Renal Replacement Therapy

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Intraabdominal fat-free volume, but not fat volume, predicts the development of peritonitis in patients on peritoneal dialysis: a retrospective cohort study

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Abstract

Introduction Increased intraabdominal fat volume (IAFV) is associated with systemic inflammation and various cardiometabolic diseases. However, the clinical implication of IAFV in patients on peritoneal dialysis (PD) is unclear. In addition, the association of intraabdominal fat-free volume (IAFFV), which could mainly reflect the volume of visceral organs that serve as a potential source of inflammatory uremic toxins, with PD-associated clinical outcomes remains unknown.

Methods We retrospectively measured IAFV and IAFFV in the 108 patients on PD using abdominal computed tomography at initiation of PD. The participants were followed up until PD cessation, death, or study completion. We investigated the relationships between IAFV and IAFFV and the risks of peritonitis and PD discontinuation (defined by a composite endpoint of death or transfer to hemodialysis).

Results The median follow-up period was 46 (interquartile range 24–82) months. The baseline obesity-related traits significantly ($P < 0.05$) differed between high-IAFV (≥ 2935 cm^3) and low-IAFV (< 2935 cm^3) groups. However, the log-rank tests found no differences in the incidence of peritonitis and PD discontinuation between groups. In contrast, both peritonitis-free survival and time on PD therapy were shorter in high-IAFFV (≥ 4796 cm^3) group than in low-IAFFV (< 4796 cm^3) group (all $P < 0.05$). In the Cox regression models, IAFFV remained a strong risk factor for peritonitis even after adjusting for confounders (hazard ratio: 2.16, 95% confidence interval: 1.07–4.38).

Conclusions We demonstrate that IAFFV is an independent risk factor of peritonitis in patients o nPD. Additional studies are needed to identify specific intraabdominal component(s) involved in the pathogenesis of PD-associated adverse events.

Keywords Peritoneal dialysis, Peritonitis, Visceral fat, Obesity, PD discontinuation

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Introduction

Peritoneal dialysis (PD) is a form of renal replacement therapy that provides potential advantage such as better preservation of residual renal function, improved quality of life, and enhanced patient satisfaction compared with hemodialysis (HD) [1, 2]. Nevertheless, PD accounts for only about 10% of the dialysis population worldwide, mainly owing to PD discontinuation [3, 4]. Indeed, it has been reported that approximately 20% of patients on PD switch to HD within 2 years after starting PD [5, 6]. Although the incidence of PD-associated peritonitis has significantly decreased with technical advances in the connection system and improved control of risk factors over the decades, peritonitis still remains the main cause of morbidity, mortality, and PD discontinuation [6, 7]. These observations shed light on the importance of clearly specifying the risk factors associated with peritonitis in patients on PD.

In the general population, obesity, especially visceral obesity, is an important risk factor of cardiometabolic complications, such as type 2 diabetes mellitus (DM), metabolic syndrome, chronic kidney disease (CKD), and cardiovascular disease [8]. However, the effect of obesity on clinical outcomes in patients on PD is unclear because of contradictory results from different studies, which have reported that people with obesity and overweight have better survival rates [9, 10], whereas other studies found that obesity is positively or not associated with increased risk of adverse events such as peritonitis and PD discontinuation [11–14]. The reasons for the differences among studies could be explained by the potential limitations of the body mass index (BMI), which is the most widely used parameter to diagnose obesity but lacks the ability to differentiate intraabdominal fat, a key mediator of systemic inflammation [15], from other fat depots. In addition, data obtained from the recent studies have found that mass of high-metabolic-rate organs, which is calculated by subtracting fat, skeletal muscle, and bone masses from whole-body weight, is correlated with the protein catabolic rate, a surrogate marker of production of uremic toxin involved in systemic inflammation and adverse clinical events [16–19]. It is therefore possible that intraabdominal fat-free volume (IAFFV), which could reflect the volume of visceral organs, may affect the clinical outcomes in patients on PD.

The purpose of the present study is to investigate the associations of intraabdominal fat volume (IAFV), a key indicator of visceral obesity, and IAFFV with clinical outcomes in patients on PD. To this end, we retrospectively measured IAFV and IAFFV by using abdominal computed tomography (CT) and evaluated the relationships between these intraabdominal components and the risks of (i) PD-associated peritonitis and (ii) PD discontinuation (defined by a composite endpoint of death or transfer to HD).

Methods

Study population and design

This is a single-center retrospective cohort study conducted in Keio University Hospital. The study protocol was approved by the Research Ethics Committee of Keio University School of Medicine (approval no. 20221032) and adhered to the principles of the Declaration of Helsinki. We first assessed for the eligibility of 131 patients aged ≥ 18 years who newly initiated PD between 1 January 2011 and 31 March 2020. We then excluded the patients who were transferred to PD from HD ($n=5$), those who had polycystic kidney disease ($n=3$), those with ascites or pleural effusion ($n=14$), and those who did not undergo a CT within 6 months before initiation of PD ($n=1$). Thus, this study included 108 patients (Supplementary Fig. 1).

Follow-up

The study subjects were followed up from the initiation of PD until PD cessation (HD transfer or kidney transplantation), death, or study completion. Our primary and secondary endpoints were time from initiation of PD to diagnosis of PD-associated peritonitis and PD discontinuation, respectively. PD-associated peritonitis was diagnosed when at least two of the following clinical features were present: abdominal pain and/or cloudy dialysis effluent; dialysis effluent white blood cell count > 100/μL or $> 0.1 \times 10^9$ /L, with > 50% polymorphonuclear leukocytes; positive dialysis effluent culture [20]. PD discontinuation was defined by a composite endpoint of death or transfer to HD from PD [21].

Data collection

Demographics, comorbidities, and laboratory data were collected from electronic medical records at the time of initiation of PD. The Charlson comorbidity index (CCI) was calculated on the basis of the clinical parameters as previously described [22]. BMI was calculated as weight (kg)/height^2 (m^2). Estimated glomerular filtration rate (eGFR) was calculated using the serum creatinine concentration by three-variable Japanese equations [23]. The Geriatric Nutritional Risk Index (GNRI) was calculated using BMI and serum albumin measurements.

Intraabdominal fat volume and intraabdominal fat-free volume measurements

The patients underwent multislice helical CT with a 1.25–5.00 mm slice thickness, starting from the upper edge of the liver to the pelvis within 6 months before initiation of PD. All imaging analyses were performed

on a dedicated Advantage Workstation (version 3.2, GE Healthcare). Intraabdominal volume and IAFV were determined using a semi-automated method that required a slice-by-slice manual definition of borders on CT axial images. The intraabdominal area was defined as intraabdominal tissue, and the intraabdominal fat area was defined as intraabdominal tissue with density in the fat attenuation range as we previously described [24, 25]. The fatty tissue was defined between −200 and −40 Hounsfield units. The IAFFV (cm^3) was calculated by subtracting IAFV from intraabdominal volume. Therefore, IAFFV mainly represents the volumes of liver, abdominal gastrointestinal tract, spleen, pancreas, kidney, pelvic organs, and blood vessels.

Statistical analyses

Data are presented as median (25–75th percentiles) for continuous variables and number and percentage for categorical variables. The comparisons between the low- and high-IAFV and IAFFV groups were assessed using the Mann–Whitney test for continuous variables and Fisher's exact test for categorical variables.

Survival curves are plotted using the Kaplan–Meier method and were compared using the log-rank tests. The Cox proportional hazards model was used to calculate a hazard ratio (HR). In the adjusted model 1, age, sex, and BMI were included as independent variables. Model 2 included CCI and urine volume as independent covariates in addition to those included in model 1. Model 3 included plasma brain natriuretic peptide (BNP) concentration, as an indicator of body fluid status, and the presence of constipation, a risk factor for peritonitis [26], and a potential confounder affecting IAFFV, as independent covariates in addition to those included in model 2. For simplicity, the same variables were selected as potential covariates for the multivariate analyses to assess their associations with peritonitis and PD discontinuation-free survival and time on PD therapy. We conducted sensitivity analyses using Gray's test, the Fine–Gray subdistribution hazard model, and propensity score matching. Details are provided in the Supplementary Material.

All statistical analyses were performed using EZR, a graphical user interface for R (version 4.2.2). All significance tests were two-tailed, and $P<0.05$ was considered statistically significant.

Results

Patient characteristics

The baseline clinical characteristics of the 108 patients on PD included in this study are summarized in Supplementary Table 1. The median age was 60 years, and 75.0% were male. Thirty-six percent and 27.8% had DM and CCVD, respectively. The median follow-up period was 46 (interquartile range 24–82) months. During the follow-up period, 48 patients (44.4%) developed PD-associated peritonitis, 68 patients (63.0%) were transferred to HD (46 patients, 42.6%) or died (22 patients, 20.4%), and 6 patients (5.6%) underwent kidney transplantation. Peritonitis, heart failure, inadequate dialysis, and social reason accounted for 45.7%, 19.6%, 13.0%, and 10.9% of HD transfer, respectively.

Associations between IAFV and the risks of peritonitis and PD discontinuation in patients on PD

We first divided the patients into two groups according to the median IAFV value: the low-IAFV group (IAFV < 2935 cm^3, $n=54$) and the high-IAFV group (IAFV ≥ 2935 cm^3, $n=54$) (Table 1). As expected, obesity-related cardiometabolic traits such body weight, BMI, serum triglyceride concentration, total and high-density lipoprotein (HDL) cholesterol concentrations, eGFR, and plasma BNP concentration significantly differed between the two groups (all $P<0.05$). In addition, IAFFV, the proportion of males, serum albumin concentration, and GNRI were higher in the high-IAFV group than in the low-IAFV group (all $P<0.05$).

Twenty-one (38.8%) and 27 (50.0%) patients developed PD-associated peritonitis during the study period in the low-IAFV and high-IAFV groups, respectively. The log-rank tests found no difference in peritonitis-free survival between the two groups (Figs. 1A, B). In addition, 39 (72.2%) and 29 (53.7%) patients were switched to HD or died in the low-IAFV and high-IAFV groups, respectively. We found no difference in time on PD therapy between groups (Figs. 1C, D).

Associations between IAFFV and the risks of peritonitis and PD discontinuation in patients on PD

We next investigated the relationship between IAFFV and the risks of peritonitis and PD discontinuation and categorized the patients into the two groups according to the median IAFFV value: the low-IAFFV group (IAFFV < 4796 cm^3, $n=54$) and the high-IAFFV group (IAFFV ≥ 4796 cm^3, $n=54$) (Table 2). IAFFV, the proportion of males and DM, CCI, systolic blood pressure, body weight, BMI, and serum C-reactive protein (CRP) concentration were significantly higher in the high-IAFFV group than in the low-IAFFV group (all $P<0.05$). Age and serum albumin concentration were significantly lower in the high-IAFFV group than in the low-IAFFV group (all $P<0.05$).

During the follow-up period, PD-associated peritonitis was observed in 19 (35.2%) and 29 (53.7%) patients in the low-IAFFV and high-IAFFV groups, respectively.

Table 1 Comparisons of low-IAFV and high-IAFV patients

Variable	All patients ($n=108$)			Propensity-matched patients ($n=42$)		
	Low-IAFV ($n=54$)	High-IAFV ($n=54$)	*P*	Low-IAFV ($n=21$)	High-IAFV ($n=21$)	*P*
Age (years)	65 [53, 74]	58 [53, 65]	0.07	68 [59, 74]	65 [58, 75]	0.79
Sex (male)	33 (61.1)	48 (88.9)	< 0.01	17 (81.0)	17 (81.0)	> 0.99
APD/CAPD (at the commencement of PD)	0/54 (0/100)	0/54 (0/100)	> 0.99	0/21 (0/100)	0/21 (0/100)	> 0.99
Diabetes mellitus	15 (27.8)	24 (44.4)	0.10	9 (42.9)	10 (47.6)	> 0.99
Cerebrocardiovascular disease	14 (25.9)	16 (29.6)	0.83	7 (33.3)	6 (28.6)	> 0.99
Antihypertensive drugs						
ACEi/ARB	32 (59.3)	41 (75.9)	0.09	14 (66.7)	12 (57.1)	0.75
Calcium channel blocker	50 (92.6)	47 (87.0)	0.52	17 (81.0)	18 (85.7)	> 0.99
Mineralocorticoid receptor antagonist	1 (1.9)	0 (0.0)	> 0.99	0 (0.0)	0 (0.0)	> 0.99
β-Blocker	9 (16.7)	16 (29.6)	0.17	5 (23.8)	6 (28.6)	> 0.99
α-Blocker	4 (7.4)	8 (14.8)	0.35	1 (4.8)	2 (9.5)	> 0.99
Loop diuretics	22 (40.7)	23 (42.6)	> 0.99	9 (42.9)	8 (38.1)	> 0.99
Thiazide diuretics	0 (0.0)	4 (7.4)	0.11	0 (0.0)	1 (4.8)	> 0.99
Constipation	22 (40.7)	20 (37.0)	0.84	8 (38.1)	7 (33.3)	> 0.99
Laxatives	9 (16.7)	8 (14.8)	> 0.99	4 (19.0)	5 (23.8)	> 0.99
Histamine-2 receptor antagonist	0 (0)	0 (0)	> 0.99	0 (0)	0 (0)	> 0.99
Proton pump inhibitor	15 (27.8)	11 (20.4)	0.50	5 (23.8)	5 (23.8)	> 0.99
Intraabdominal fat volume (cm^3)	1502 [1146, 2221]	4470 [3720, 5261]	< 0.01	1450 [1186, 1970]	4061 [3687, 4610]	< 0.01
Intraabdominal fat-free volume (cm^3)	4607 [3977, 5281]	4908 [4447, 5984]	0.03	4818 [4001, 5291]	4790 [4112, 5801]	0.64
Charlson comorbidity index	3.0 [2.0, 4.0]	3.5 [2.0, 4.0]	0.23	3.0 [3.0, 4.0]	4.0 [2.0, 4.0]	0.71
Systolic blood pressure (mmHg)	133 [124, 150]	139 [127, 155]	0.28	135 [124, 151]	141 [126, 164]	0.15
Diastolic blood pressure (mmHg)	79 [67, 84]	81 [75, 90]	0.06	79 [70, 83]	84 [75, 95]	0.17
Body weight (kg)	55.5 [46.8, 66.1]	71.1 [62.9, 82.3]	< 0.01	60.1 [55.0, 68.2]	61.3 [58.9, 67.4]	0.33
Body mass index (kg/m^2)	21.5 [19.5, 23.9]	26.2 [23.3, 28.1]	< 0.01	23.4 [21.4, 26.4]	23.7 [22.7, 26.3]	0.58
Serum albumin (g/dL)	3.50 [3.10, 3.70]	3.70 [3.30, 3.98]	0.01	3.50 [3.20, 3.80]	3.40 [3.20, 3.80]	0.80
Serum urea nitrogen (mg/dL)	77.8 [62.2, 88.9]	74.8 [61.5, 88.2]	0.49	81.4 [63.2, 88.7]	79.9 [59.9, 92.2]	0.81
Serum creatinine (mg/dL)	8.96 [8.13, 9.86]	8.38 [7.53, 9.41]	0.17	8.38 [8.20, 9.32]	8.80 [7.92, 9.44]	0.82
eGFR ($mL/min/1.73m^2$)	4.98 [4.16, 5.66]	5.81 [4.91, 6.74]	< 0.01	5.47 [4.91, 5.88]	5.18 [4.03, 5.92]	0.57
Urine volume (mL/day)	1300 [900, 1500]	1450 [1050, 1750]	0.09	1200 [900, 1500]	1150 [600, 1637]	0.88
Serum calcium (mg/dL)	8.65 [7.82, 9.17]	8.10 [7.32, 9.00]	0.15	8.50 [7.20, 9.00]	8.40 [7.20, 9.50]	0.68
Serum phosphorus (mg/dL)	5.70 [5.03, 6.68]	5.85 [4.88, 6.77]	0.98	5.60 [5.20, 6.60]	6.10 [5.10, 6.90]	0.74
Serum intact parathyroid hormone (pg/mL)	331 [166, 495]	388 [293, 521]	0.11	330 [244, 557]	410 [228, 500]	0.90
Serum triglycerides (mg/dL)	93 [69, 133]	148 [100, 200]	< 0.01	87 [69, 115]	168 [117, 205]	< 0.01
Serum total cholesterol (mg/dL)	188 [162, 232]	173 [140, 186]	0.04	175 [152, 194]	184 [173, 209]	0.38
Serum LDL cholesterol (mg/dL)	90 [76, 111]	87 [71, 103]	0.31	86 [76, 114]	90 [79, 108]	0.82
Serum HDL cholesterol (mg/dL)	48 [38, 60]	37 [31, 45]	< 0.01	52 [40, 65]	38 [31, 46]	0.01
Casual plasma glucose (mg/dL)	99 [92, 118]	113 [96, 138]	0.09	98[92, 125]	114 [101, 138]	0.16
HbA1c (%)	5.40 [5.10, 5.70]	5.50 [5.07, 6.10]	0.21	5.50 [5.10, 5.90]	5.40 [5.20, 6.10]	0.75
Serum C-reactive protein (mg/dL)	0.05 [0.02, 0.20]	0.08 [0.03, 0.18]	0.36	0.05 [0.02, 0.13]	0.13 [0.03, 0.31]	0.24
Plasma brain natriuretic peptide (pg/mL)	150 [62, 290]	82 [30, 173]	< 0.01	185 [90, 413]	133 [43, 233]	0.33
Geriatric nutritional risk index	92.5 [87.2, 98.1]	103.3 [97.6, 108.8]	< 0.01	94.7 [92.5, 102.9]	97.8 [94.0, 100.9]	0.87

IAFV intraabdominal fat volume, *APD* automated peritoneal dialysis, *CAPD* continuous ambulatory peritoneal dialysis, *ACEi/ARB* angiotensin covering enzyme inhibitor/angiotensin II receptor blocker, *eGFR* estimated glomerular filtration rate, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *P* (*P*) value was obtained using the Mann–Whitney *U* test

Peritonitis-free survival was significantly lower in the high-IAFFV group than in the low-IAFFV group (36 versus 141 months; $P<0.01$) (Fig. 2A). The cumulative incidence of PD-associated peritonitis was significantly higher in the high-IAFFV group than in low-IAFFV group ($P<0.01$, Gray's test). Data obtained from the Cox

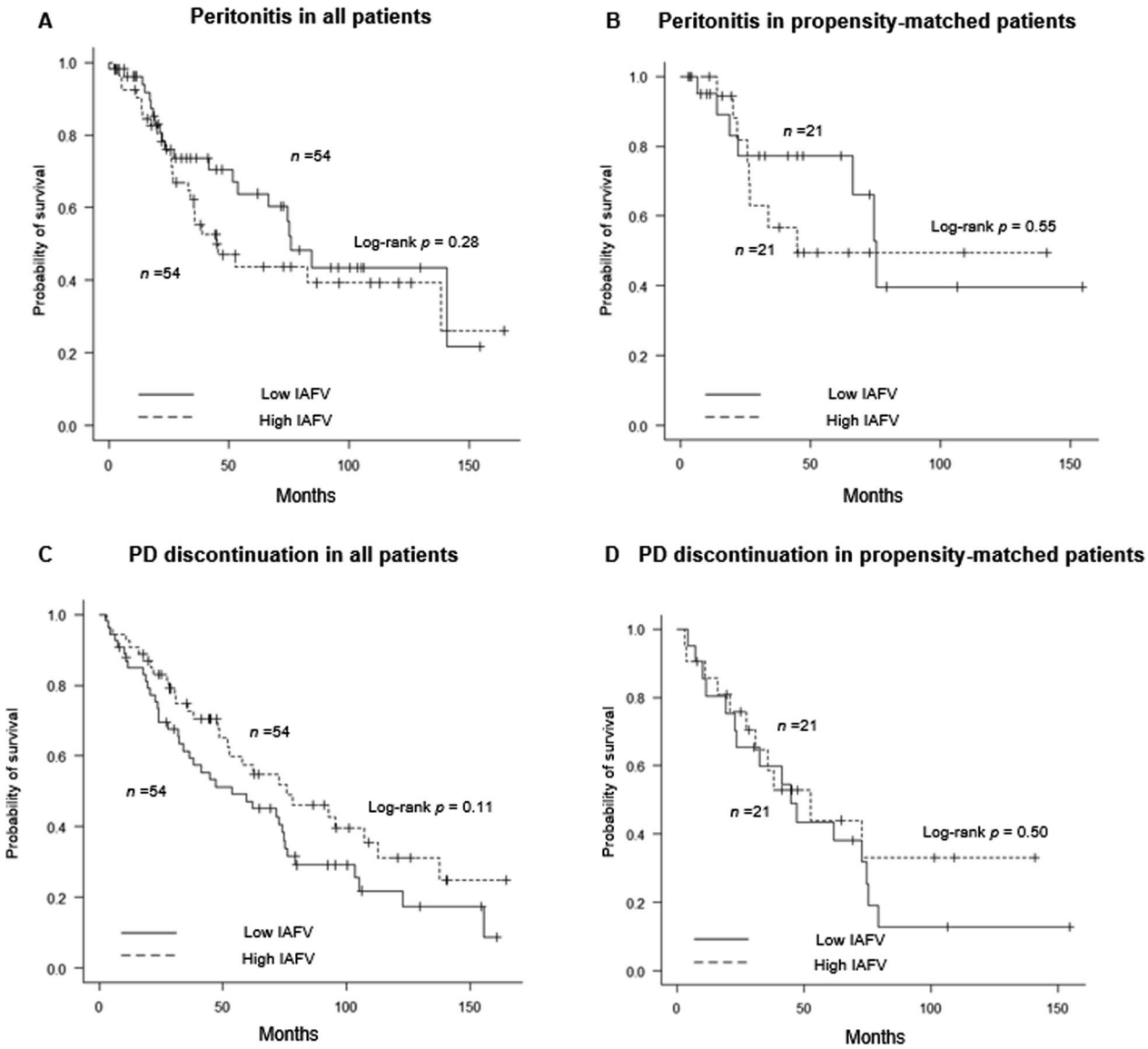

Fig. 1 Kaplan–Meier curves of peritonitis-free survival and time on PD therapy according to the intraabdominal fat volume (IAFV) categories. Peritonitis-free survival in all patients (**A**) ($n=54$ per group) and propensity-matched patients (**B**) ($n=21$ per group). Time on PD therapy in all patients (**C**) ($n=54$ per group) and propensity-matched patients (**D**) ($n=21$ per group)

hazard regression models found that, even after adjusting for multiple confounding covariates including age, sex, BMI, CCI, urine volume, plasma BNP concentration, and presence of constipation [26–29], IAFFV remained significantly correlated with an increased risk of PD-associated peritonitis (model 3; HR: 2.16, 95% confidence interval [CI]: 1.07–4.38) (Table 3). The subdistribution hazard regression models revealed a similar result (model 3; HR: 1.91, 95%CI: 1.02–3.58). After a 1:1 propensity score matching (Table 2), peritonitis-free survival was still significantly lower in the high-IAFFV group than in the low-IAFFV group (36 versus not reached months, respectively; $P=0.01$) (Fig. 2B).

Thirty-three (61.1%) and 35 (64.8%) patients encountered PD discontinuation in the low-IAFFV and high-IAFFV groups, respectively. Time on PD therapy was significantly shorter in the high-IAFFV group than in the low-IAFFV group (49 versus 76 months; $P=0.01$) (Fig. 2C). The cumulative incidence of PD discontinuation was higher in the high-IAFFV group compared with the low-IAFFV group, although the difference was not statistically significant ($P=0.06$, Gray's test). In the Cox hazard regression models, the difference remained

Table 2 Comparisons of low-IAFFV and high-IAFFV patients

Variable	All patients ($n=108$)			Propensity-matched patients ($n=46$)		
	Low-IAFFV ($n=54$)	High-IAFFV ($n=54$)	*P*	Low-IAFFV ($n=23$)	High-IAFFV ($n=23$)	*P*
Age (years)	65 [55, 71]	56 [49, 65]	0.01	60 [54, 70]	61 [52, 74]	0.95
Sex (male)	34 (63.0)	47 (87.0)	< 0.01	17 (73.9)	19 (82.6)	0.72
APD/CAPD (at the commencement of PD)	0/54 (0/100)	0/54 (0/100)	> 0.99	0/23 (0/100)	0/23 (0/100)	> 0.99
Diabetes mellitus	9 (16.7)	30 (55.6)	< 0.01	7 (30.4)	6 (26.1)	> 0.99
Cerebrocardiovascular disease	16 (29.6)	14 (25.9)	0.83	4 (17.4)	5 (21.7)	> 0.99
Antihypertensive drugs						
ACEi/ARB	34 (63.0)	39 (72.2)	0.41	15 (65.2)	15 (65.2)	> 0.99
Calcium channel blocker	47 (87.0)	50 (92.6)	0.52	19 (82.6)	21 (91.3)	0.66
Mineralocorticoid receptor antagonist	0 (0.0)	1 (1.9)	> 0.99	0 (0.0)	1 (4.3)	> 0.99
β-Blocker	14 (25.9)	11 (20.4)	0.64	7 (30.4)	4 (17.4)	0.49
α-Blocker	5 (9.3)	7 (13.0)	0.76	3 (13.0)	2 (8.7)	> 0.99
Loop diuretics	17 (31.5)	28 (51.9)	0.05	7 (30.4)	8 (34.8)	> 0.99
Thiazide diuretics	1 (1.9)	3 (5.6)	0.61	0 (0.0)	0 (0.0)	> 0.99
Constipation	18 (33.3)	24 (44.4)	0.32	7 (30.4)	12 (52.2)	0.23
Laxatives	8 (14.8)	9 (16.7)	> 0.99	3 (13.0)	4 (17.4)	> 0.99
Histamine-2 receptor antagonist	0 (0)	0 (0)	> 0.99	0 (0)	0 (0)	> 0.99
Proton pump inhibitor	14 (25.9)	12 (22.2)	0.82	6 (26.1)	5 (21.7)	> 0.99
Intraabdominal fat volume (cm^3)	2598 [1614, 4033]	3246 [1357, 4599]	0.29	3400 [2282, 4364]	2953 [1180, 4247]	0.43
Intraabdominal fat-free volume (cm^3)	4169 [3629, 4529]	5727 [5200, 6353]	< 0.01	4353 [4126, 4523]	5453 [5124, 6014]	< 0.01
Charlson comorbidity index	3.0 [2.0, 3.0]	4.0 [2.3, 4.0]	< 0.01	2.0 [2.0, 4.0]	3.0 [2.0, 3.5]	0.91
Systolic blood pressure (mmHg)	130 [122, 145]	141 [132, 156]	0.01	133 [127, 155]	139 [132, 149]	0.62
Diastolic blood pressure (mmHg)	80 [71, 84]	80 [73, 90]	0.31	84 [78, 89]	77 [73, 88]	0.19
Body weight (kg)	57.0 [50.7, 64.3]	71.0 [61.1, 82.5]	< 0.01	61.0 [54.3, 66.9]	63.4 [55.5, 71.9]	0.36
Body mass index (kg/m^2)	22.6 [20.2, 23.9]	26.2 [22.9, 29.4]	< 0.01	23.2 [21.3, 24.7]	23.3 [20.3, 26.2]	0.90
Serum albumin (g/dL)	3.60 [3.40, 3.88]	3.35 [3.02, 3.77]	< 0.01	3.50 [3.30, 3.80]	3.70 [3.20, 3.85]	0.80
Serum urea nitrogen (mg/dL)	73.2 [60.7, 88.5]	77.2 [64.8, 89.2]	0.58	78.4 [63.2, 87.7]	75.2 [65.0, 87.1]	0.93
Serum creatinine (mg/dL)	8.38 [6.99, 9.44]	8.80 [7.83, 9.99]	0.09	8.60 [7.88, 9.98]	8.80 [7.58, 9.95]	0.89
eGFR ($mL/min/1.73m^2$)	5.39 [4.17, 6.02]	5.35 [4.79, 6.19]	0.51	4.95 [3.92, 6.16]	5.25 [4.79, 5.99]	0.46
Urine volume (mL/day)	1300 [900, 1500]	1400 [1000, 1750]	0.08	1350 [1025, 1680]	1300 [900, 1700]	0.76
Serum calcium (mg/dL)	8.50 [7.50, 9.10]	8.30 [7.61, 9.07]	0.77	8.10 [7.30, 8.95]	8.30 [7.75, 9.20]	0.60
Serum phosphorus (mg/dL)	5.70 [4.80, 6.68]	5.90 [5.10, 6.85]	0.46	5.90 [4.90, 6.85]	5.30 [4.95, 6.30]	0.25
Serum intact parathyroid hormone (pg/mL)	348 [205, 546]	388 [226, 500]	0.79	384 [299, 574]	434 [188, 597]	0.53
Serum triglycerides (mg/dL)	140 [83, 182]	115 [83, 148]	0.23	150 [87, 191]	91 [80, 156]	0.20
Serum total cholesterol (mg/dL)	178 [152, 209]	173 [141, 225]	0.75	175 [159, 201]	186 [170, 217]	0.52
Serum LDL cholesterol (mg/dL)	90 [80, 103]	82 [71, 114]	0.42	97 [83, 102]	88 [76, 109]	0.62
Serum HDL cholesterol (mg/dL)	42 [36, 54]	40 [32, 53]	0.60	40 [34, 46]	41 [34, 54]	0.69
Casual plasma glucose (mg/dL)	101 [94, 121]	105 [92, 139]	0.97	98 [92, 118]	98 [87, 108]	0.29
HbA1c (%)	5.40 [5.00, 5.70]	5.50 [5.10, 6.15]	0.12	5.40 [5.00, 6.00]	5.40 [5.10, 6.00]	0.89
Serum C-reactive protein (mg/dL)	0.05 [0.02, 0.13]	0.10 [0.03, 0.36]	0.04	0.05 [0.03, 0.12]	0.10 [0.02, 0.29]	0.61
Plasma brain natriuretic peptide (pg/mL)	99 [44, 202]	120 [44, 215]	0.69	91 [32, 193]	136 [37, 307]	0.48
Geriatric nutritional risk index	96.2 [91, 103]	100.6 [92.2, 104.9]	0.15	94.0 [89.1, 103.4]	99.2 [88.1, 104.1]	0.75

IAFFV intraabdominal fat-free volume, *APD* automated peritoneal dialysis, *CAPD* continuous ambulatory peritoneal dialysis, *ACEi/ARB* angiotensin covering enzyme inhibitor/angiotensin II receptor blocker, *eGFR* estimated glomerular filtration rate, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *P* (*P*) value was obtained using the Mann–Whitney *U* test

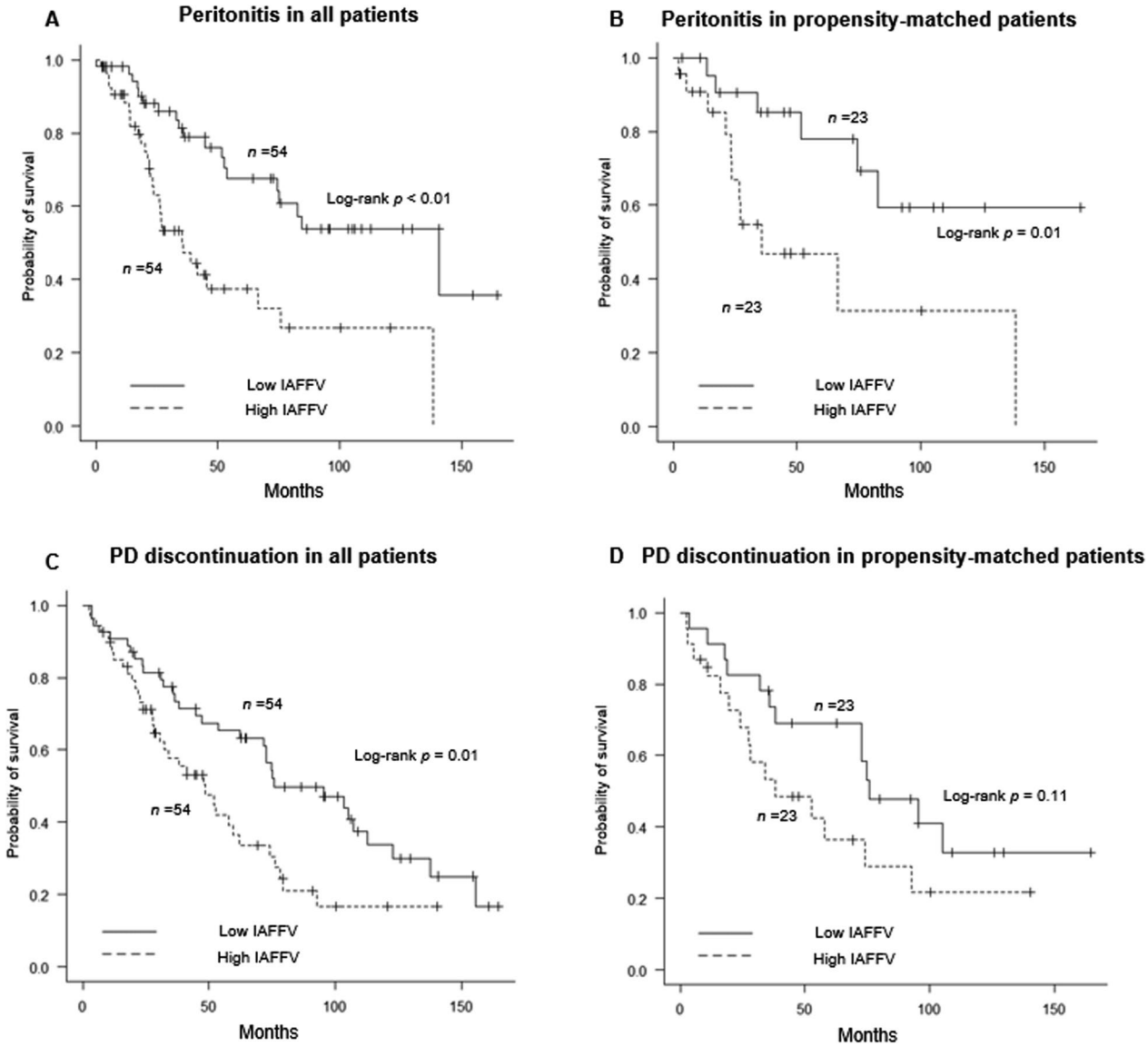

Fig. 2 Kaplan–Meier curves of peritonitis-free survival and time on PD therapy according to the intraabdominal fat-free volume (IAFFV) categories. Peritonitis-free survival in all patients (**A**) ($n=54$ per group) and propensity-matched patients (**B**) ($n=23$ per group). Time on PD therapy in all patients (**C**) ($n=54$ per group) and propensity-matched patients (**D**) ($n=23$ per group)

significant after adjustment of age, sex, and BMI (model 1; HR: 1.84, 95% CI: 1.12–3.01) (Table 3). The subdistribution hazard regression models found a similar result (model 1; HR: 1.84, 95% CI: 1.12–3.01). These differences became insignificant after adjustment of additional covariates such as urine volume and plasma BNP concentration (models 2 and 3). Time on PD therapy tended to be shorter in the high-IAFFV group than in the low-IAFFV group after propensity score matching ($P=0.11$) (Fig. 2D). In addition, we separately analyzed the associations between IAFFV and the outcomes of death and HD transfer.

IAFFV was not significantly associated with the outcome of death in either the log-rank test or the Cox proportional hazards model (all $P>0.05$) (Supplementary Fig. 2A). Although IAFFV showed a significant association with HD transfer outcome in the log-rank test ($P=0.01$) (Supplementary Fig. 2B), this association did not remain significant after adjustment in the multivariable Cox regression in model 3 ($P=0.32$), indicating that IAFFV may be associated with PD discontinuation due to HD transfer rather than death.

Table 3 Associations between intraabdominal fat-free volume and the risks of peritonitis and PD discontinuation using standard Cox regression model and Fine and Gray subdistribution hazards model

	Peritonitis		PD discontinuation	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Cause-specific hazards				
Crude	2.85 (1.56–5.22)	< 0.01	1.85 (1.13–3.02)	0.01
Model 1	2.53 (1.31–4.86)	< 0.01	2.06 (1.21–3.53)	< 0.01
Model 2	2.18 (1.11–4.27)	0.02	1.65 (0.94–2.90)	0.07
Model 3	2.16 (1.07–4.38)	0.03	1.65 (0.93–2.92)	0.08
Subdistribution hazards				
Crude	2.25 (1.29–3.95)	< 0.01	1.51 (0.93–2.42)	0.09
Model 1	2.28 (1.26–4.14)	< 0.01	1.84 (1.12–3.01)	0.01
Model 2	1.97 (1.10–3.55)	0.02	1.47 (0.88–2.46)	0.14
Model 3	1.91 (1.02–3.58)	0.04	1.42 (0.85–2.36)	0.18

Model 1 adjusted for age, sex, and BMI. Model 2 adjusted for the same variables as model 1 in addition to CCI and urine volume. Model 3 adjusted for the same variables as model 2 in addition to BNP and presence of constipation

IAFFV intraabdominal fat-free volume, *HR* hazard ratio, *CI* confidence interval, *BMI* body mass index, *CCI* Charlson comorbidity index, *BNP* brain natriuretic peptide

Discussion

The present study revealed the robust relationship between IAFFV and the increased risk of peritonitis in patients on PD even after adjusting for key potential confounders. The mechanisms underlying the observed relationship remain unclear, but could involve the overproduction of uremic toxins produced by high-metabolic-rate organs [16–19]. Data obtained from the studies conducted in chronic HD patients found the protein catabolic rate, calculated from urea kinetics models, strongly correlates with mass of high-metabolic-rate organs, indicating that uremic toxins are generated mainly from visceral organs such as liver and gut [16]. In addition, mounting evidence suggests that excess uremic toxins could induce chronic systemic inflammation by affecting immune cells and gut microbiome [30, 31]. Consistent with these findings, we found that the baseline serum CRP concentration was higher in the high-IAFFV group than in the low-IAFFV group. It was also reported that high serum CRP concentration predicts peritonitis risk in patients on PD [32, 33]. Given that patients on PD with high IAFFV tended to increase the incidence of PD discontinuation compare with those with low-IAFFV in this study, these findings indicate that IAFFV, which could reflect the volume of visceral organs, likely represents the mass of key uremiogenic visceral organ(s), and overproduction of uremic toxins and subsequent chronic inflammation may contribute to the development of PD-associated peritonitis and PD discontinuation.

Data obtained from previous studies demonstrate the importance of excess intraabdominal fat accumulation as a key inflammatory mediator of cardiometabolic diseases [15]. In contrast, we found that, although IAFV significantly correlated with obesity-related cardiometabolic traits at baseline, it did not predict the development of peritonitis or PD discontinuation in patients on PD. These findings are consistent with the results from previous studies that have shown that excess accumulation of intraabdominal fat is not associated with survival in patients on PD [34, 35], although conflicting results were also reported [36]. Nevertheless, we cannot exclude the possibility that IAFV is involved in high risk of cardiovascular complications not tested in this study. Indeed, recent studies suggest that visceral obesity is a risk factor of carotid atherosclerosis and endothelial dysfunction in patients on PD [37–39]. It is also possible that specific-intraabdominal fat depot(s), such as omental fat, mesenteric fat, and perirenal fat, are correlated with poor PD outcomes. Additional studies are required to precisely understand the pathogenic roles of visceral obesity in patients on PD.

The present study has several limitations. First, this was a retrospective observational cohort study, and thus we were unable to determine the causality between the outcomes. Second, the study was conducted at a single center with relatively small sample sizes and short follow-up periods, which could limit generalizability and statistical power. Third, we did not evaluate the known cardiovascular risk factors associated with both PD and visceral obesity, such as endothelial dysfunction, vascular calcification, and serum vitamin D concentration [37–40]. Fourth, although we used urine output as an indicator of residual renal function, we were unable to include other key parameters in multivariate analyses, such as Kt/V and serum β_2-microglobulin, owing to missing data. Fifth, gastrointestinal tract volume could vary depending on luminal contents, fecal matter, and intraluminal air, and kidney volume and bladder volume could be affected by cyst formation and urinary retention, respectively, all of which potentially confound the study outcomes. Finally, the study did not measure the volume(s) of specific visceral organ(s) or other body composition components including skeletal muscle mass and fluid volume. This issue is particularly relevant in patients on PD because previous studies have demonstrated the dynamic alterations in body composition, including overhydration, muscle wasting, and fat gain, after PD initiation [41, 42].

In summary, the results from our study demonstrate that IAFFV at the initiation of PD is an independent risk factor of peritonitis in patients on PD. Additional studies are needed to identify specific intraabdominal component(s) involved in the pathogenesis of PD-associated adverse events.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41100-025-00651-6.

Additional file 1.

Acknowledgements
The authors are grateful to the study participants for their participation. We also thank members in the Yoshino lab for critical discussions and suggestions.

Author contributions
J.Y. conceptualized and designed the project. R.M., K.M., K.K., D.K., T.N., T.N., E.Y., S.T., Y.Y., and J.Y. analyzed the data. R.M., M.J., K.U., N.W., T.K., T.A., T.Y., K.H., and J.Y. provided critical intellectual input for the data interpretation and contributed to discussion. All authors reviewed and approved the manuscript.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials
No datasets were generated or analyzed during the current study.

Declarations

Ethics approval
This study protocol was approved by the Research Ethics Committee of Keio University, School of Medicine (approval no. 20221032).

Consent to participate
Informed consent was obtained by the opt-out method.

Competing interests
The authors declare no competing interests.

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Received: 12 March 2025 Accepted: 10 June 2025
Published online: 29 June 2025

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