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CLINICAL STUDY

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The association between body mass index and mortality in diabetic patients with end-stage renal disease is different in hemodialysis and peritoneal dialysis

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ABSTRACT

Background and hypothesis: There are diverse results in terms of the association between body mass index (BMI) and mortality risk in patients with end-stage renal disease (ESRD). The aim was to examine if there is an association between BMI and the risk of all-cause mortality in patients with diabetes mellitus (DM) and ESRD on hemodialysis (HD) or peritoneal dialysis (PD).

Methods: Included were 3,235 patients (mean age 66 ± 14 years, 66% men) with DM on dialysis treatment (2,452 HD, 783 PD) that were followed for 3.9 ± 3.5 years. BMI was calculated as weight (kg)/[height (m)]^2 and defined as the mean BMI value during the study period. Relationships between BMI and all-cause mortality were examined by Cox-models to estimate hazard ratios (HR) and 95% confidence intervals (CI) in univariate and multivariate analyses adjusted for demographics, laboratory findings and comorbidity. BMI between 18.5 and 25 kg/m^2 was used as the reference group.

Results: During the study, 1,688 (53%) patients died (1,275 on HD, 413 on PD). In multivariate analyses, patients on HD with BMI ≤ 18.5 kg/m^2 had an increased risk of all-cause mortality (HR1.94, CI 1.47–2.54). In contrast, mortality risk was decreased in the BMI groups of 25.1–30 kg/m^2 (HR0.84, CI0.73–0.96), 30.1–35 kg/m^2 (HR0.66, CI0.55–0.78), and 35.1–40 kg/m^2 (HR0.65, CI0.49–0.85). In multivariate analyses, no associations between BMI and mortality risk were found in patients on PD.

Conclusion: An increased risk of mortality in underweight DM patients on HD was found. Overweight, class 1 and class 2 obesity were associated with better survival in HD.

Key learning points: The association between BMI and risk of mortality is different in patients with DM on maintenance HD or PD.

What was known (maximum 50 words): The association between BMI and risk of mortality in ESRD population on dialysis treatment is very divers and different study have shown different results.

This study adds (maximum 50 words): High BMI associated with better survival in patients with diabetes and HD but this finding did not observed with PD.

Potential impact (on practice or understanding, maximum 50 words): The importance to examine time-varying BMI frequently as independent covariance in patients with dialysis treatment.

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BMI; diabetes mellitus; hemodialysis; peritoneal dialysis; mortality

Introduction

In the general population, obesity is associated with an increased risk of mortality [1]. In contrast, most studies in patients on maintenance hemodialysis (HD) indicate that overweight and obesity are associated with a decreased risk of mortality [2,3]. In a study by Kalantar-Zadeh et al. HD patients with a body mass index (BMI) < 20 kg/m^2 had a significantly higher risk of all-cause mortality [4]. This paradox is called reverse epidemiology [2]. It was suggested that high-rate mortality among underweight patients on HD is mostly caused by protein–energy wasting (PEW) [2]. PEW is

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defined as loss of muscle mass and a deficiency of systemic protein, which leads to a decrease in BMI in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) [5].

In patients with peritoneal dialysis (PD), the association between BMI and mortality is complex and show diverse results. While a number of studies in PD patients found no association between BMI and mortality [6,7], reverse epidemiology and a better survival in overweight patients were the main finding of other studies [8,9].

The prevalence of diabetes mellitus (DM) increases globally [10], and DM is the leading cause of ESRD and dialysis treatment in most parts of the world [11]. Even if it is well-established that the combination of DM and obesity increases the risk of mortality in the general population, the relationship is still not clear in patients on dialysis.

The aim of this study was to examine if there is an association between BMI and the risk of all-cause mortality in patients with DM on HD or PD.

Materials and methods

Data collection

Data were collected from the Swedish Renal Registry (SRR) – a national computerized, web-based quality register for patients with CKD in Sweden. Each year, all dialysis units in Sweden report data for all patients about comorbidities and primary kidney diseases at the start of renal replacement therapy as well as data about dialysis prescriptions and treatment effects (laboratory values, weight) at cross-sectional surveys.

Patients and methods

In this study, 3,235 adult patients with DM on maintenance dialysis treatment – HD ($n = 2{,}452$) or PD ($n = 783$), were followed from January 2008 to September 2018. The mean follow-up period was 3.9 ± 3.5 years. In this study, DM included both type 1 and type 2 diabetes. BMI was calculated as weight (kg)/[height (m)]^2, and was defined as the mean BMI value during the study period. The patients with less than two months on dialysis ($n = 187$), and patients who switched from PD to HD, or vice versa, during the study period ($n = 441$) were excluded. Age was defined as baseline age, whereas the mean value during follow-up was used in the analyses of BMI, blood pressure (BP), and laboratory variables. All laboratory examinations were performed at local laboratories in hospitals and dialysis units in Sweden. All data of cardiovascular disease (CVD) and malignancies were obtained from the SRR. BMI was classified according to WHO classification for White, Hispanic, and Black individuals (Table 1) [12].

The Regional Ethical Review Board in Gothenburg in Sweden approved the study (DNR698-17, date of approval: 09-21-2017). According to the Swedish law and regulations (Patientdatalagen [SFS 2008:355]), written informed consent is not always required from patients registered in a quality registry. Verbal informed consent was obtained at the time of registration in the registry.

Table 1. The classification of BMI (kg/m^2) used in this study.

BMI ≤ 18.5	Underweight
18.5 < BMI ≤ 25	Normal weight
25 < BMI ≤ 30	Overweight
30 < BMI ≤ 35	Moderate obesity (class1)
35 < BMI ≤ 40	Severe obesity (class 2)
BMI > 40	Very severe obesity (class 3)

Statistical analyses

Clinical and biochemical characteristics are presented as the mean values ± standard deviation (SD) or as proportions (*n*, %). Initially Kaplan–Meier survival curves were used to evaluate differences in survival between BMI groups. Further, cox proportional hazards regression models were used to evaluate associations between BMI and the risk of all-cause mortality in the HD and PD populations. In the analyses, the patients were divided into six BMI groups with BMI 18.5 < BMI ≤ 25 kg/m^2 (normal weight) used as the reference group. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for the risk of all-cause mortality in the various BMI groups in comparison with the reference group. Adjustments were made for the following variables: age, sex, serum cholesterol, systolic and diastolic BP, hemoglobin, C-reactive protein (CRP), serum albumin, serum phosphate, parathyroid hormone (PTH), HbA1c, previous history of CVD and previous history of malignancy.

Additionally, to reduce the influence of unmeasured confounders we preformed propensity score matching in both HD an PD population.

A p value < 0.05 was defined as statistically significant. IBM SPSS version 25 (IBM Corp., Armonk, NY) was used for all statistical analyses.

Results

Clinical and biochemical characteristics in patients on HD

The clinical and biochemical characteristics of the 2452 patients on HD are shown in Table 2. The mean age was 66 ± 14 years and 66% were male. Since the mean BMI during the study was 27 ± 6 kg/m^2, the HD population was slightly overweight. The mean value of HbA1c was 6.5 ± 3.5% and mean serum albumin was 34 ± 5 g/L. Nearly 20% of the patients had a history of CVD and 6% had a previous malignancy.

Clinical and biochemical characteristics in patients with PD

The clinical and biochemical characteristics of the 783 patients on PD are described in Table 2. The mean age was 65 ± 14 years, and 67% were male, and mean BMI was 26 ± 5 kg/m^2. The mean value of HbA1c was 6.8 ± 3.5%, which

Table 2. Clinical and biochemical characteristics of diabetic patients receiving HD or PD treatment.

	HD patients $n=2,452$	PD Patients $n=783$
Age (years)	66 ± 14	65 ± 14
Men (%)	66%	67%
HbA1c (unit as %)	6.5 ± 3.5	6.8 ± 3.5
Systolic blood pressure (mmHg)	143 ± 23	137 ± 20
Diastolic blood pressure (mmHg)	72 ± 14	76 ± 11
Mean arterial pressure (MAP)	96 ± 14	96 ± 12
BMI (kg/m^2)	27 ± 6	26 ± 5
Hemoglobin (g/L)	114 ± 11	118 ± 12
CRP (mg/mL)	17 ± 32	12 ± 19
Serum albumin (g/L)	34 ± 5	31 ± 5
Serum phosphate (mg/dL)	4.9 ± 1.4	4.8 ± 1.0
PTH (pg/mL)	311 ± 292	268 ± 190
Total cholesterol (mmol/L)	4.1 ± 1.5	4.6 ± 2.0
Previous history of CVD (%)	20%	24%
Previous history of malignancy (%)	6%	4%
Hypertension treatment (%)	80%	90%

Data are presented as means ± SD or frequencies (%= column %). Age was defined as baseline age, whereas BMI, blood pressure, and biochemical variables were defined as the mean value during the study period.
n: number; CRP: C-reactive protein; CVD: cardiovascular disease

Table 3. Univariate and multivariate analyses of the association between BMI and the risk of all-cause mortality in the HD population.

Mean BMI (kg/m^2)	Mortality n (%)	Univariate analyses HR (95% CI)	Multivariate analyses[a] HR (95% CI)
BMI ≤ 18.5 $n=101$	64 (63%)	1.57* (1.21 – 2.04)	1.94* (1.47 – 2.54)
18.5 < BMI ≤ 25 $n=931$	516 (55%)	1 (reference group)	1 (reference group)
25 < BMI ≤ 30 $n=756$	405 (54%)	0.88 (0.77 – 1.01)	0.84* (0.73 – 0.96)
30 < BMI ≤ 35 $n=428$	191 (45%)	0.66* (0.56 – 0.78)	0.66* (0.55 – 0.78)
35 < BMI ≤ 40 $n=154$	63 (41%)	0.60* (0.46 – 0.78)	0.65* (0.49 – 0.85)
BMI > 40 $n=82$	36 (44%)	0.86 (0.61 – 1.20)	0.88 (0.62 – 1.26)

[a]In the multivariate model, hazard ratios (HR) and 95% confidence intervals (CI) were adjusted for the following covariates: age, gender, MAP, CRP, serum albumin, hemoglobin, serum phosphate, PTH, HbA1c, BP-treatment, history of CVD, and history of malignancy. *$p<0.01$.

was slightly higher than that in HD patients, but the mean serum albumin value of 31 ± 5 g/L was lower compared to HD patients. The history of CVD and malignancy was 24% and 4%, respectively.

Association between BMI and all-cause mortality in HD patients

During the study, 1,275 (52%) of the patients with HD died. The highest mortality rate was observed in the 101 patients with BMI ≤ 18.5 kg/m^2, of whom 64 patients (63%) died. In contrast, the mortality rate was lower in patients with BMI > 25 kg/m^2 ($n=1420$). Of these patients, 695 (49%) died.

In the multivariate analysis (Table 3), HD patients with BMI ≤ 18.5 kg/m^2 (HR 1.94, CI 1.47–2.54) had an increased risk of all-cause mortality compared to the reference group (18.5 < BMI ≤ 25 kg/m^2). In contrast, patients with BMI 25 < BMI ≤ 30 kg/m^2 (HR 0.84, CI 0.73–0.96), 30 < BMI ≤ 35 kg/m^2 (HR 0.66, CI 0.55–0.78), and 35 < BMI ≤ 40 kg/m^2 (HR 0.65, CI 0.49–0.85) had a better survival compared to the reference group.

In our study, 82 patients had class 3 obesity (BMI > 40 kg/m^2), of whom 36 (44%) died during the study. In the multivariate model, BMI > 40 kg/m^2 was not significantly associated with mortality. As shown in Figure 1, the group with BMI ≤ 18.5 kg/m^2 had the highest mortality rate, whereas patients with BMI > 25 kg/m^2 had a better survival (both in the unadjusted and adjusted models).

The association between BMI and the risk of all-cause mortality in the HD population was adjusted by propensity score matching and the main results were confirmed (Supplementary Table S1).

Finally, the cumulative survival was shortest in the subgroup with BMI ≤ 18.5 kg/m^2 as illustrated by Kaplan–Meier survival curves (Figure 2).

Association between BMI and all-cause mortality in PD patients

Among the 783 patients on PD, 413 (53%) died during the study. Mortality was close to 50% in all subgroups except for the group with BMI > 40 kg/m^2. In contrast to the HD population, BMI > 25 kg/m^2 was not significantly associated with decreased risk of mortality in the multivariate analysis. Among the 15 patients with BMI ≤ 18.5 kg/m^2, 8 (53%) patients died. In the multivariate analysis, BMI ≤ 18.5 kg/m^2 was not associated with a higher risk of mortality. Only seven patients had BMI > 40 kg/m^2, and all these patients died during the study period. In the unadjusted model, BMI > 40 kg/m^2 was significantly associated with an increased risk of mortality (HR 2.40, CI 2.12–5.10). However, in the adjusted model, the risk of mortality was no longer significant (Table 4, Figure 3).

The adjustment of association between BMI and the risk of all-cause mortality in the PD population by propensity score matching did not change the result and BMI was not associated with risk of mortality (Supplementary Table S2).

Survival analysis by Kaplan Meier curves showed mortality risk was similar between groups except in the group with BMI > 40 kg/m^2 (Figure 4). However, as mentioned earlier in the adjusted model, BMI > 40 kg/m^2 was not further significantly associated with higher risk of mortality.

Discussion

The aim of this study was to examine the association between BMI and the risk of mortality in patients with DM and maintenance HD or PD. We included 2,452 patients on HD and 783 on PD treatment. The main finding was that the

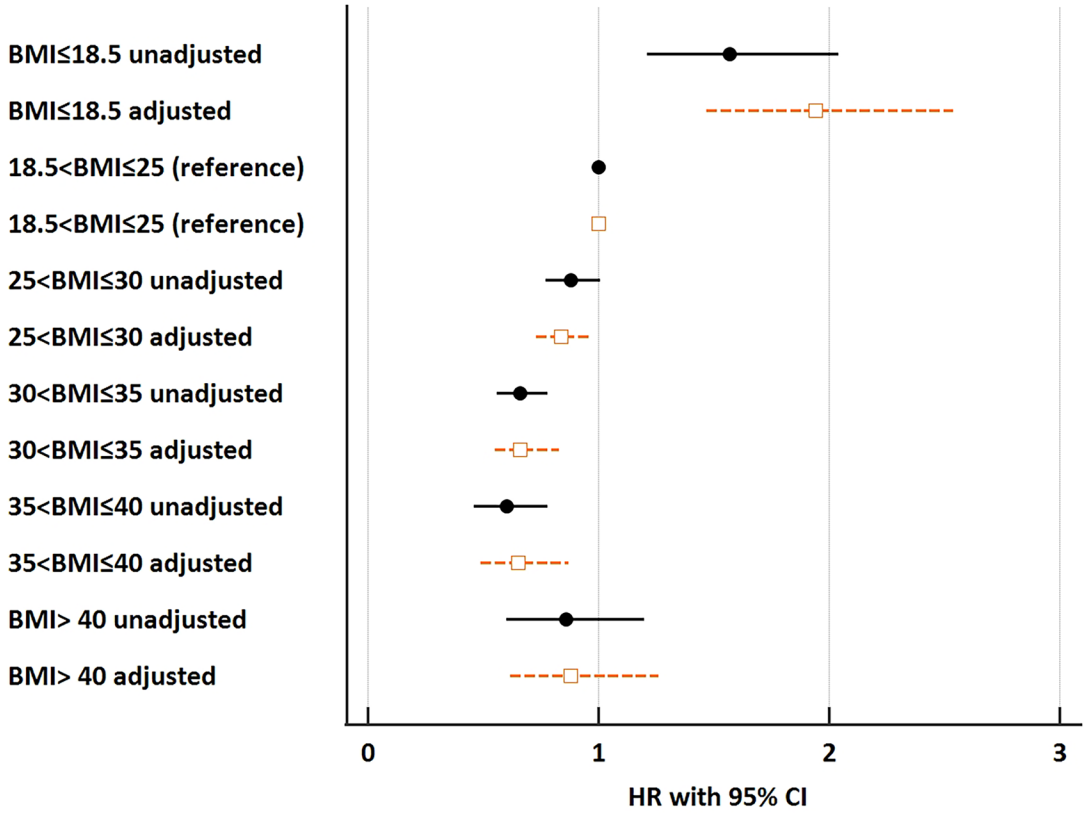

Figure 1. Hazard ratio (HR) for all-cause mortality based on univariate (unadjusted HR) and multivariate Cox-regression (adjusted HR) among HD patients.

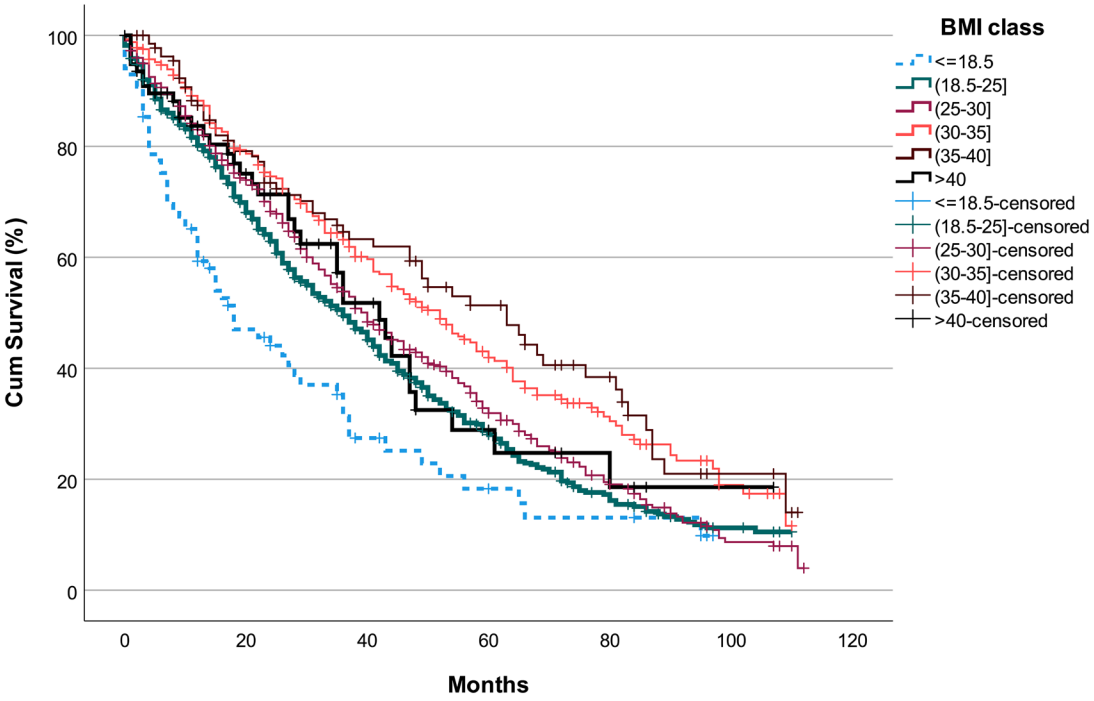

Figure 2. Survival curves (Kaplan–Meier curves) among HD patients according to BMI class.

association between BMI according to the WHO classification [12] and mortality was different in HD and PD patients with DM. In HD patients, underweight was associated with an increased risk of mortality, whereas overweight patients with class 1 and 2 obesity in contrast had a better survival. This finding was not observed in the PD population as the results

of our study indicated a non-significant relationship between BMI and mortality risk in patients with DM on PD.

The association between BMI and the risk of mortality in patients on dialysis has been mostly evaluated in HD. The results of earlier studies have mostly confirmed that high BMI at baseline is associated with better survival [3]. This phenomenon is known as the obesity paradox or reverse epidemiology, which has been observed in other chronic diseases like severe heart failure and chronic obstructive pulmonary disease [13]. However, the protective effect of high BMI and adiposity on survival in a dialysis population is not completely understood. Higher dietary intake could lead to improved nutritional status and a more stable hemodynamic situation in obese patients, which in turn might be associated with better survival during dialysis [14]. Additionally, it has been suggested that obesity in moderate and severe renal dysfunction could modify the neurohormonal stress response and increase cardiac function by higher levels of TNF-α receptors, which could influence the impact of TNF-α on cardiac damage [15]. Finally, it is possible that the increased mortality risk in dialysis patients is derived from malnutrition, which could be more important for outcome in the short-term perspective than the risk associated with conventional risk factors like obesity [3].

In this study, BMI > 40 kg/m^2 (class 3 obesity) was not associated with better survival or increased mortality risk with HD. In a previous study by Vashista et al. BMI > 35 kg/m^2 was most prominently associated with better survival in patients aged >75 years [16]. Doshi et al. showed that BMI > 40 kg/m^2 at baseline was associated with better survival over time, and this was also the case even when using a marginal structural model (MSM) – a technique that accounts for time-varying confounders [17]. Furthermore, in a study by Johansen et al. even extremely high BMI levels were associated with better survival in most patients beginning dialysis, which led the authors to suggest high BMI to be advantageous if patients starting dialysis [18]. However, we only included patients with diabetes, and our results therefore

Table 4. Univariate and multivariate analyses of the association between BMI and the risk of all-cause mortality in PD population.

Mean BMI (kg/m^2)	Mortality n (%)	Univariate analyses HR (95% CI)	Multivariate analyses[a] HR (95% CI)
BMI ≤ 18.5 $n=15$	8 (53%)	1.43 (0.70 – 2.92)	1.31 (0.63 – 2.68)
18.5 < BMI ≤ 25 $n=301$	161 (52%)	1 (reference group)	1 (reference group)
25 < BMI ≤ 30 $n=307$	171 (52%)	0.93 (0.75 – 1.16)	0.86 (0.67 – 1.09)
30 < BMI ≤ 35 $n=99$	54 (55%)	0.93 (0.69 – 1.26)	0.94 (0.67 – 1.31)
35 < BMI ≤ 40 $n=24$	12 (50%)	0.85 (0.47 – 1.54)	0.93 (0.48 – 1.77)
BMI > 40 $n=7$	7 (100%)	2.40* (1.12 – 5.10)	1.65 (0.74 – 3.70)

[a]In the multivariate model, hazard ratios (HR) and 95% confidence intervals (CI) were adjusted for the following covariates: age, gender, MAP, CRP, serum albumin, hemoglobin, serum phosphate, PTH, HbA1c, BP-treatment, history of CVD, and history of malignancy. *$p<0.05$.

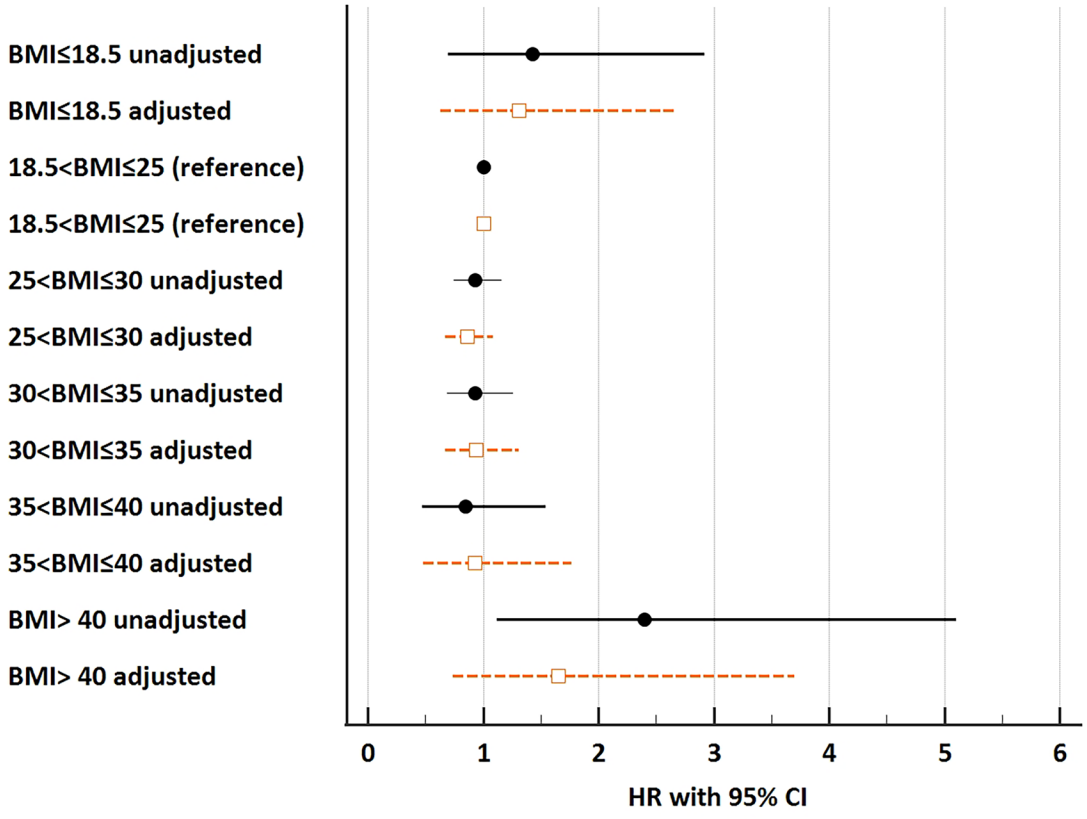

Figure 3. Hazard ratio (HR) for all-cause mortality based on univariate (unadjusted HR) and multivariate Cox-regression (adjusted HR) among PD patients.

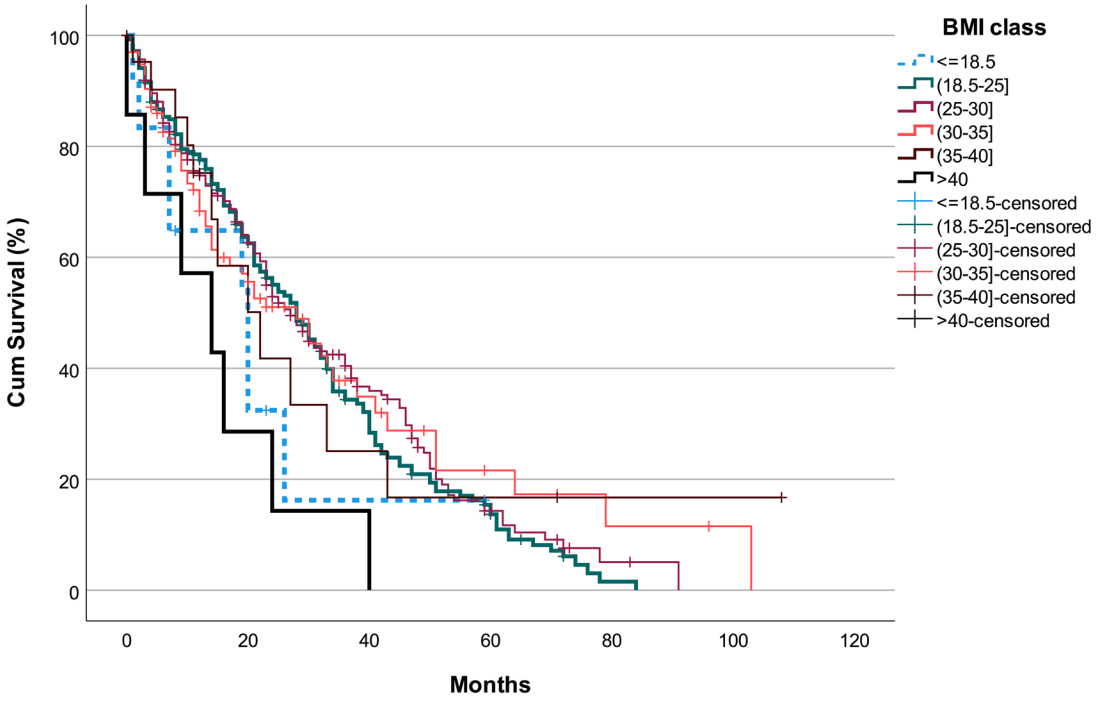

Figure 4. Survival curves (Kaplan–Meier curves) among PD patients according to BMI-class.

probably suggest that BMI > 40 kg/m^2 is not associated with better survival in diabetic patients on maintenance HD.

Most studies have revealed that in patients on HD, at least in a short-term perspective, low BMI was associated with increased risk of mortality [19]. This increased risk of mortality with low BMI could mostly be the consequence of PEW [5]. The causes of PEW are multifactorial and include poor appetite with decreased protein intake, the presence of inflammation, and a high prevalence of frailty in ESRD patients on dialysis with low BMI [20]. Low muscle mass, which is common in dialysis patients, is associated with an increased risk of mortality [21]. It is also common that dialysis patients have low levels of serum albumin, prealbumin, and transferrin, which are established biomarkers of PEW [3].

The association between BMI measured at baseline and mortality risk might be different when BMI is measured during follow-up. Lower baseline BMI was associated with an increased risk of 1-year mortality, but during longer dialysis duration, low BMI was not associated with an increased risk of mortality [22]. Furthermore, patients with lower BMI, who had limited comorbidity and better physical functioning, had better survival even in the beginning of dialysis [23]. In contrast, HD patients with chronic disease and low BMI have a considerably higher risk of mortality [24]. In this study, we used the mean value of BMI during the study that had a mean follow-up of 3.9 ± 3.5 years. However, even so, low BMI was associated with nearly a two-times higher risk of mortality compared to normal weight patients with HD. This finding was still significant in the multivariate analyses that included adjustment for previous history of CVD or malignancy.

The results of studies on the association between BMI and mortality risk in patients receiving PD are quite diverse. Thus, the reverse epidemiology observed in HD is more controversial in PD. High glucose load from dialysis solutions and loss of proteins have an influence BMI in PD [25], and as a result, the association between BMI and mortality is more complicated. Additionally, obesity is, at least to some extent, a contraindication to start PD due to the higher risk of abdominal herniation, catheter failure, and peritonitis. In some studies, overweight and even obesity was associated with better survival in PD [26,27]. Furthermore, a study by Prasad et al. showed poor survival outcome in underweight PD patients with diabetes [28]. A U-shaped relationship between BMI and mortality has also been observed in PD patients [29]. However, in line with our results, marginal or non-significant relationships between BMI and PD have been the main findings of several studies [6,7]. Interestingly, in the study by Hwang et al. BMI > 25.7 kg/m^2 at baseline was associated with a higher risk of mortality in non-diabetic patients receiving PD, whereas this association was non-significant in diabetic patients undergoing PD [30].

In this study, all seven patients with PD and BMI > 40 kg/m^2 died during the study period. In the unadjusted analysis, BMI > 40kg/m^2 was associated with a more than 2-fold increase in the risk of mortality, but when we added age in the adjusted model, the association lost statistical significance. Further sub-analyses showed that the mean age of the patients with BMI > 40kg/m^2 was considerably higher than that seen in our entire population (71 *vs.* 65 years). This finding reveals that in severely obese patients with ESRD, mostly elderly patients begin or proceed with PD.

To assess the association between BMI and mortality, most studies have used a single value of BMI at baseline [30,31]. However, time-varying BMI values or changes in BMI

over time have been evaluated in only a few studies [32,33]. In a study by Ladhani et al. each 1 kg/m^2 increase in BMI was associated with 3–4% decreased risk of cardiovascular mortality in maintenance HD, whereas there was no such association in patients receiving PD [34]. Furthermore, in a study by Xiong et al. a decline of more than 0.80% BMI during the first year of PD therapy increased the risk of mortality [35]. Finally, the results of a study by Fernandes et al. indicated that the risk of mortality was significantly increased by body weight loss >3.1% during the first year of PD treatment [7].

Changes in body composition are also associated with increased risk of mortality in PD. In a study by Kim et al. longitudinal changes in lean tissue index (LTI) and fat tissue index (FTI) were more markedly associated with the risk of all-cause mortality in PD patients than were single LTI and FTI values [36].

The pattern of weight change, at least in the beginning of dialysis, is different in HD and PD patients. In the early months of HD, it was observed that most patients have rapid weight losses [4,37,38]. Furthermore, during the first 12 months of HD treatment, greater weight loss was associated with higher mortality risk while weight gain was associated with increased survival [2,38]. In contrast, most PD patients gain weight after the start of dialysis [39]. However, weight gain during PD is not associated with better survival and is mostly related to fluid overload and changes in body composition with increased fat mass and reduced lean mass [40]. Finally, it has been shown that visceral fat mass increases predominantly when initiating PD, which is not observed in HD, and is mostly the result of glucose-containing PD solutions [41].

In this study, the mean value of BMI was 27 kg/m^2 in the HD group compared to 26 kg/m^2 in the PD group. Therefore, our PD population was slightly thinner than the HD population. Furthermore, we performed an additional analysis of baseline BMI that showed that HD patients had a baseline or first BMI value of 28 kg/m^2 compared to 27 kg/m^2 in PD patients. These results likely suggest that in patients on maintenance dialysis with a mean follow-up time of 3.9 ± 3.5 years as in this study, HD is associated with weight loss, whereas in contrast, the weight gain in the early phase of PD is later reversed. However, this finding needs to be validated in future studies with longer follow-up times.

This study has several strengths. First, the association between BMI and the risk of mortality may be more accurate when using the mean value of BMI during the study period instead of single BMI values. Our data were extracted from the SRR that includes most dialysis populations receiving routine treatment according to the national guidelines in Sweden. This likely resulted in increased statistical power and generalizability of our findings. Relevant confounders were added in adjusted models, which likely improved the external validity of our study.

There are some limitations of our study. This was an observational study, and therefore it cannot be determined if the observed associations are causal. It is important to note that BMI is not entirely accurate for screening of body fatness and obesity. First, a high BMI can be related to both excess fat stores and high muscle mass [42]. The term sarcopenic obesity is defined as a combination of loss of muscle mass and obesity [43]. Sarcopenic obesity is common among a dialysis population and is associated with increased risk of mortality [44]. Second, central obesity, which is related to dyslipidaemia, insulin resistance and increased risk of cardiovascular events, cannot entirely be identified by BMI measurements [45]. In contrast, waist-to-hip ratio (WHR) and waist circumference are more accurate to estimate central obesity [46]. Finally, the influence of fluid statues on BMI may be significant. In dialysis, volume overload might lead to increased BMI, and weight loss due to fluid removal to decreased BMI. We did not have information of change in Kt/V as a measure of dialysis adequacy and residual renal function during the study. There are data on CVD and malignancy, but data on other diseases and comorbidities were not available. Overweight and obesity are practically contraindicated for starting PD, which could increase the possibility of selection bias. Unknown confounders like nutritional interventions, quality of life and daily exercise need to be assessed in future randomized clinical trials. Lastly, we did not include ethnicity as an independent variable. The divergent results in terms of the association between BMI and mortality during dialysis may partially be related to the fact that BMI is classified according to racial origin, which may be supported by the slightly different results found in Asian and Western populations [8,47]. Therefore, further studies are warranted to investigate whether the impact of ethnicity on BMI is greater in PD than in HD.

In conclusion, in patients with DM on maintenance dialysis, the association between BMI and the risk of all-cause mortality is different in patients receiving HD and PD. Underweight dialysis patients with HD had a higher risk of mortality, whereas overweight and class 1 and 2 obesity were related to better survival. Finally, our findings suggest that the association between BMI and mortality is non-significant in PD patients with DM.

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Authors' contributions

HA, SN and BP researched literature and conceived the study. SN collected data. SN, HA, and BP analyzed data. HA wrote the first draft of the manuscript. SN, BP, AW, HR, and JS writing review and editing. All the authors read and approved the manuscript.

Disclosure statement

The authors declare no conflict of interest related to this study.

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Data availability statement

The raw data used in this study are restricted to protect participant privacy, as required by data protection acts in Sweden. Data can be made accessible by request for researchers after permission from the Swedish Ethics Review Authority. Data cannot be shared publicly because of data policy regulations at Skaraborg Hospital. Data are available from the Skaraborg Hospital Institutional Data Access for researchers who meet the criteria for access to confidential data.

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