric acid levels in CKD. More than 70% of women and nearly 50% of men presented elevated uric acid levels in our study cohort. Interestingly, even the youngest patients (18 to < 35 years) in our cohort had similar median uric acid levels, and hyperuricemia and uric acid rates did not correlate with age significantly in either sex. Suliman et al [52] identified no significant correlation between age und uric acid in CKD stage 5 patients either. In contrast, the prevalence of hyperuricemia in the US general population rose with age and was diagnosed in 17.1% of 20 to 39-year-olds compared with 29.2% in elderly persons (60–79 years). About a third (32%) of all patients in our cohort were taking uric acid reducers. Jing et al reported similar values [29], with 32.5% of their patients in the German CKD study taking uric acid–lowering therapy. Remarkably, only 10% of men and about 20% of women younger than 35 years presenting elevated uric acid levels in our study were taking uric acid reducers. This suggests that hyperuricemia might be given inadequate consideration in young patients with ESRD. A reason for their overall low intake rate might be the restrained recommendation for treating an asymptomatic hyperuricemia [53] and the adverse effects of allopurinol [54], the current standard of care. In our retrospective analysis we detected no influence on the prevalence of cardiovascular comorbidities despite of the high frequency of hyperuricemia. More prospective studies with clinical endpoints are necessary to clarify the pathophysiological mechanisms of vascular [55] and kidney damage [28,29,52] due to hyperuricemia in CKD patients.

Studies on elevated CRP serum levels in patients on dialysis and with advanced chronic kidney disease who were not on dialysis, have already been reported [16–19,21]. They described median CRP values of 7 mg/L in a cohort of peritoneal dialysis patients [17] and median values of 5.1 mg/L in predialysis patients (elevated levels ≥ 10 mg/L were reported in 17% of the patients) [18]. Zimmermann et al analyzed 280 patients on hemodialysis; 46% of them had CRP values > 8 mg/L [16]. Our results were similar, as our population had elevated CRP values, especially the patients on dialysis. Risk factors were diabetes mellitus and obesity. A protective influence of mildly elevated BMI levels (25.5 kg/m^2) on chronic inflammation has been reported [20]. It remains questionable whether a higher BMI protects patients with CKD against chronic inflammation or represents a cardiovascular risk factor. Despite lower frequencies of diabetes and obesity in patients younger than 35 years, CRP was elevated in 41% of them, and we noted that those comorbidities had no significant influence on inflammation in that group. There must therefore be other reasons for the inflammatory situation in this group; it is probably because their kidney disorder's influence is even stronger.

About a fifth of our patients had hypoalbuminemia. Median lower albumin values in patients on dialysis is perhaps attributable to malnutrition, but then one would also expect an association with BMI. Another reason might be the more frequent presence of chronic inflammation in patients on dialysis and a consecutive decrease in albumin values as anti-acute phase protein [56]. Unlike all other laboratory values we analyzed, median albumin values varied significantly among age-based groups (Table 2) as did the frequency of values outside the normal range (Fig 2). Sridhar et al reported comparable results in their cohort of patients on hemodialysis, as age correlated negatively with albumin [57]. There, lower protein intake in elderly persons has been discussed as a possible cause.

Chronic inflammation was associated with anemia and hypoalbuminemia in our study. The prevalence of an advanced anemia rose from 12% in patients with low CRP values to 36% in those with CRP levels > 10 mg/dL. Also, hypoalbuminemia was much less common (19.2%) in patients with CRP ≤ 10 mg/dL than in the group with elevated CRP values (33.3%). The patients on peritoneal dialysis in our cohort had the highest prevalence of elevated CRP levels and the lowest albumin levels, highlighting the association between these values (Table 3). This finding falls in line with previous studies reporting an association between inflammation and hypoalbuminemia in peritoneal dialysis patients [58]. Another study reported that the increased mortality in patients with hypoalbuminemia in patients undergoing dialysis is partly due to inflammation and not just to malnutrition [56]. Inflammation is one of the most important risk factors for developing anemia and erythropoietin resistance in patients with CKD. This is one of the factors attributable to increased secretion of hepcidin, which is a protein that reduces the enteral iron resorption an iron release from the reticuloendothelial system [22–24]. In addition to the increased mortality due to inflammation [21,56,59], anemia [8,60] and hypoalbuminemia [14,61] are also independent risk factors for increased morbidity and mortality in patients with advanced CKD.

A high prevalence of anemia in patients with CKD has been reported in the literature. Stauffer and Fan found anemia (defined as Hb levels ≤ 12 g/dL in women and ≤ 13 g/dL in men) in 53.4% of patients with CKD at stage 5 [62]. In 120 patients undergoing peritoneal dialysis, 28% had Hb levels < 11 g/dL, but the mean patient age was 58 years [63].

Surprisingly, 26.6% of our patients between 18 und 35 years of age presented severe anemia with Hb levels < 10.0 g/dL, making them the group with the highest prevalence of anemia. The Hb goal should be within 11 to 13 g/dL [9] but not > 13 g/dL. A total of 25% of our anemic patients had

not been treated with ESAs. On the other hand, 42% of the patients with Hb levels > 13 g/dL were taking ESAs and were thus being treated unnecessarily and subject to an increased risk of cardiovascular complications with no extra benefit [9–12]. The ESA treatment rate was similar in our young patients (18 to < 35 years) suffering most frequently from anemia.

Decreasing total and LDL cholesterol values accompanied by a serious decline in GFR have been reported in former studies [38]. In general population studies in Germany [64], the prevalence of hypercholesterinemia in healthy patients without CKD was 56.6% in men and 60.5% in women. Our cohort's prevalence of hypercholesterinemia (only 40.3%) was lower compared with those data. Elevated LDL cholesterol values were even more seldom in our cohort, being diagnosed in only 14%. LDL cholesterol as a risk marker for the reported elevated cardiovascular mortality in patients with CKD and dyslipidemia has come into question because of the low serum values compared with the normal population. In addition, there have been generally disappointing study results questioning the benefit of cholesterol-lowering statin therapy [44,45,65–67]. The HDL cholesterol values were within the normal range in only about 50% of our patients, with < 34% in men (normal: 35–55 mg/dL) and women (normal: 45–65 mg/dL). The previously supposed protective benefit of HDL cholesterol has been seriously questioned according to the most recent investigations [39–43,68], which postulate aU-curve pattern, offering no benefit and potentially even greater risk of cardiovascular mortality in patients with CKD and elevated HDL cholesterol. Zewinger et al [68] analyzed 3307 patients undergoing coronary angiography and examined the association between HDL cholesterol and all-cause and cardiovascular mortality. In patients with a normal eGFR (> 90 mL/min/1.73 m^2), HDL cholesterol was associated with reduced cardiovascular and all-cause mortality. Conversely, in patients with eGFR < 60 mL/min/1.73 m^2 there was no association between HDL cholesterol and reduced mortality.

At this point in time there seems to be no evidence of a protective effect of having elevated HDL cholesterol in patients with CKD; however, there are no clinical trial findings revealing a negative influence of elevated HDL cholesterol values on cardiovascular outcomes. However, taking molecular study findings of modified and toxic HDL particles in patients with CKD into account, our subgroups with elevated HDL cholesterol levels (m: 14%; w: 21%) might be carrying a greater risk because of the toxic effect of having excessive and modified HDL molecules. Prospective studies on this subgroup with clinical endpoints like cardiovascular morbidity and mortality would be desirable. Table 2 and Fig 2 illustrate that dyslipidemia is similarly distributed in younger patients. Despite similar laboratory values, the intake rate of lipid reducers was only about 20% in our patients younger than 35 years compared with about a third (34%) of the whole population. The generally restrained international recommendations on the therapy of dyslipidemia in patients with CKD [69] are the most likely reason for such reported therapy rates.

CONCLUSIONS

Even in younger patients (< 50 years) listed for renal transplantation, there is a similar risk profile regarding cardiovascular parameters compared with older CKD patients.

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