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ORIGINAL ARTICLE

Kt/V: achievement, predictors and relationship to mortality in hemodialysis patients in the Gulf Cooperation Council countries: results from DOPPS (2012–18)

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ABSTRACT

Background. Dialysis adequacy, as measured by single pool *Kt/V*, is an important parameter for assessing hemodialysis (HD) patients' health. Guidelines have recommended *Kt/V* of 1.2 as the minimum dose for thrice-weekly HD. We describe *Kt/V* achievement, its predictors and its relationship with mortality in the Gulf Cooperation Council (GCC) (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and the United Arab Emirates).

Methods. We analyzed data (2012–18) from the prospective cohort Dialysis Outcomes and Practice Patterns Study for 1544 GCC patients ≥18 years old and on dialysis >180 days.

Results. Thirty-four percent of GCC HD patients had low *Kt/V* (<1.2) versus 5%–17% in Canada, Europe, Japan and the USA. Across the GCC countries, low *Kt/V* prevalence ranged from 10% to 54%. In multivariable logistic regression, low *Kt/V* was more common ($P < 0.05$) with larger body weight and height, being male, shorter treatment time (TT), lower blood flow rate (BFR), greater comorbidity burden and using HD versus hemodiafiltration. In adjusted Cox models, low *Kt/V* was strongly related to higher mortality in women [hazard ratio (HR) = 1.91, 95% confidence interval (CI) 1.09–3.34] but not in men (HR =

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1.16, 95% CI 0.70–1.92). Low BFR (<350 mL/min) and TT (<4 h) were common; 41% of low *Kt/V* cases were attributable to low BFR or TT (52% for women and 36% for men).

Conclusion. Relatively large proportions of GCC HD patients have low *Kt/V*. Increasing BFR to ≥350 mL/min and TT to ≥4 h thrice weekly will reduce low *Kt/V* prevalence and may improve survival in GCC HD patients—particularly among women.

Keywords: attributable fraction, dialysis adequacy, GCC, hemodialysis, *Kt/V*, mortality, sex

INTRODUCTION

For end-stage kidney disease patients on hemodialysis (HD), life is sustained by regular and adequate removal of uremic toxins. Although these toxins include a variety of small and middle molecules, assessment of the adequacy of toxin removal by HD is based on urea measurements. This has been a standard practice since the publication of the National Cooperative Dialysis Study (NCDS) in 1981 which showed that higher dialysis dose based on the rate of urea removal reduced morbidity [1]. The most commonly used method for measuring HD adequacy, based upon urea clearance, is *Kt/V*. This measure was developed by Gotch and Sargent through a *post hoc* mechanistic study of the NCDS data [2]. Despite its limitations [3], single pool *Kt/V* is the preferred measure of dialysis dose–adequacy in the majority of dialysis units. American, European, Japanese and Canadian treatment guidelines recommend a minimum *Kt/V* dose of 1.2 for patients dialyzing thrice weekly [4–7].

Dialysis dose as measured by *Kt/V* can be influenced by many factors, especially treatment time (TT) and blood flow rate (BFR), but also by dialysate flow, session interruption (hypotension or clotting), access functionality (stenosis and recirculation), needle size and placement, dialyzer characteristics and proper blood sampling [7]. Many studies have indicated that lower than recommended *Kt/V* may increase mortality [8–12], especially in females [9, 13].

Although the international medical literature is rich in data describing dialysis dose and its impact on morbidity and mortality, little originates in the Gulf Cooperation Council (GCC) countries of Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and the United Arab Emirates (UAE). This is despite a high regional prevalence of risk factors for chronic kidney disease and a growing dialysis population in the GCC, even though the mean age of GCC HD patients is substantially lower than that of HD patients in North America, Western Europe and Japan [14]. In 2016, Alyousef *et al.* [15] described HD practice patterns, including BFR, TT and achieved dialysis dose in GCC HD patients participating in the Dialysis Outcomes and Practice Patterns Study (DOPPS) Phase 5. In this current work, we further describe this population's *Kt/V* achievement, its predictors and its relationship with mortality in the GCC.

MATERIALS AND METHODS

Data source

We examined GCC data collected for adult HD patients, ≥18 years old, in the international, prospective DOPPS Phases 5 (2012–15) and 6 (2015–18) cohorts. Study patients were enrolled randomly from a representative sample of dialysis facilities within each nation at the start of each study phase, with departing patients replaced as described previously [16–18]. Each DOPPS phase was approved by national and/or local ethics committees per local regulations, with informed consent obtained as required. Demographic data, comorbidities, laboratory values and prescribed dialysis treatment information at baseline were abstracted from patient records. Mortality events were collected during study follow-up. Body surface area (BSA) was calculated using the Du Bois formula [19].

Analyses were restricted to patients who were on dialysis ≥180 days, receiving thrice-weekly HD and had data reported to calculate single pool *Kt/V* by the second generation Daugirdas formula [20]. From an initial sample of 2186 GCC patients, we excluded 642 patients as follows: 80 (4%) patients had no dialysis information, 141 (6%) were not receiving thrice-weekly dialysis, 195 (9%) had been on dialysis <180 days and 226 (10%) lacked required *Kt/V* information. Consequently, 1544 GCC patients were included in our study sample, with 43% from Saudi Arabia. Mortality analyses included only 1106 patients from facilities that followed mortality events. For nationally representative prevalence estimates, we included only the 1231 patients enrolled at the start of each DOPPS phase.

Statistical analysis

Characteristics of the GCC study sample were assessed, overall, by GCC country, sex and *Kt/V* level (Tables 1 and 2), with international *Kt/V* comparisons limited to DOPPS 6 data (Figure 1).

We examined the relationship of low *Kt/V* (<1.2) with all-cause mortality using Cox regression, with adjustments as indicated in Table 3, using the robust sandwich covariance estimator to account for facility clustering [21]. Patients were followed from the time of *Kt/V* measurement until death or 7 days after the earliest of dialysis modality switch, withdrawal from dialysis, the return of renal function, kidney transplantation, transfer to another facility or end of follow-up. Median follow-up time was 1.3 years for patients who survived and 0.8 years for patients who died.

We assessed the association of patient characteristics with low *Kt/V* (<1.2) using mixed-effects logistic regression (Table 4). The model included TT and BFR as the exposures of interest. Adjustments (Table 4) included a comorbidity score calculated as the sum of indicators for the 13 comorbidities listed in Table 1, with a random facility intercept to account for facility clustering. The proportion of cases of low *Kt/V* attributable to TT <4 h and/or BFR <350 mL/min (Table 5 and Supplementary data, Table S1) was obtained by estimating the attributable fraction for those exposed (AFE) to TT or BFR below these thresholds and the population attributable fraction (PAF) for the entire studied population.

To estimate the attributable fractions for TT, we used the fitted logistic regression model, with TT as a continuous exposure, and to predict for each exposed patient (i.e. with TT <4 h), the probability of low *Kt/V* if their TT was counterfactually raised to the threshold (i.e. 4 h). To estimate AFE, we averaged these counterfactual predicted probabilities among exposed patients, then divided by the observed prevalence of low *Kt/V* among the exposed patients and finally subtracted the result from 1. To estimate PAF, we averaged the counterfactual predicted probabilities among the exposed together with the observed prevalence of low *Kt/V* among the unexposed (patients having TT ≥4 h), then divided by the observed prevalence of low *Kt/V* among all patients and finally subtracted the result from 1.

Table 1. Study patient characteristics in the GCC, by country and by sex

		Country						Sex	
Characteristics	All ($n = 1544$)	Bahrain ($n = 59$)	Kuwait ($n = 258$)	Oman ($n = 147$)	Qatar ($n = 143$)	Saudi Arabia ($n = 664$)	UAE ($n = 273$)	Females ($n = 639$)	Males ($n = 905$)
Female, %	41	34	43	41	35	44	40	100	100
Age, years	55 ± 15	55 ± 15	55 ± 16	53 ± 16	60 ± 13	53 ± 16	57 ± 14	55 ± 15	54 ± 16
Vintage, years	2.7 (1.1, 5.3)	3.5 (1.6, 5.5)	2.7 (1.2, 5.0)	3.7 (1.5, 6.7)	2.5 (1.1, 4.7)	2.6 (1.0, 5.5)	2.5 (1.2, 4.8)	2.9 (1.2, 5.5)	2.5 (1.1, 5.2)
Weight, kg	70.7 ± 19.5	81.1 ± 24.7	75.9 ± 19.0	63.8 ± 17.5	75.8 ± 20.0	67.3 ± 18.4	72.8 ± 19.2	67.8 ± 19.5	72.7 ± 19.3
Height, cm	163 ± 9	164 ± 10	164 ± 10	163 ± 10	164 ± 9	162 ± 9	163 ± 10	157 ± 7	167 ± 9
BMI, kg/m^2	26.7 ± 6.8	30.1 ± 8.0	28.6 ± 6.7	23.9 ± 5.9	28.3 ± 7.4	25.6 ± 6.3	27.5 ± 6.8	27.5 ± 7.6	26.1 ± 6.2
BSA, m^2	1.75 ± 0.24	1.86 ± 0.29	1.82 ± 0.23	1.68 ± 0.24	1.81 ± 0.22	1.71 ± 0.23	1.77 ± 0.24	1.67 ± 0.23	1.80 ± 0.24
Urine volume >200 mL/day, %	27	12	23	37	45	26	18	25	28
Serum albumin, g/dL	3.5 ± 0.5	3.6 ± 0.6	3.4 ± 0.4	3.8 ± 0.5	3.6 ± 0.6	3.6 ± 0.5	3.3 ± 0.4	3.5 ± 0.5	3.6 ± 0.5
Serum Creatinine, mg/dL	9.6 ± 3.0	9.4 ± 2.6	9.2 ± 3.1	10.2 ± 3.4	9.2 ± 2.8	10.0 ± 3.1	9.3 ± 2.7	8.6 ± 2.4	10.4 ± 3.2
Predialysis BUN, mg/dL	53.1 ± 23.4	59.2 ± 23.3	52.3 ± 20.2	59.7 ± 21.5	36.2 ± 11.5	53.9 ± 26.4	55.3 ± 19.9	51.1 ± 22.6	54.5 ± 23.8
Blood flow rate, mL/min	299 ± 48	314 ± 53	289 ± 30	278 ± 32	295 ± 30	297 ± 51	324 ± 56	292 ± 46	304 ± 49
Treatment time, h	3.7 ± 0.4	3.7 ± 0.4	3.7 ± 0.4	3.7 ± 0.3	3.9 ± 0.3	3.7 ± 0.5	3.8 ± 0.4	3.7 ± 0.4	3.7 ± 0.4
Hemodiafiltration, %	20	75	58	17	0	4	25	17	22
Access type, %									
Fistula	62	41	45	83	65	66	61	59	65
Graft	5	5	2	6	6	6	3	5	4
Catheter	33	53	53	11	28	28	37	36	31
Comorbidities, %									
Diabetes	54	71	69	55	66	41	63	56	53
Coronary artery disease	30	33	34	23	35	26	35	28	31
Congestive heart failure	19	7	10	27	7	20	29	19	19
Hypertension	92	90	96	88	96	89	96	92	92
Other cardiovascular disease	15	17	16	10	17	14	15	16	14
Cerebrovascular disease	8	3	15	7	8	6	7	7	8
Peripheral vascular disease	19	38	15	22	30	14	24	17	20
Gastrointestinal bleeding	4	2	4	2	2	4	5	2	5
Lung disease	5	7	8	1	1	4	6	5	4
Neurologic disease	7	0	8	4	2	8	8	9	6
Psychiatric disorder	9	3	5	9	1	12	11	10	8
Recurrent cellulitis	9	17	10	8	11	7	10	8	10
Cancer (other than skin)	2	2	2	1	4	1	1	3	1
Comorbidity score	2.7 ± 1.7	2.9 ± 1.5	2.9 ± 1.6	2.6 ± 1.5	2.8 ± 1.4	2.5 ± 1.6	3.1 ± 1.9	2.7 ± 1.6	2.7 ± 1.7

Characteristics reported as mean ± standard deviation, median (IQR) or %. Comorbidity score = the sum of indicators for the 13 listed comorbidities. BMI = body mass index; BSA = body surface area; IQR = interquartile range.

Table 2. Study patient characteristics in the GCC by sex and Kt/V category

		Females, by Kt/V				Males, by Kt/V			
Characteristics	All ($n = 1544$)	<1.2 ($n = 174$)	1.2–1.4 ($n = 121$)	1.4–1.6 ($n = 134$)	≥1.6 ($n = 210$)	<1.2 ($n = 359$)	1.2–1.4 ($n = 198$)	1.4–1.6 ($n = 158$)	≥1.6 ($n = 190$)
Age, years	55 ± 15	54 ± 14	54 ± 15	58 ± 15	55 ± 16	54 ± 15	54 ± 16	54 ± 15	54 ± 17
Vintage, years	2.7 (1.1, 5.3)	2.7 (1.1, 5.5)	3.1 (1.0, 5.2)	3.0 (1.3, 5.2)	3.2 (1.3, 6.1)	2.3 (1.0, 4.9)	3.0 (1.2, 5.2)	2.6 (1.1, 5.1)	2.7 (1.1, 6.0)
Weight, kg	70.7 ± 19.5	72.0 ± 20.8	72.1 ± 20.7	69.0 ± 18.8	61.0 ± 16.0	77.7 ± 20.1	74.2 ± 19.6	68.7 ± 16.8	65.1 ± 16.2
Height, cm	163 ± 9	159 ± 7	158 ± 8	157 ± 7	155 ± 7	168 ± 9	168 ± 9	166 ± 9	164 ± 9
BMI, kg/m^2	26.7 ± 6.8	28.6 ± 7.9	29.0 ± 8.3	28.3 ± 7.8	25.4 ± 6.2	27.4 ± 6.5	26.4 ± 6.5	25.0 ± 5.3	24.2 ± 5.3
BSA, m^2	1.75 ± 0.24	1.73 ± 0.23	1.72 ± 0.24	1.69 ± 0.21	1.59 ± 0.20	1.86 ± 0.24	1.83 ± 0.23	1.76 ± 0.22	1.70 ± 0.21
Urine volume >200 mL/day, %	27	21	27	27	25	28	33	29	22
Serum albumin, g/dL	3.5 ± 0.5	3.5 ± 0.5	3.5 ± 0.4	3.5 ± 0.5	3.4 ± 0.5	3.6 ± 0.5	3.6 ± 0.5	3.5 ± 0.5	3.6 ± 0.5
Serum Creatinine, mg/dL	9.6 ± 3.0	8.7 ± 2.7	8.8 ± 2.3	8.5 ± 2.3	8.4 ± 2.1	10.7 ± 3.4	10.7 ± 3.2	10.1 ± 3.1	9.9 ± 2.9
Predialysis BUN, mg/dL	53.1 ± 23.4	50.0 ± 22.5	52.2 ± 19.5	48.9 ± 23.2	52.6 ± 23.9	56.6 ± 25.2	53.2 ± 22.8	51.3 ± 23.8	54.3 ± 21.9
Blood flow rate, mL/min	299 ± 48	272 ± 41	286 ± 41	292 ± 36	312 ± 49	291 ± 40	299 ± 42	308 ± 45	329 ± 63
Treatment time, h	3.7 ± 0.4	3.6 ± 0.4	3.6 ± 0.5	3.7 ± 0.4	3.8 ± 0.4	3.7 ± 0.5	3.8 ± 0.4	3.8 ± 0.4	3.8 ± 0.3
Hemodiafiltration, %	20	21	17	13	17	23	17	21	28
Access type, %									
Fistula	62	56	57	60	61	62	66	68	67
Graft	5	2	3	7	9	3	4	4	6
Catheter	33	43	40	34	30	35	29	28	27
Comorbidities, %									
Diabetes	54	57	58	66	48	58	50	52	49
Coronary artery disease	30	31	31	28	23	33	34	28	28
Congestive heart failure	19	19	21	17	20	18	16	19	23
Hypertension	92	91	93	95	91	92	91	90	94
Other cardiovascular disease	15	19	23	14	12	18	11	9	12
Cerebrovascular disease	8	9	11	8	2	8	10	5	12
Peripheral vascular disease	19	18	23	24	11	25	19	16	16
Gastrointestinal bleeding	4	2	2	3	2	5	5	3	4
Lung disease	5	7	6	5	3	4	3	3	7
Neurologic disease	7	11	10	6	9	5	6	5	7
Psychiatric disorder	9	9	11	9	11	9	11	4	6
Recurrent cellulitis	9	10	8	7	6	14	7	5	9
Cancer, other than skin	2	1	2	4	5	1	1	1	1
Comorbidity score	2.7 ± 1.7	2.8 ± 1.7	3.0 ± 1.7	2.8 ± 1.5	2.5 ± 1.5	2.9 ± 1.7	2.6 ± 1.8	2.4 ± 1.5	2.7 ± 1.8

Characteristics reported as mean ± standard deviation, median (IQR) or %. Comorbidity score = the sum of indicators for the 13 listed comorbidities. BMI = body mass index; BSA = body surface area; IQR = interquartile range.

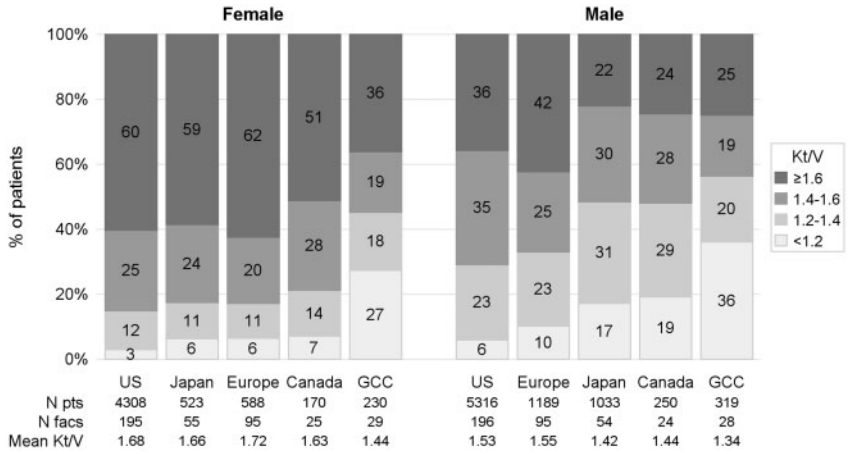

FIGURE 1: Kt/V by region and sex, using initial representative sample from DOPPS 6.

Table 3. HRs of all-cause mortality for low Kt/V (<1.2) in the GCC

			Unadjusted		Adjusted	
Subgroup	*n*, pts	Deaths	HR (95% CI)	P-value	HR (95% CI)	P-value
All patients	1106	178	1.35 (0.97–1.86)	0.07	1.32 (0.92–1.89)	0.13
Males	659	107	1.26 (0.87–1.84)	0.22	1.16 (0.70–1.92)	0.56
Females	447	71	1.53 (0.94–2.48)	0.09	1.91 (1.09–3.34)	0.02

HR are based on Cox regression. HRs >1 indicate greater hazard of death for low Kt/V versus Kt/V ≥1.2. Separate Cox regression models were fit for all patients, males and females. All models, including the 'unadjusted' models, were stratified by DOPPS phase and country. Adjustments were age, sex, dialysis vintage, BMI, catheter use, hemodiafiltration use, predialysis BUN, residual urine volume >200 mL/day, serum albumin, serum creatinine and a score of 13 comorbidities. pts = patients.

We repeated these calculations using the same fitted logistic model for BFR alone and also for TT and BFR together. For the latter calculations, when a patient was considered exposed to either TT or BFR below its threshold, all low values were raised to the indicated thresholds. Finally, we repeated the entire attributable fraction analysis separately by sex, body mass index (BMI) ≤26 or >26 and predialysis blood urea nitrogen (BUN) ≤55 or >55 mg/dL. We also estimated the odds ratio (OR) of low Kt/V for each treatment exposure by fitting a separate logistic model in which the exposure was coded as a binary indicator for being below its threshold, thus the OR represents the increase in odds of low Kt/V for exposed patients.

We used multiple imputations, implemented by IVEware [22], to impute missing covariate values. Missingness was low at <6% for all covariates. We imputed 20 complete datasets, performed all analyses with each dataset and combined the results using Rubin's rules [23].

All analyses used SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Table 4. Adjusted odds ratios of low Kt/V (<1.2) in the GCC

Patient factor	OR (95% CI)	P
TT, per h	0.44 (0.30–0.66)	<0.001
BFR, per 50 mL/min	0.62 (0.50–0.77)	<0.001
Age, per 10 years	0.99 (0.89–1.09)	0.82
Male	1.91 (1.38–2.65)	<0.001
Weight, per 10 kg	1.50 (1.38–1.64)	<0.001
Height, per cm	1.02 (1.00–1.04)	0.02
Vintage in years, per doubling	0.93 (0.84–1.04)	0.23
Comorbidity score, per 1	1.15 (1.05–1.26)	0.003
Hemodiafiltration use (yes vs. no)	0.52 (0.30–0.89)	0.02
Urine volume >200 mL/day	0.90 (0.63–1.28)	0.55
Serum albumin, per g/dL	1.10 (0.79–1.53)	0.56
Serum creatinine, per mg/dL	1.02 (0.96–1.08)	0.52
Predialysis BUN, per 10 mg/dL	0.97 (0.90–1.04)	0.34
Catheter use (yes vs. no)	1.28 (0.94–1.74)	0.12
DOPPS Phase 6 (versus 5)	0.85 (0.40–1.81)	0.68

Based on logistic regression, modeling probability of low Kt/V, adjusting for all factors listed in the table plus each GCC country.

RESULTS

Study participants from the GCC had a mean age of 55 years, 41% were female and a median dialysis vintage of 2.7 years (Table 1). The mean BMI was lower for men at 26.1 kg/m^2 versus 27.5 for women; across GCC countries, mean BMI ranged from 23.9 kg/m^2 in Oman to 30.1 in Bahrain. However, the mean BSA was higher for men (1.80 m^2) than for women (1.67 m^2). Across countries, the mean BSA ranged from 1.68 m^2 in Oman to 1.86 m^2 in Bahrain. The percentage of patients having urine output >200 mL/day varied >3-fold across countries from 12% in Bahrain to 45% in Qatar, while mean predialysis BUN varied from 52 to 60 mg/dL across all GCC countries except for being much lower in Qatar (36 mg/dL). Fifty-four percent of all patients had diabetes, ranging from 41% in Saudi Arabia to 71% in Bahrain. Of the 13 comorbidities listed in Table 1, the mean number of comorbidities was 2.7. Among both men and women,

Table 5. Proportion of low Kt/V (<1.2) cases in the GCC attributable to treatment practices below a specified threshold, for all study patients and by sex

Subgroup	Low Kt/V, prev (%)	Treatment practice	Tx practice, prev (%)	AFE (%)	PAF (%)	OR (95% CI)
All patients ($n = 1544$)	34	TT <4 h	43	30	15	1.9 (1.4–2.7)
		BFR <350 mL/min	80	33	29	1.5 (1.0–2.5)
		Either low TT or BFR	85	44	41	2.2 (1.3–3.8)
Males ($n = 905$)	39	TT <4 h	37	27	12	1.8 (1.2–2.8)
		BFR <350 mL/min	77	30	26	1.6 (0.9–2.8)
		Either low TT or BFR	81	39	36	2.5 (1.4–4.5)
Females ($n = 639$)	27	TT <4 h	50	33	19	2.1 (1.2–3.6)
		BFR <350 mL/min	85	43	40	1.6 (0.7–3.9)
		Either low TT or BFR	89	54	52	2.6 (0.9–7.4)

Based on logistic regression, modeling probability of low Kt/V, adjusting for age, sex, country, dialysis vintage, weight, height, catheter use, HDF use, predialysis BUN, residual urine volume, serum albumin, serum creatinine, a score of 13 comorbidities and DOPPS phase. Model was fit separately in each subgroup. The adjusted odds ratio (OR) indicates the odds of low Kt/V for patients with a treatment practice below versus above the treatment threshold. Although the logistic model was fit with all patients in each subgroup, the estimated prevalences used to calculate AFE and PAF were based only on patients enrolled at the start of each DOPPS phase, as this subset is more representative of the GCC dialysis population. Prev = prevalence; Tx = treatment; TT = treatment time; BFR = blood flow rate; AFE = attributable fraction among the exposed; PAF = population attributable fraction.

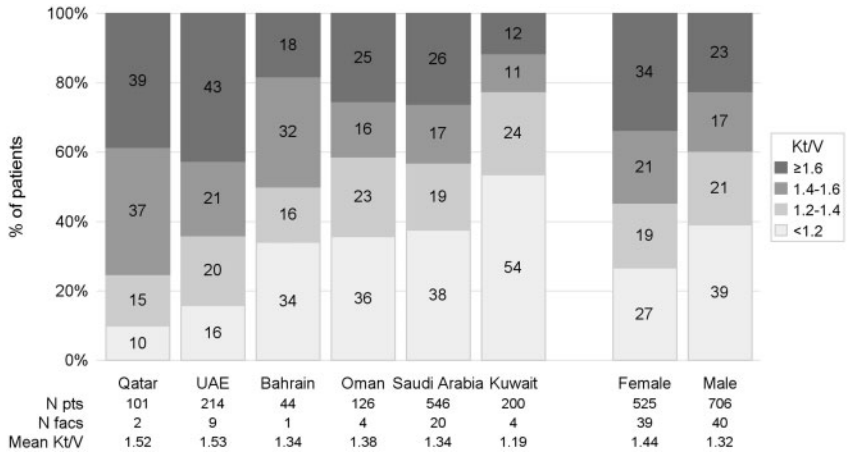

FIGURE 2: Kt/V in the GCC, by country and sex, combining initial representative samples from DOPPS 5 and 6.

achieved Kt/V levels tended to be higher at lower mean BMI and BSA levels (Table 2).

Figure 1 provides an international comparison of Kt/V achievement in the GCC, Europe, Japan, Canada and the USA based on the initial prevalent cross-section of HD patients at the start of DOPPS 6 (2015–18). The GCC region displayed the highest proportion of patients with low Kt/V (<1.2), with 27% of female GCC patients having low Kt/V compared with 3–7% of females in other regions/countries and with 36% of male GCC patients having low Kt/V compared with 6–19% of males in other regions/countries. The GCC also displayed lower mean Kt/V than in other regions.

Figure 2 shows the distribution of Kt/V in individual GCC countries, combining the prevalent cross-sections from DOPPS 5 and 6 to provide a larger sample size per GCC country than if based on a single study phase. Kuwait had the highest proportion of patients with Kt/V <1.2 (54%) and the lowest proportion achieving Kt/V >1.4 (23%). In contrast, Qatar had the lowest proportion of patients with Kt/V <1.2 (10%) and the highest proportion achieving Kt/V >1.4 (76%). A higher proportion of men had Kt/V <1.2 than women (39% versus 27%).

Mean TT (Figure 3) was between 3.7 and 3.8 h in all GCC countries and for both men and women, though the proportion of patients with TT ≤3 h varied from 2% in Qatar to 10–11% in the UAE and Oman to 16–22% in Bahrain, Kuwait and Saudi Arabia. In all GCC countries except Oman, most patients had TT ≥4 h, ranging from 52% of patients in Kuwait to 70% in the UAE. By comparison, only 41% of Omani patients had TT ≥4 h but their body weight, BMI and BSA were considerably lower than in other GCC countries (Table 1).

Substantial differences were seen in the distribution of BFRs used across the GCC countries (Figure 4). Mean BFR ranged from 279 mL/min in Oman to 291–298 mL/min in Kuwait, Qatar and Saudi Arabia and up to 325 mL/min in the UAE and Bahrain. The percentage of patients treated with a BFR <300 mL/min varied more than 3-fold across countries, from 14–19% of patients in Bahrain, Qatar and the UAE to 28–31% in Kuwait and Saudi Arabia and reaching 52% in Oman. The percentage of patients treated with a BFR >300 mL/min ranged from 7–10% in Qatar, Oman and Kuwait to 42–50% in the UAE and Bahrain. Men had higher mean BFR levels than women (306 versus 293 mL/min), and men were less likely to have BFR <300 mL/min (25% versus 34%).

BFR tended to vary by vascular access type, with higher mean BFRs achieved with grafts and fistulae (313 and 305 mL/min, respectively) than with catheters (287 mL/min). Catheter usage was high in many of the GCC countries (Figure 5), ranging from 10% in Oman to 25–51% in the other GCC countries. Large differences were seen across the GCC countries in the use of the two main dialysis techniques: hemodiafiltration (HDF) and HD

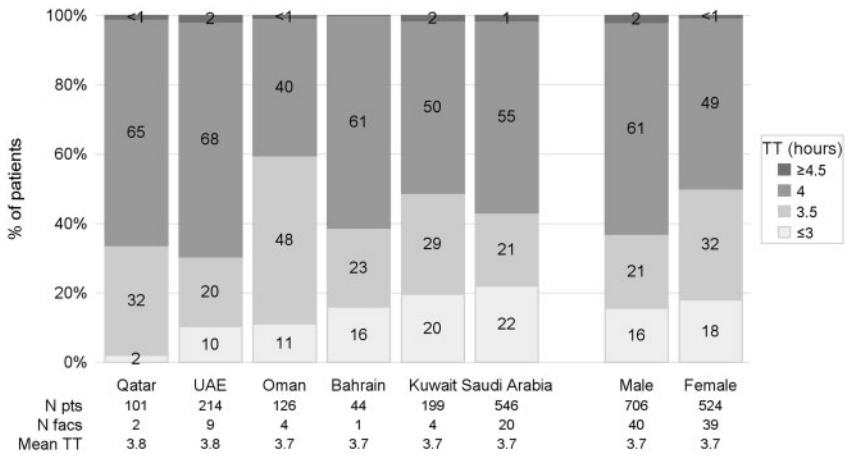

FIGURE 3: Treatment time in the GCC, by country and sex, combining initial representative samples from DOPPS 5 and 6.

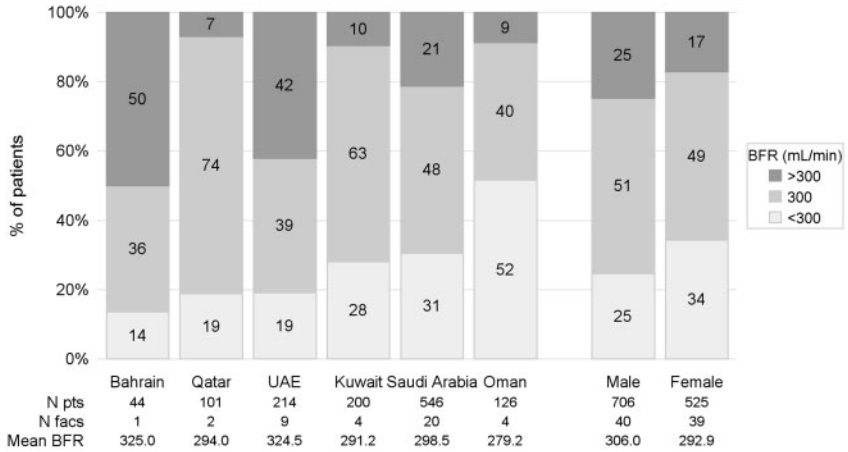

FIGURE 4: Blood flow rate in the GCC, by country and sex, combining initial representative samples from DOPPS 5 and 6.

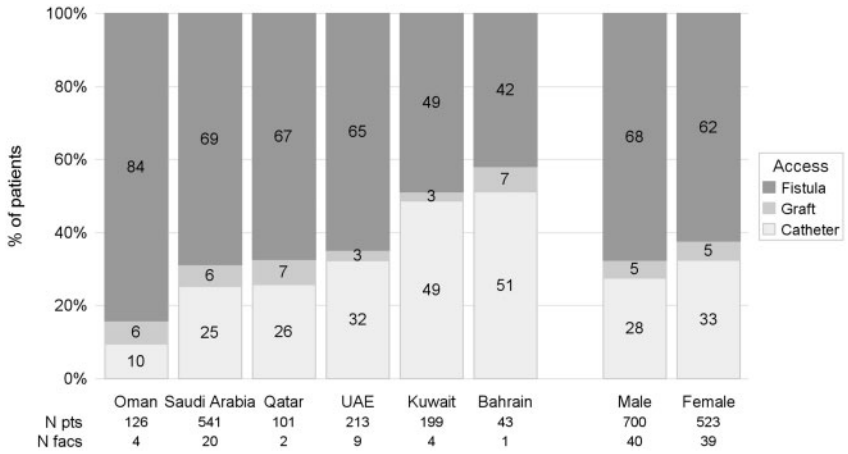

FIGURE 5: Vascular access type in the GCC, by country and sex, combining initial representative samples from DOPPS 5 and 6.

(Figure 6). HDF was used for 80% of patients in Bahrain, 55% of patients in Kuwait, 28% in the UAE, 16% in Oman and 5% in Saudi Arabia, with no use reported in Qatar. Prescribed convective volumes were >20 L for 21% of HDF patients, 15–20 L in 25%, 4–15 L for 32% and <4 L in the remaining 22% of HDF patients. The replacement fluid was postdilutional in 81% of patients. Overall, HDF usage was slightly more common among men (23%) than women (16%). In other analyses (data not shown), the median values for the product of TT and BFR divided by predialysis body weight were lower in nearly all GCC countries than in the majority of other DOPPS countries.

To assess how *Kt/V* achievement differed between males and females, we compared mean *Kt/V* by sex at different levels of three indices of body size: body weight, BMI and BSA

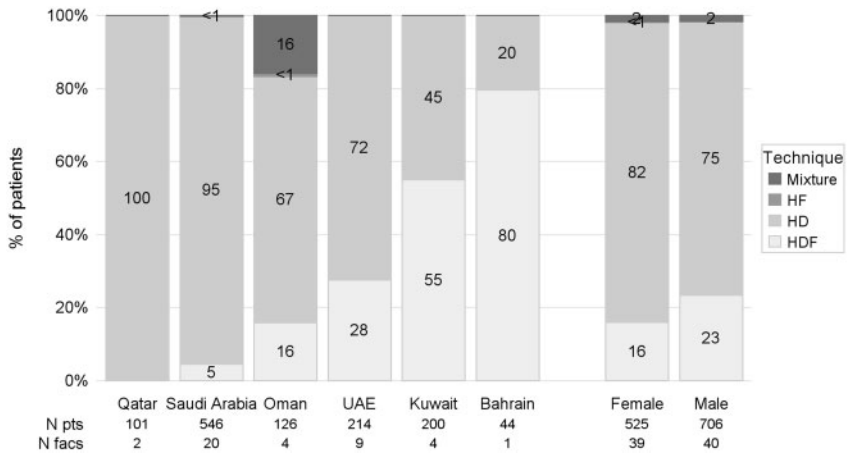

FIGURE 6: Dialysis technique in the GCC, by country and sex, combining initial representative samples from DOPPS 5 and 6. The 'mixture' technique means a patient used HD on some days, and HDF or HF on other days.

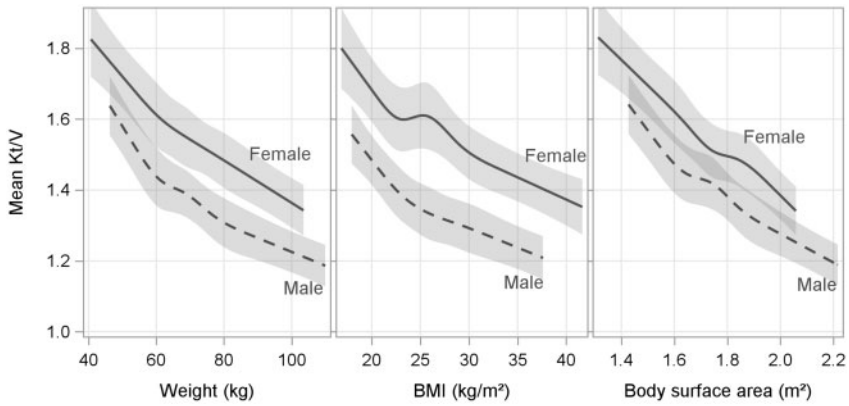

FIGURE 7: Mean *Kt/V* (95% CI) in the GCC, by sex and different measures of body size and shape, with TT = 4 h and BFR = 350 mL/min. The panels show that *Kt/V* tends to be higher for women, even when controlling for TT, BFR and either (i) postdialysis weight, (ii) BMI or (iii) BSA. To create the figure for weight, we modeled *Kt/V* as a function of sex, weight, TT and BFR. We used a cubic spline for weight and included two-way interactions between sex and each of weight, TT and BFR. We fit the model using data from all patients and then used the model to estimate mean *Kt/V* by sex and weight, plugging in TT = 4 and BFR = 350. We then plotted the estimated *Kt/Vs* for weights between the 5th and 95th sex-specific percentiles of weight. We repeated this process for both BMI and BSA in place of weight.

(Figure 7). Mean *Kt/V* tended to be lower for those with larger bodies, and at each indicated level of weight, BMI and BSA, mean *Kt/V* was higher for females than for males. *Kt/V* sex differences were largest when comparing equivalent BMI levels and smallest for equivalent BSA levels.

The overall all-cause mortality rate was 12.8 deaths/100 patient-years (Table 6). A trend toward higher all-cause mortality was seen for patients having a low *Kt/V* [adjusted hazard ratio (HR) 1.32, 95% confidence interval (CI) 0.92–1.89] compared with a *Kt/V* ≥ 1.2 (Table 3). When this relationship was examined separately for males and females, the relationship of mortality with low *Kt/V* was found to be much stronger among females (adjusted HR = 1.91, 95% CI 1.09–3.34) than males (adjusted HR = 1.16, 95% CI 0.70–1.92). In additional models, neither TT nor BFR was significantly associated with mortality, with or without adjustment for *Kt/V*.

In multivariate analyses, higher TT and BFR were both strongly associated with lower odds of low *Kt/V* (Table 4). Patient factors associated with lower odds of low *Kt/V* at the 0.05 significance level were HDF use, female sex, lower weight and height, and lower comorbidity score. The overall prevalence of low *Kt/V* was 34%, with 43% prevalence for low TT (<4 h) and

Table 6. Kt/V and crude mortality in the GCC

Subgroup	Median *Kt/V* (IQR)	Deaths per 100 pt-yrs
All patients	1.35 (1.10–1.61)	12.8
Males	1.29 (1.07–1.54)	13.3
Females	1.42 (1.16–1.68)	12.1

IQR = interquartile range; pt-yrs = patient-years.

80% for low BFR (<350 mL/min). If patients with TT <4 h were raised to TT = 4 h, then the proportion of low *Kt/V* cases would decline by an estimated 30% among these patients (AFE) and by 15% in the whole population (PAF; Table 5). Similarly, if patients with BFR <350 mL/min were raised to BFR = 350 mL/min, the proportion of low *Kt/V* cases would decline by an estimated 33% among these patients and by 29% in the whole population. If both low TT and low BFR could be eliminated by raising these levels to 4 h and 350 mL/min, respectively, then the proportion of low *Kt/V* cases would fall by an estimated 44% among patients with either low TT or BFR and by 41% in the whole population. Subgroup analyses (Table 5 and Supplementary data, Table S1) show how the percentage of low *Kt/V* cases attributed

to these two key treatment practices differed according to the indicated patient subgroups. Notably, among females, 52% of all low *Kt/V* cases were predicted to increase to a *Kt/V* ≥1.2 if both TT and BFR were increased to target levels (PAF), while among males, only 36% of all low *Kt/V* cases would be predicted to increase to a *Kt/V* ≥1.2.

DISCUSSION

Dialysis adequacy measured by single pool *Kt/V* urea [2] is the most frequently applied measure of delivered dialysis dose. Despite its known limitations [3], it is recommended by the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines as a meaningful measure of dialysis effect on patient survival. The KDOQI guidelines recommend a target *Kt/V* of 1.4 per HD session for patients treated thrice weekly, with a minimally adequate delivered dose being a *Kt/V* of 1.2 [4].

Substantially poorer achievement of a minimally adequate *Kt/V* was observed in national samples of HD patients in the GCC compared with those in Europe, Japan, Canada and the USA. Low *Kt/V* (<1.2) was seen for 27% of female HD patients in the GCC compared with 3–7% in the other international regions and for 36% of males compared with 6–19% in other regions. Our results suggest that part of the explanation for this observed higher prevalence of low *Kt/V* in the GCC may be due to the lower HD TTs and BFRs prescribed for GCC HD patients than in other DOPPS countries with patients of comparable body sizes since our attributed fraction analyses predict that a substantial fraction of GCC HD patients would not have low *Kt/V* if TT and BFR levels were increased to levels typically prescribed for HD patients in North America and Western Europe.

Dialysis factors varied widely between GCC countries, in particular, achieved *Kt/V* level, TT, BFR, vascular access type and the use of HDF versus HD. Patient-level analyses indicated not only poorer *Kt/V* achievement among males than females in the GCC but also a strong association of shorter TT, lower BFR, larger body weight and greater comorbidity scores with low *Kt/V*. Other studies have similarly found larger body weight, male sex, shorter TT and lower BFR to be associated with lower dialysis dose [9, 24–26].

Catheter complications can impact mean BFR by reducing achieved *Kt/V* [27]. These often result from a mechanical malfunction (catheter kinking and catheter pushed against the vessel wall) or thrombosis (internal intraluminal thrombosis or external thrombosis, catheter-associated thrombus or a fibrin sheath [28]). However, we did not find a significant association between catheter use and low achieved *Kt/V* in multivariate analyses although a possible trend was observed in this regard.

HDF may not improve survival as compared with high flux HD [29–31] although this issue is still contested [32]. The current recommended convective volume in the postdilutional mode of a thrice-weekly treatment schedule is >23 L/session [32, 33], which is higher than that prescribed for the great majority of GCC patients using HDF in the present study. Yet despite the low convective volumes employed, HDF use was still associated with lower odds of low *Kt/V* (<1.2) in GCC patients. However, because only 21% of HDF patients received convective volumes >20 L, sound conclusions cannot be made regarding the impact of HDF on *Kt/V*. If adequate convective volumes were more common, then the impact of HDF on *Kt/V* may have been even greater.

Our findings indicate that if all patients were prescribed TT ≥4 h and BFR ≥350 mL/min, the overall prevalence of low *Kt/V* would be expected to fall substantially in the GCC—by an estimated 52% among women and 36% among men. We chose these thresholds of TT ≥4 h and BFR ≥350 mL/min as they are already achieved by the majority of patients across DOPPS countries and should thus be achievable in the GCC. As prior studies have shown, increasing TT and BFR can not only increase *Kt/V* [34–37], but longer TT may also positively influence patient survival beyond *Kt/V* achievement [11, 12, 38–40].

The above analyses also suggest that there are additional factors beyond these two HD practices that impact *Kt/V* achievement among GCC HD patients. Dialyzer type can impact achieved dialysis adequacy; thus, a study limitation is that we did not collect information on dialyzer types used in GCC HD units. Data regarding needle size and dialysate flow were also not collected. In addition, some reported *Kt/V* values may reflect incorrect sampling—either pre- or post-HD. For example, drawing pre-HD blood after a few minutes of circulation, or if diluted with saline in the tubing, can result in an inaccurately low pre-HD reading, leading to a very low observed *Kt/V*.

Adjusting for TT and BFR, the estimated mean *Kt/V* was higher for females at any weight, BMI or BSA. These *Kt/V* sex differences were smallest when compared at equivalent BSAs, suggesting that BSA may provide more equivalent representation of dialyzable volume in both female and male HD patients than either BMI or body weight. In Japan, Kimata *et al.* [9] observed similar findings of lower achieved *Kt/V* for male versus female HD patients at the same body weight groupings. We speculate that, at a given BMI or body weight, women may have a smaller dialyzable volume than men due to more of a woman's mass being due to fat, which, largely, is not dialyzable; males tend to have more muscle mass, which is dialyzable. Rescaling the dose of dialysis to BSA has been suggested [41] but this could face challenges [42].

Our all-cause mortality analyses suggested a strong association of low *Kt/V* (<1.2) with poorer survival for GCC females (HR = 1.91, 95% CI 1.09–3.34) but not males (HR = 1.16, 95% CI 0.71–1.92), even with adjustment for numerous patient characteristics. Low *Kt/V* has been strongly associated with higher mortality in numerous studies [8–12]. Although this association has been somewhat stronger for women in prior studies [9, 13, 43–45], low *Kt/V* has been strongly associated with reduced survival even among male HD patients from other international regions. Thus, we were surprised to not see a strong association between low *Kt/V* and mortality among GCC males in the current study. This raises the question of whether there is something different about the GCC HD patient population that may explain this observation, or are there higher competing risks for mortality that diminish the ability to see a meaningful relationship between low *Kt/V* and survival in male HD patients in the GCC? Prior studies have shown TT to be positively associated with survival, independent of achieved *Kt/V* level [10, 12]. However, in this GCC HD patient study sample, we failed to observe a meaningful association between TT or BFR with survival, although this may reflect an insufficient sample size and/or inadequate range in the variability of prescribed TTs and BFRs across GCC HD patients.

Our finding that 27% of female and 36% of male patients had a single pool *Kt/V* <1.2 motivates a call for action to address practices associated with low *Kt/V* achievement across HD units in the GCC. This can be accomplished by (i) implementing long-term quality monitoring and reporting of *Kt/V* achievement, (ii) sharing and communicating best practices across centers and (iii) determining practice changes needed for the greater achievement of an adequate dialysis dose. We recommend levels of *Kt/V* achievement higher than the minimally adequate

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level as improved survival was seen for female HD patients at Kt/V levels beyond 1.2.

A limitation lies in that we cannot conclude causality from our observational study design. Although we adjusted for numerous patient characteristics, residual confounding such as lack of information regarding comorbidity severity could remain, impacting the observed relationships between low Kt/V and mortality and between patient-level factors and Kt/V. Furthermore, for cross-sectional analyses, we cannot conclude the predictor/outcome directionality for the associations of patient-level characteristics with low Kt/V. Data inconsistency may exist in that the reported Kt/V values and laboratory measures needed to calculate single pool Kt/V reflect the practices and sampling approaches of each of the participating dialysis units and were not based upon a standardized protocol or centralized laboratory. Information was not collected on how physicians prescribed dialysis dose for individual patients.

CONCLUSIONS

Mean Kt/V was lower for the patients in the GCC than in all other DOPPS regions, and with males displaying lower mean Kt/V than females in all areas. Low Kt/V appears related in part to short TT and low BFR and may increase mortality rates, especially in females. While increasing TT and BFR is a good first step toward the greater achievement of Kt/V target levels, a call for action is warranted—we must implement long-term quality monitoring directed at improving and increasing awareness of dialysis adequacy for HD patients in the GCC.

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CONFLICT OF INTEREST STATEMENT

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