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Original Article

ORIGINAL ARTICLE

Association of obesity with 3-month mortality in kidney failure patients with COVID-19

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ABSTRACT

Background. In the general population with coronavirus disease 2019 (COVID-19), obesity is associated with an increased risk of mortality. Given the typically observed obesity paradox among patients on kidney function replacement therapy (KFRT), especially dialysis patients, we examined the association of obesity with mortality among dialysis patients or living with a kidney transplant with COVID-19.

Methods. Data from the European Renal Association COVID-19 Database (ERACODA) were used. KFRT patients diagnosed with COVID-19 between 1 February 2020 and 31 January 2021 were included. The association of Quetelet's body mass index (BMI) (kg/m^2), divided into: <18.5 (lean), 18.5–24.9 (normal weight), 25–29.9 (overweight), 30–34.9 (obese I) and ≥35 (obese II/III), with 3-month mortality was investigated using Cox proportional-hazards regression analyses.

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Results. In 3160 patients on KFRT (mean age: 65 years, male: 61%), 99 patients were lean, 1151 normal weight (reference), 1160 overweight, 525 obese I and 225 obese II/III. During follow-up of 3 months, 28, 20, 21, 23 and 27% of patients died in these categories, respectively. In the fully adjusted model, the hazard ratios (HRs) for 3-month mortality were 1.65 [95% confidence interval (CI): 1.10, 2.47], 1 (ref.), 1.07 (95% CI: 0.89, 1.28), 1.17 (95% CI: 0.93, 1.46) and 1.71 (95% CI: 1.27, 2.30), respectively. Results were similar among dialysis patients ($N = 2343$) and among those living with a kidney transplant ($N = 817$) ($P_{interaction} = 0.99$), but differed by sex ($P_{interaction} = 0.019$). In males, the HRs for the association of aforementioned BMI categories with 3-month mortality were 2.07 (95% CI: 1.22, 3.52), 1 (ref.), 0.97 (95% CI: 0.78. 1.21), 0.99 (95% CI: 0.74, 1.33) and 1.22 (95% CI: 0.78, 1.91), respectively, and in females corresponding HRs were 1.34 (95% CI: 0.70, 2.57), 1 (ref.), 1.31 (95% CI: 0.94, 1.85), 1.54 (95% CI: 1.05, 2.26) and 2.49 (95% CI: 1.62, 3.84), respectively.
Conclusion. In KFRT patients with COVID-19, on dialysis or a kidney transplant, obesity is associated with an increased risk of mortality at 3 months. This is in contrast to the obesity paradox generally observed in dialysis patients. Additional studies are required to corroborate the sex difference in the association of obesity with mortality.

Keywords: COVID-19, kidney failure, mortality, obesity paradox, reverse epidemiology

INTRODUCTION

Obesity is a well-established risk factor for mortality in the general population, such that Quetelet's body mass index (BMI) over 30 kg/m² is associated with a sharp increase in the risk of mortality [1]. However, the relationship between obesity and mortality has not been observed consistently across all population subgroups. Among patients on kidney function replacement therapy (KFRT), especially dialysis patients, obesity is reported to be associated with better survival, a phenomenon known as the 'obesity paradox' [2].

Early in the coronavirus disease 2019 (COVID-19) pandemic, obesity was identified as a key risk factor for severe complications including death among the general population with COVID-19 [3]. To our knowledge, there has not been a comprehensive study to investigate the association of obesity with the risk of mortality among patients on KFRT with COVID-19, and consequently, it is unclear whether the 'obesity paradox' holds true also among patients on KFRT with COVID-19 infection [4].

Given the high COVID-19 case-fatality rate among patients on KFRT [5] and thereby the need to understand risk factors for severe COVID-19, we aimed to investigate the relationship of obesity with mortality and other major disease-related outcomes among patients on KFRT with COVID-19 using data from the European Renal Association COVID-19 Database (ERACODA), the largest European database of patients on KFRT with COVID-19, which prospectively collected detailed information on patient and disease characteristics.

MATERIALS AND METHODS

Study design and participants

The ERACODA database was established in March 2020 and currently involves the cooperation of approximately 220 physicians representing over 140 centers in 33 countries, mostly in Europe. Data were collected on adult (≥18 years) patients with kidney failure, either on dialysis or living with a functioning kidney allograft, who were diagnosed with COVID-19 based on a positive result on a real-time polymerase chain reaction assay or rapid antigen test of nasal and/or pharyngeal swab specimens and/or compatible findings on CT scan or chest X-ray. Data were voluntarily reported from outpatients and hospitalized patients by physicians responsible for their care [6].

The ERACODA database is hosted at the University Medical Center Groningen, the Netherlands. Data are recorded using REDCap software (Research Electronic Data Capture, Vanderbilt University Medical Center, Nashville, TN, USA) for data collection [7]. Patient information is stored pseudonymized. The study was approved by the Institutional Review Board of the University Medical Center Groningen, the Netherlands. Because of the observational, non-interventional nature, the institutional review board deemed the collection and analysis of data exempt from ethics review regarding the Medical Research Involving Human Subjects Act (WMO).

Data collection

Detailed information was collected on the patient (age, sex, ethnicity, height, weight, frailty, comorbidities, hospitalization and medication use) and COVID-19-related characteristics (symptoms, vital signs and laboratory test results) at presentation. Frailty was assessed using the Clinical Frailty Score developed by Rockwood *et al.* [8]. BMI was calculated by dividing body weight by the square of height, expressed in kg/m², and used to assess obesity categorized as per World Health Organization (WHO) classification i.e. <18.5 (underweight), 18.5–24.9 (normal), 25–29.9 (overweight), 30–34.9 (obesity Class I) and ≥35 kg/m² (obesity Class II/III) [9]. Obesity classes II and III were merged to allow sufficient patients in this category.

The primary outcome of this study was vital status at 3 months after COVID-19 diagnosis and the secondary outcomes were hospitalization, Intensive Care Unit (ICU) admission and, in-hospital mortality. All patients who presented between 1 February 2020 and 31 January 2021 and for whom information on BMI, type of KFRT, date of presentation and 3-month vital status was available, were included in the analysis (Supplementary data, Figure S1).

Statistical analysis

Baseline characteristics are presented for the total population, and by categories of BMI. Characteristics were compared between groups using ANOVA for continuous variables (Kruskal–Wallis test for non-normally distributed data) and Pearson chi-squared statistics for categorical variables.

For the association of BMI (18.5–24.9 kg/m² as reference) with primary and secondary outcomes, hazard ratios (HRs) with corresponding 95% confidence intervals (CIs), were estimated for the total population and dialysis patients and those living with kidney transplants separately using Cox proportional-hazards regression analyses. To account for potential confounders, multiple models were constructed in a stepwise manner. Model 1

Table 1. Baseline demographic and clinical characteristics of patients on kidney function replacement therapy with COVID-19 by Quetelet's body mass index (BMI) categories

Variable	Total (N = 3160)	BMI categories					P-value
		Underweight <18.5 (N = 99)	Normal 18.5–24.9 (N = 1151)	Overweight 25–29.9 (N = 1160)	Obesity I 30–34.9 (N = 525)	Obesity II/III ≥35 (N = 225)	
Patient characteristics							
Male sex, %	61.1	47.5	61.2	66.9	58.1	44.0	<0.001
Age, year	64.8	60.7	64.8	65.4	65.7	62.3	0.002
BMI, kg/m^2	26.8	17.2	22.4	27.2	32.1	39.2	<0.001
Race							0.08
White or Caucasian, %	84.6	77.8	85.5	83.3	85.0	88.3	
Non-White, %	15.4	22.2	14.5	16.7	15.0	11.7	
Tobacco use							0.01
Current, %	5.8	8.1	7.5	4.4	4.6	5.8	
Prior, %	20.9	15.2	19.4	23.5	20.8	18.7	
Never, %	41.6	42.4	42.5	40.2	44.4	37.8	
Unknown, %	31.7	34.3	30.7	31.9	30.3	37.8	
Clinical frailty scale, AU	3.6	4.2	3.6	3.5	3.7	4.1	<0.001
Reason for screening[a]							0.04
Symptoms only, %	66.9	61.4	64.3	66.2	70.7	77.4	
Symptoms & COVID + Contact, %	15.2	17.1	14.5	16.4	15.4	11,3	
COVID + Contact only, %	9.6	8.6	11.8	9.0	8.1	5.1	
Routine, %	8.3	12.9	9.4	8.4	5.9	6.2	
Comorbidities							
Hypertension, %	83.6	73.7	80.5	85.7	87.6	84.0	<0.001
Diabetes mellitus, %	40.7	19.2	30.2	42.4	56.2	59.1	<0.001
Coronary artery disease, %	31.4	25.3	32.1	29.8	33.7	32.9	0.30
Heart failure, %	20.9	17.2	19.8	20.7	22.7	24.4	0.36
Chronic lung disease, %	11.8	15.2	10.7	11.6	12.4	16.0	0.16
Active malignancy, %	5.3	4.0	6.5	5.5	3.2	3.1	0.03
Auto-immune disease, %	4.2	9.1	4.5	3.9	3.0	4.9	0.08
Primary kidney disease							
Primary glomerulonephritis, %	14.5	12.1	16.7	15.7	9.5	9.8	<0.001
Pyelonephritis, %	2.0	0.0	2.6	2.0	1.0	1.8	0.12
Interstitial nephritis, %	3.0	6.1	2.8	2.6	3.4	3.6	0.33
Hereditary kidney disease, %	8.6	5.1	10.8	8.4	6.5	4.9	0.003
Congenital diseases, %	2.2	4.0	3.1	1.4	2.1	1.8	0.06
Vascular diseases, %	15.9	17.2	16.5	15.8	16.8	10.3	0.19
Sec. glomerular disease, %	7.9	12.1	6.9	7.8	8.6	9.8	0.24
Diabetic kidney disease, %	20.4	7.1	16.1	20.6	27.7	29.9	<0.001
Other, %	16.2	22.2	14.6	15.8	17.6	20.5	0.07
Unknown, %	9.4	14.1	9.9	10.0	6.9	7.6	0.09
Kidney replacement type							0.07
Dialysis, %	74.1	82.8	75.9	72.2	72.8	74.2	
Transplant, %	25.8	17.2	24.1	27.8	27.2	25.8	
Time since transplantation[b]							0.01
<1 year, %	10.3	11.8	6.5	9.9	18.9	8.6	
1–5 years, %	37.6	29.4	36.1	40.4	37.1	32.8	
>5 years, %	51.6	58.8	57.0	49.1	44.1	56.9	
Medication use							
RAAS inhibition use, %	26.2	23.2	24.0	27.3	29.3	25.8	0.05
Immunosuppressants use[b]							0.55
Triple therapy, %	62.1	52.9	59.2	63.7	61.5	70.7	
Dual therapy, %	35.0	41.2	38.6	33.5	32.9	29.3	
Mono therapy, %	2.1	5.9	1.4	2.5	2.8	0	
Disease-related characteristics							
Presenting symptoms							
Sore throat, %	13.5	7.2	13.2	13.8	16.3	9.6	0.002
Cough, %	52.4	42.5	50.0	51.1	60.4	56.9	0.001
Shortness of breath, %	35.1	34.2	33.9	33.1	37.8	45.8	0.009
Fever, %	58.7	51.4	56.6	60.4	61.0	58.3	0.23
Headache, %	12.4	12.0	12.2	12.7	12.2	13.3	0.37

Table 1. Continued

Variable	Total (*N* = 3160)	BMI categories: Underweight < 18.5 (*N* = 99)	Normal 18.5–24.9 (*N* = 1151)	Overweight 25–29.9 (*N* = 1160)	Obesity I 30–34.9 (*N* = 525)	Obesity II/III ≥35 (*N* = 225)	P-value
Nausea or vomiting, %	11.8	12.0	12.4	10.4	13.0	12.7	0.26
Diarrhea, %	15.8	12.0	15.9	16.0	15.4	16.8	0.72
Myalgia or arthralgia, %	23.0	16.9	23.0	22.7	23.4	26.9	0.03
Vital signs							
Temperature, °C	37.4	37.3	37.4	37.5	37.4	37.6	0.18
Respiration rate/min	19.1	19.3	18.6	19.1	19.9	20.2	<0.001
O2 saturation room air, %	93.9	93.2	94.3	93.9	93.8	92.9	0.08
Systolic BP, mmHg	135.4	128.7	135.4	134.7	137.8	135.9	0.08
Diastolic BP, mmHg	74.9	76.6	74.5	75.2	75.2	73.2	0.48
Pulse rate, BPM	82.7	86.2	82.0	83.1	82.8	83.6	0.27
Laboratory test results							
eGFR	42.8	37.8	45.6	43.3	38.4	40.1	0.61
Lymphocytes, ×1000/μL	0.8 (0.5, 1.4)	0.8 (0.5, 1.3)	0.8 (0.6, 1.3)	0.9 (0.6, 1.3)	0.9 (0.6, 1.4)	0.9 (0.6, 1.5)	0.62
CRP, mg/L	28 (7, 82)	30 (6, 74)	23 (6, 70)	28 (7, 84)	33 (10, 88)	44 (10, 107)	<0.001

Continuous variables are reported as mean ± SD or median (IQR). Groups were compared using one way ANOVA, Kruskal–Wallis test or chi-squared test as appropriate. Obesity is defined as BMI >30 kg/m^2.

ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; BMI, body mass index; RAAS, renin-angiotensin-aldosterone system; CNI, calcineurin inhibitor; °C, degree Celsius; CRP, C-reactive protein; BP, blood pressure; O_2, oxygen; eGFR, estimated glomerular filtration rate.

[a]664 patients missing information of identification method.

[b]Among kidney transplant recipients (*n* = 817).

was unadjusted. In Model 2 we adjusted for age (continuous) and sex (male/female) and in Model 3 additionally for type of KFRT (except when analyzing dialysis patients and those living with kidney transplants separately). Model 4 was additionally adjusted for factors known to be associated with COVID-19 outcomes, i.e. smoking (never, current, former), hypertension (no/yes), diabetes (no/yes), coronary artery disease (no/yes), heart failure (no/yes) and chronic lung disease (no/yes). Finally, in Model 5, we further adjusted for clinical frailty score (continuous). Heterogeneity in the association of BMI and mortality in dialysis patients and those living with kidney transplants was investigated by testing the interaction between type of KFRT (dialysis/kidney transplant) and BMI in a fully adjusted model. The proportional-hazards assumption was investigated by comparing the fully adjusted model with and without the interaction of log(time) with individual covariates. Kaplan–Meier curves were plotted to show cumulative 3-month survival by BMI categories.

Several additional analyses were performed to assess the robustness of our findings. First, the association between BMI and mortality was investigated across key subgroups including age (<65/≥65 years), sex (female/male), clinical frailty score (<4/≥4), the reason for COVID-19 screening (symptoms-based screening/positive COVID-19 contact or routine screening), hypertension (no/yes) and diabetes mellitus (no/yes). Heterogeneity of associations between aforementioned subgroups was investigated by testing the interaction between a subgroup and BMI in Model 5. Second, to allow modeling of any nonlinear association between BMI and mortality, we explored the association between BMI (continuous) and 3-month mortality using restricted cubic splines. We prespecified the use of three knots to ensure enough flexibility to the model while also not making the model oversensitive to small fluctuations. Third, to investigate the association of BMI with mortality during the earlier phase of the disease, the association was investigated for 28-day mortality instead of 3-month mortality. Finally, to account for missing values for BMI, we imputed missing values using multiple imputations by chained equations and repeated our analyses. In total, 10 imputed datasets were created with 100 iterations. Estimated coefficients and corresponding standard errors across imputed datasets were pooled as per Rubin's Rules [10].

All analyses were performed using Stata version 14.0 (College Station, TX, USA). A 2-sided value of <0.05 indicated statistical significance.

RESULTS

Baseline characteristics

A total of 3160 patients were analyzed, of which 3% were underweight, 36% normal weight, 37% overweight, 17% obesity class I and 7% obesity class II/III (Table 1). When compared with normal weight, the higher obesity categories were characterized by lower age, more women and higher frailty. Hypertension and diabetes were more prevalent in the obesity categories compared with the normal weight category. Also, the prevalence of cough, shortness of breath and myalgia/arthralgia was higher in the obesity categories compared with the normal weight category, as was the level of C-reactive protein (CRP). Dialysis patients on average were older and had a higher comorbidity burden than those living with a kidney transplant. However, the mean BMI, the prevalence of obesity and the trends in the distribution of patient demographics, comorbidities and disease characteristics across BMI categories in dialysis patients and transplant recipients were similar to trends in the total population (Supplementary data, Tables S1 and S2).

Association of BMI with 3-month mortality

The percentage of patients who experienced 3-month mortality was 28.3, 20.2, 21.0, 23.0 and 26.7% in the underweight, normal weight, overweight, obesity class I and obesity class II/III

categories, respectively. The 3-month cumulative survival was lower in underweight and obesity class II/III categories compared with other BMI categories, with similar results among dialysis patients and transplant recipients (Figure 1). Compared with the normal weight category, the HR for the association of 3-month mortality in the fully adjusted model was 1.65 (95% CI: 1.10, 2.47) in underweight, 1.07 (95% CI: 0.89, 1.28) in overweight, 1.17 (95% CI: 0.93, 1.46) in obesity class I and 1.71 (95% CI: 1.27, 2.30) in obesity class II/III categories (Table 2). These HRs were essentially similar in dialysis patients and those living with a kidney transplant (Table 2, Figure 2). There was no interaction between the type of KFRT (dialysis/kidney transplant) and BMI categories ($P_{interaction} = 0.99$ in the fully adjusted model). The models that were used demonstrated no violation of the proportional-hazards assumption (*P* for the difference in fully adjusted model with and without time-varying covariates = .13 in the total population, .21 in dialysis patients and .62 in transplant recipients).

Association of BMI with hospitalization, ICU admission and in-hospital mortality

The association between BMI and hospitalization rate was not statistically significant in the total study population, nor in dialysis patients or transplant recipients when analyzed separately (Supplementary data, Table S3). The chance to be admitted to an ICU was higher with increasing BMI, with similar results among dialysis patients and transplant recipients ($P_{interaction} = 0.37$) (Supplementary data, Table S4). Results for in-hospital mortality were essentially similar to the results for overall mortality (Supplementary data, Table S5).

Additional analyses

The association between obesity class II/III (versus normal weight) and 3-month mortality was consistent across all examined subgroups except for sex (Figure 3). In general, Kaplan-Meier-curves demonstrated the lowest cumulative survival in the underweight category among men and in the obese class II/III category in women (Supplementary data, Figure S2). Obesity class II/III was significantly associated with 3-month mortality among females but not in males ($P_{interaction} = 0.019$ in the fully adjusted model) (Figures 3 and 4, Table 3). The association between BMI (continuous) and mortality indicated a consistent increase in the risk of mortality in patients with BMI >28 kg/m^2 (Supplementary data, Figure S3). Among men, the risk appeared to increase from BMI >28 kg/m^2 and in women from BMI >25 kg/m^2 (Supplementary data, Figure S3). No interaction was observed between BMI and sex for the risk of ICU admission ($P_{interaction} = 0.44$) (Supplementary data, Table S5). Results for 28-day mortality were essentially similar to the results for 3-month mortality (Supplementary data, Tables S7 and S8). A total of 640 patients (18.1%) had missing information on BMI, who were predominantly Caucasian males and were less likely to have comorbidities compared with those having information on BMI (Supplementary data, Table S9). Results after imputing missing values corroborated our overall findings (Supplementary data, Table S10).

DISCUSSION

In this large cohort of patients on KFRT with COVID-19, we showed an independent association between obesity and increased risk of mortality. This association was consistent among dialysis patients and those living with a kidney transplant.

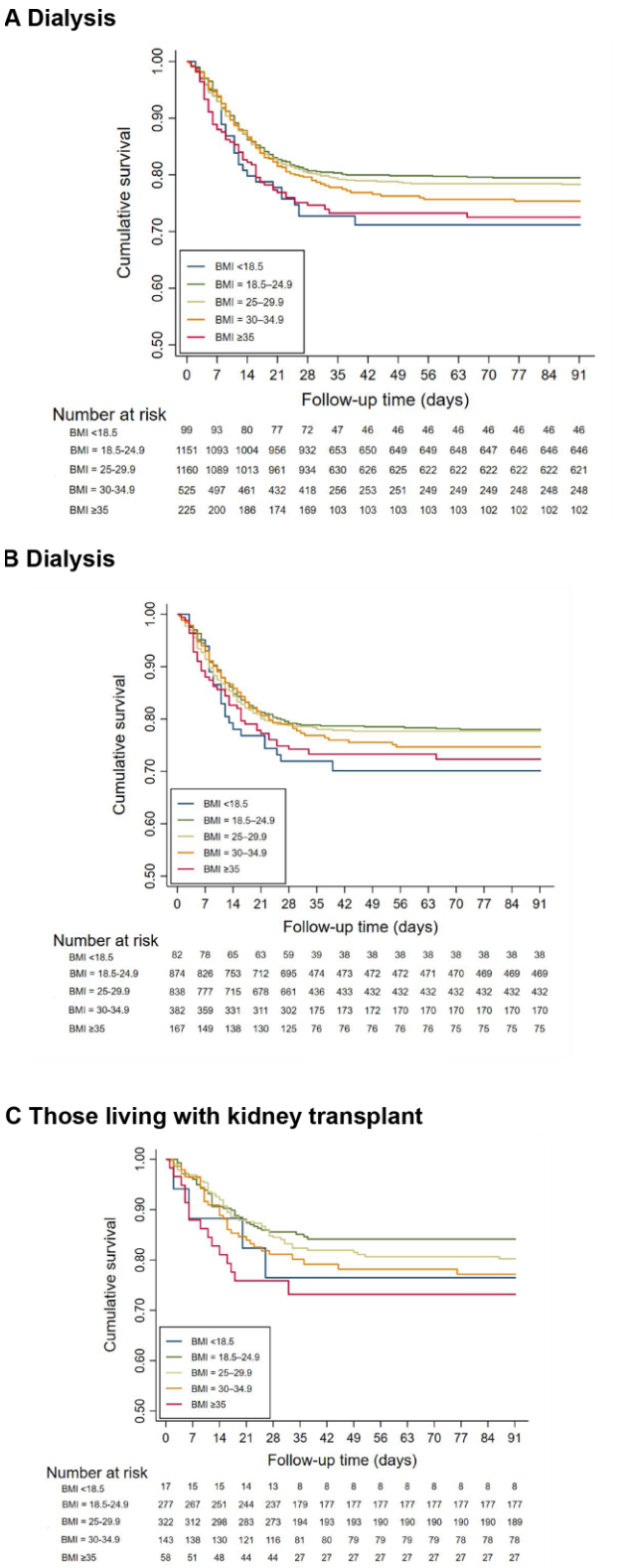

FIGURE 1: Kaplan–Meier curves showing cumulative survival (3 months vital status) by Quetelet's body mass index (BMI) categories. (**A**) Total. (**B**) Dialysis. (**C**) Those living with kidney transplant.

Table 2. Association of Quetelet's body mass index (BMI) with 3 months vital status in total population and by type of kidney function replacement therapy

	BMI categories				
	Lean <18.5	Normal 18.5–24.9	Overweight 25–29.9	Obese I 30–34.9	Obese II/III ≥35
Total (*N* = 3160)	(*N* = 99)	(*N* = 1151)	(*N* = 1160)	(*N* = 525)	(*N* = 225)
Events, *n* (%)	28 (28.3)	232 (20.2)	244 (21.0)	121 (23.0)	60 (26.7)
Model 1	1.47 (1.00, 2.18)	Ref.	1.05 (0.88, 1.26)	1.16 (0.93, 1.44)	1.40 (1.06, 1.86)
Model 2	1.82 (1.23, 2.70)	Ref.	1.06 (0.89, 1.27)	1.22 (0.98, 1.52)	1.94 (1.45, 2.59)
Model 3	1.87 (1.26, 2.77)	Ref.	1.06 (0.88, 1.26)	1.20 (0.97, 1.50)	1.97 (1.47, 2.63)
Model 4	1.96 (1.32, 2.92)	Ref.	1.05 (0.87, 1.26)	1.15 (0.92, 1.45)	1.88 (1.40, 2.53)
Model 5	1.65 (1.10, 2.47)	Ref.	1.07 (0.89, 1.28)	1.17 (0.93, 1.46)	1.71 (1.27, 2.30)
Dialysis (*N* = 2343)	(*N* = 82)	(*N* = 874)	(*N* = 838)	(*N* = 382)	(*N* = 167)
Events, *n* (%)	24 (29.3)	189 (21.6)	184 (22.0)	90 (23.6)	45 (27.0)
Model 1	1.41 (0.92, 2.15)	Ref.	1.03 (0.84, 1.26)	1.10 (0.86, 1.41)	1.30 (0.94, 1.80)
Model 2	1.83 (1.19, 2.80)	Ref.	1.02 (0.83, 1.25)	1.17 (0.91, 1.51)	1.87 (1.34, 2.61)
Model 4	1.94 (1.26, 2.98)	Ref.	1.02 (0.83, 1.25)	1.16 (0.89, 1.50)	1.86 (1.33, 2.61)
Model 5	1.68 (1.08, 2.61)	Ref.	1.03 (0.83, 1.26)	1.13 (0.87, 1.47)	1.67 (1.18, 2.34)
Transplant (*N* = 817)	(*N* = 17)	(*N* = 277)	(*N* = 322)	(*N* = 143)	(*N* = 58)
Events, *n* (%)	4 (23.5)	43 (15.5)	60 (18.6)	31 (21.7)	15 (25.9)
Model 1	1.64 (0.59, 4.56)	Ref.	1.21 (0.82, 1.78)	1.44 (0.91, 2.29)	1.87 (1.04, 3.37)
Model 2	1.60 (0.57, 4.53)	Ref.	1.16 (0.79, 1.72)	1.23 (0.78, 1.95)	2.07 (1.14, 3.76)
Model 4	1.54 (0.54, 4.38)	Ref.	1.11 (0.75, 1.64)	1.11 (0.69, 1.77)	1.84 (0.99, 3.41)
Model 5	1.16 (0.40, 3.39)	Ref.	1.17 (0.79, 1.74)	1.22 (0.75, 1.96)	1.79 (0.96, 3.34)

Model 1: crude.
Model 2: age, sex.
Model 3: model 2 + type of kidney function replacement therapy (expect when analyzing dialysis patients/kidney transplant recipients separately).
Model 4: model 3 + hypertension, diabetes, coronary artery disease, chronic lung disease, heart failure, smoking.
Model 5: model 4 + frailty.

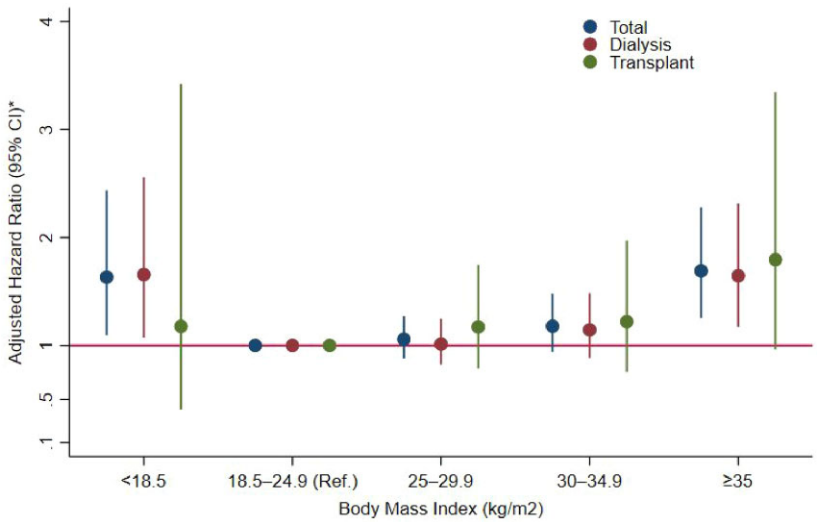

FIGURE 2: Association of Quetelet's BMI with 3 months vital status among patients on kidney function replacement therapy with COVID-19 (presented results are from Model 5*). *Model 5: adjusted for age, sex, type of kidney function replacement therapy (except when analyzing dialysis patients/those living with kidney transplant separately), hypertension, diabetes, coronary artery disease, chronic lung disease, heart failure, smoking, frailty.

Interestingly, the association was different among males and females, such that the risk of mortality associated with obesity versus normal weight was higher in females compared with males.

Several previous studies have reported an association between obesity and increased risk of COVID-19-related complications including mortality in the general population with COVID-19 [11–20]. To our knowledge, the present study is the first to report comprehensively on the obesity–mortality relationship among patients on KFRT with COVID-19. In our study, compared with the WHO-defined category of normal weight, obesity class II/III was associated with an increased risk of mortality. Of note, when the association between BMI and mortality was investigated on a continuous scale, the risk of mortality appeared to

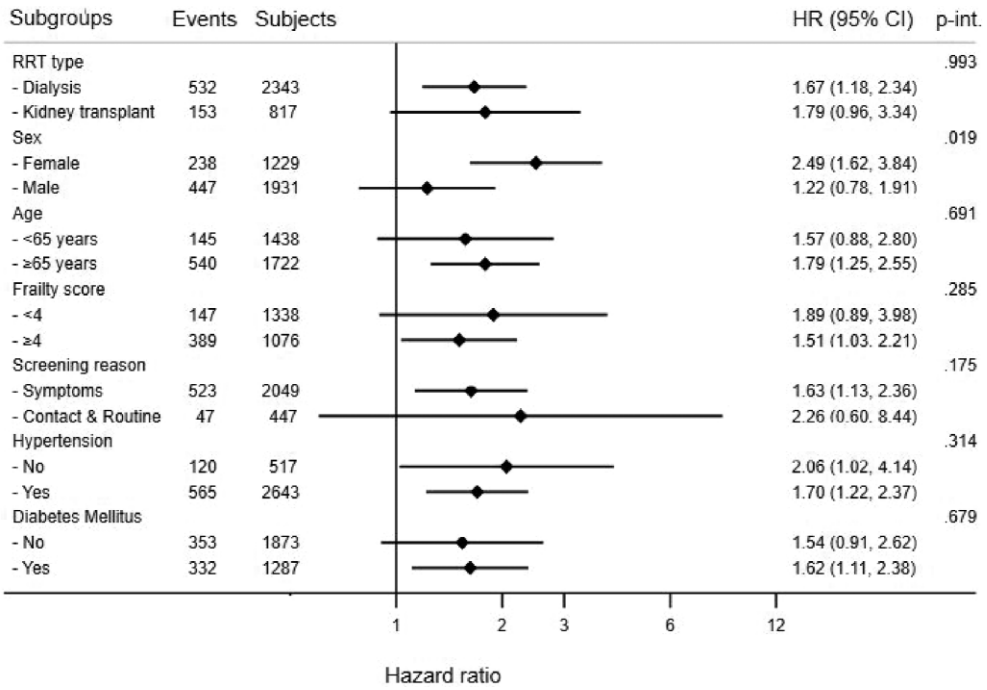

FIGURE 3: Association of Quetelet's BMI (≥35 kg/m^2 versus 18.5–24.9 kg/m^2) with 3 months vital status across subgroups. RRT, renal replacement therapy/kidney function replacement therapy; p-int., *P* for interaction.

increase from a BMI over approximately 28 kg/m^2. An increased mortality risk above a BMI of approximately 28 kg/m^2 has also been observed in a meta-analysis of 28 studies (N = 112 682) among the general population with COVID-19 [21] and in a large study (N ~6.9 million) investigating the association between BMI and COVID-19-related complications in the general population [22]. These studies in the general population also reported increased mortality risk at low BMI as in our study. Consequently, the results observed in our study are in line with the previous studies in the general population, but in contrast to the often observed 'obesity paradox' among patients on KFRT. Especially obese dialysis patients are at lower long-term non-COVID-19 mortality risk when compared with dialysis patients with normal weight [2]. The reversal of the 'obesity paradox' among patients on KFRT with COVID-19 could be related to several factors. First, the influence of obesity on mortality may differ in acute versus chronic diseases. Patients on KFRT that are in poor physical condition due to an underlying illness often lose weight. Thus, obesity may reflect the absence of debilitating disorders and therefore contribute to better long-term outcomes of chronic conditions, such as cardiovascular diseases [23]. However, COVID-19 is an acute viral illness and causes rapid clinical outcomes. Therefore, the survival advantage associated with obesity among patients on KFRT may not be seen when these patients suffer from COVID-19, as this occurs especially in the long term. Second, intubation, positioning and movement may be difficult among seriously ill patients with obesity which may complicate patients' recovery from COVID-19 [24].

Men and women exhibited a difference in the BMI–mortality relationship in our study. Previously, a large study (N = 502 493) in subjects from the general population with COVID-19, and another study in hospitalized COVID-19 patients, showed similar results regarding COVID-19-related mortality [25, 26]. Also, these studies indicated an increase in mortality with increasing obesity in women, but not in men. The exact reason for the observed difference in the BMI–mortality relationship between men and women is not fully clear to us, though it may be related to sex differences in the anatomy of the lungs and abdominal cavity [27, 28] which may cause difficulty in breathing in presence of obesity [1]. It may also be that in a population like ours, 'normal weight' among men is in part a consequence of increased comorbidity burden in men who would have been (slightly) obese if not suffering from comorbidity. Accordingly, when the association between BMI (continuous) and the risk of mortality was investigated for both sexes separately, in men the risk of mortality did not appear to be lowest among those with BMI in the 'normal weight' range as is the case in women. To our knowledge, such a difference in the association of BMI with mortality has not been observed in the general population with COVID-19.

Of note, in our study, the absolute COVID-19 mortality rate in obese men and women was similar, whereas the absolute COVID-19 mortality rate in the normal-weight category was almost two-fold higher in men compared with women. This questions whether the sex difference in our results should be interpreted as excess relative mortality in obese women when compared with obese men, or more as a higher absolute mortality rate in normal-weight men when compared with normal-weight women. Putting more emphasis on this latter finding is supported by the fact that there are far more people with normal weight in our cohort (N = 1160) than with obesity class II/III (N = 225). Future studies are required to better understand the reasons for the observed sex difference in the BMI–mortality relationship in our study.

The most important strength of our study is that it reports on a large dataset with detailed information on patients' demographics, comorbidities, reasons for COVID-19 testing, disease characteristics including symptoms and laboratory test results. This allowed accounting for known confounders in the

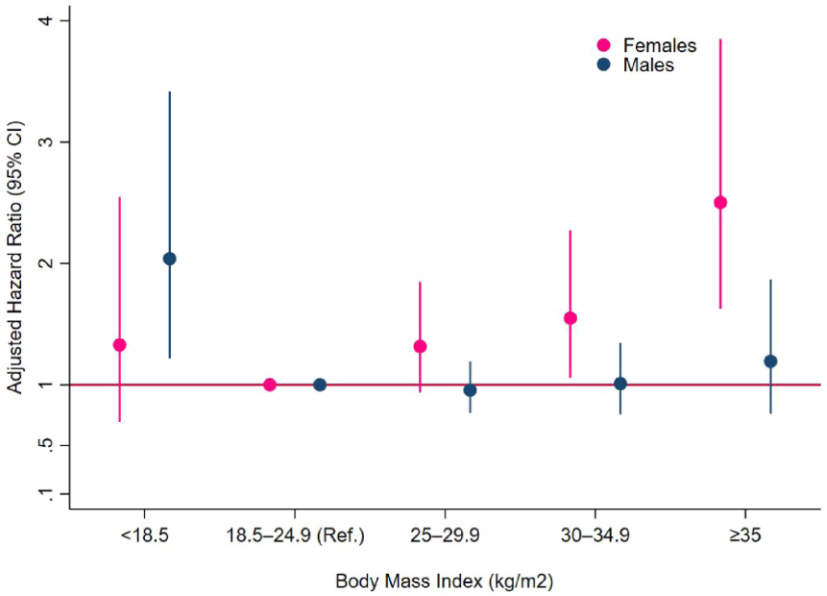

FIGURE 4: Association of Quetelet's BMI with 3 months vital status by sex (presented results are from Model 5*). *Model 5: adjusted for age, sex, type of kidney function replacement therapy (expect when analyzing dialysis patients/those living with kidney transplant separately), hypertension, diabetes, coronary artery disease, chronic lung disease, heart failure, smoking, frailty.

Table 3. Association of Quetelet's body mass index (BMI) with 3 months vital status in males and females

	BMI categories				
	Lean <18.5	Normal 18.5–24.9	Overweight 25–29.9	Obese I 30–34.9	Obese II/III ≥35
Females (*N* = 1229)	(*N* = 52)	(*N* = 447)	(*N* = 384)	(*N* = 220)	(*N* = 126)
Events, *n* (%)	11 (21.1)	66 (14.8)	74 (19.3)	51 (23.2)	36 (28.6)
Model 1	1.48 (0.78, 2.81)	Ref.	1.33 (0.96, 1.86)	1.62 (1.12, 2.33)	2.11 (1.40, 3.16)
Model 2	1.61 (0.85, 3.05)	Ref.	1.37 (0.98, 1.91)	1.67 (1.16, 2.40)	2.70 (1.78, 4.08)
Model 3	1.60 (0.84, 3.03)	Ref.	1.34 (0.96, 1.87)	1.63 (1.13, 2.35)	2.73 (1.80, 4.13)
Model 4	1.57 (0.82, 2.99)	Ref.	1.33 (0.95, 1.87)	1.51 (1.03, 2.22)	2.70 (1.76, 4.13)
Model 5	1.34 (0.70, 2.57)	Ref.	1.31 (0.94, 1.85)	1.54 (1.05, 2.26)	2.49 (1.62, 3.84)
Males (*N* = 1931)	(*N* = 47)	(*N* = 704)	(*N* = 776)	(*N* = 305)	(*N* = 99)
Events, *n* (%)	17 (36.2)	166 (23.6)	170 (21.9)	70 (22.9)	24 (24.2)
Model 1	1.66 (1.01, 2.73)	Ref.	0.93 (0.75, 1.15)	0.97 (0.74, 1.29)	1.06 (0.69, 1.63)
Model 2	2.21 (1.34, 3.64)	Ref.	0.95 (0.77, 1.18)	1.02 (0.77, 1.35)	1.45 (0.94, 2.23)
Model 3	2.29 (1.39, 3.77)	Ref.	0.95 (0.76, 1.17)	1.02 (0.77, 1.35)	1.47 (0.95, 2.26)
Model 4	2.44 (1.47, 4.05)	Ref.	0.94 (0.75, 1.17)	0.99 (0.75, 1.32)	1.38 (0.88, 2.14)
Model 5	2.07 (1.22, 3.52)	Ref.	0.97 (0.78, 1.21)	0.99 (0.74, 1.33)	1.22 (0.78, 1.91)

Model 1: crude.
Model 2: age.
Model 3: model 2 + type of kidney function replacement therapy.
Model 4: model 3 + hypertension, diabetes, coronary artery disease, chronic lung disease, heart failure, smoking.
Model 5: model 4 + frailty.

BMI–mortality relationship and examination of results across key clinical subgroups, thereby allowing a comprehensive assessment of the BMI–mortality relationship among patients on KFRT with COVID-19. However, this study also has limitations. First, patients who presented with COVID-19 may not be representative of the overall population of KFRT patients with COVID-19 which may limit the generalizability of our findings. However, it is worth noting that case-fatality rates observed in our study are comparable to those reported in other studies from patients on KFRT with COVID-19 [4, 29–33]. Second, a significant proportion of patients (18.1%) had missing information on BMI. These patients were predominantly Caucasian males and were less likely to have comorbidities than patients in the cohort with information on BMI (Supplementary data, Table S7). In a sensitivity analysis that included these patients after multiple imputations, we found no difference in the observed associations compared with our main findings. Third, because BMI is associated with disease severity and patients with severe symptoms were more likely to be tested for COVID-19, especially early in the COVID-19 pandemic, there may be a possibility of collider bias [34]. Importantly, we had information on the reason for COVID-19 testing. No heterogeneity was observed in the association between obesity and mortality when patients who were identified through routine screening and those who were identified

because of symptoms were analyzed separately, suggesting that this type of bias has no major role.

CONCLUSION

In conclusion, this study shows that among patients on KFRT with COVID-19, dialysis patients as well as transplant recipients, obesity is associated with an increased risk of mortality. This is in contrast to the obesity paradox generally observed in dialysis patients. The association of obesity with COVID-19 mortality may be different in men and women, which requires further study, including investigation of potential reasons for this difference.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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DATA AVAILABILITY STATEMENT

Collaborators that entered data in ERACODA remain the owner of these data. The database can therefore not be disclosed to any third party without the prior written consent of all data providers. Research proposals can be submitted to the Working Group via COVID.19.KRT@umcg.nl. If deemed of interest and methodological sound by the Working Group and Advisory Board, the analyses needed for the proposal will be carried out by the Management Team.

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CONFLICT OF INTEREST STATEMENT

E.T., C.I., L.B.H., R.G., M.I., D.K., C.K., F.M.M., I.N., M.L.R.-F., M.A.M.V. and A.P.J.D.V., have no conflict of interest to disclose. K.J.K. received funding from the ERA. M.N., R.T.G., and P.V. receive grants from Dutch Kidney Foundation, European Renal Association, Sandoz and Baxter as well as received unrestricted research grants for ERACODA; payments were made to the institution.

AUTHORS' CONTRIBUTIONS

All authors contributed to data collection, study design, data analysis, interpretation and drafting of this article.

APPENDIX

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The ERACODA collaboration is an initiative to study prognosis and risk factors for mortality due to COVID-19 in patients with a kidney transplant or on dialysis that is endorsed by the European Renal Association (ERA). ERACODA is an acronym for European Renal Association COVID-19 Database. The organizational structure contains a Working Group assisted by a Management Team and an Advisory Board.

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