

RESEARCH ARTICLE

Interaction between central obesity and frailty on the clinical outcome of peritoneal dialysis patients

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Abstract

Background

Frailty and obesity contribute to the adverse clinical outcome of peritoneal dialysis (PD) patients, but the interaction between frailty and obesity remains uncertain.

Objective

To examine the interaction between frailty and obesity on the clinical outcome of PD patients.

Design

Single centre prospective observational cohort study.

Patients

267 prevalent Chinese PD patients were recruited.

Measurements

Frailty was identified by a standard score. General and central obesity were determined by body mass index (BMI) and waist-hip ratio (WHR), respectively. Body composition was assessed by bioimpedance spectroscopy. All patients were followed for two years. Outcome measures included all-cause as well as cardiovascular mortality and hospitalization.

Results

Of the 267 patients, 120 (44.9%) were frail. Frail individuals were more likely to have central obesity ($p < 0.001$) but not general obesity. Although WHR did not predict patient survival, there was a significant interaction between WHR and frailty on patient survival and cardiovascular survival ($p = 0.002$ and $p = 0.038$, respectively). For patients without frailty, the two-year cardiovascular survival was 91.3% and 74.4% for those with and without central

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obesity, respectively ($p = 0.002$). For patients with frailty, however, the two-year cardiovascular survival was 64.6% and 66.7% for those with and without central obesity, respectively ($p = 0.6$). For patients without frailty, the number of hospital admission for cardiovascular disease over 2 years were 0.12 ± 0.37 and 0.34 ± 0.72 for those with and without central obesity, respectively ($p = 0.03$). For frail patients, however, the number of hospital admission was similar between those with and without central obesity.

Conclusion

There is a significant interaction between frailty and central obesity on the outcome of PD patients. The protective role of central obesity is only apparent in PD patients without frailty but not the frail ones, and there is a little prognostic value of general (non-central) obesity.

Introduction

Background

Frailty is described by Fried et al. [1] as a clinical syndrome involving at least three of the following features: unintentional weight loss (10 lbs in one year), self-reported exhaustion, weakness (as determined by grip strength), slow walking speed, and low physical activity. It is highly prevalent among patients on dialysis, with a prevalence of up to 67.7% in previous report [2].

Physical frailty has important health consequences. Frail patients are more susceptible to the development of adverse outcomes when faced with a stressor. It also leads to a decline in physical function, gait disability, increase in the risks of fall. As a result, frail peritoneal dialysis (PD) patients have a higher hospitalization risk and their hospital stay tends to be prolonged [3]. Physical frailty is also a well-established independent predictor of adverse outcomes including mortality in pre-dialysis end stage renal disease patients [4], hemodialysis (HD) patients and PD patients [3, 5].

Physical frailty causes alteration in body composition. Frail patients tend to suffer from obesity [6–9]. On the other hand, PD patients are more susceptible to central obesity [10] due to exposure to glucose-containing dialysate fluid. In contrast to general obesity, central obesity confers a worse survival in dialysis patients [11]. Previous study has shown synergistic effect on mortality between physical frailty and central obesity in HD patients. However, the interaction between physical frailty and body composition has not been explored.

Objectives

The goal of this study of was to dissect the internal relationship between obesity and frailty on the outcome of PD patients.

Methods

Study design

This is a single centre prospective cohort study. The study was approved by the Joint Chinese University of Hong Kong—New Territories East Cluster Clinical Research Ethics Committee. All study procedures were in compliance with the Declaration of Helsinki. All patients provided a written informed consent before enrollment in the study.

Study population

We recruited 267 prevalent PD patients from a single dialysis unit from 1 January 2015 to 31 December 2016. Patients with expected survival of less than 3 months, or those who were planned to receive kidney transplantation in 3 months, were excluded.

After written informed consent, assessments of frailty, anthropometry, body composition and pulse wave velocity were measured at baseline. Other clinical and laboratory data were obtained by chart review. Clinical data comprises of patient's age, gender, body weight, height, primary diagnosis of renal disease, concomitant chronic medical illnesses including diabetes mellitus, ischemic heart disease, cerebrovascular accident, peripheral vascular disease, chronic hepatitis B and C infection, chronic lung disease, malignancy and immunological diseases. Laboratory assessment included serum albumin level, serum cholesterol (including total cholesterol, high density cholesterol, low density cholesterol) level, dialysis adequacy by Kt/V, residual renal function by measuring the residual glomerular filtration rate from urine. The Charlson Comorbidity Index (CCI) was used to assess the comorbidity load. The Comprehensive Malnutrition Inflammation Score (MIS) [12] and Subjective Global Assessment (SGA) [13] were used to assess nutritional state.

Assessment of frailty

We used a validated Chinese questionnaire that consisted of 30 yes/no questions [3]. The questions involve assessment of subjective assessment of personal health, psychological state, physical state in terms of number of hospital or doctor visit and medication needs to be taken, body weight, need of assistance in different aspects of daily living and mobility. A total score was calculated; physical frailty was defined as a score of 6 or above [3]. To ensure patient adequate understanding on the 30 questions, all the recruited subjects were directly interviewed by designated well-trained interviewers at baseline.

Anthropometric and body composition assessment

Anthropometric data were measured at recruitment. Body mass index (BMI) was used to assess general adiposity; general obesity was defined as BMI more than or equals 30 kg/m^2 respectively according to the definition from World Health Organisation (WHO). Waist hip ratio (WHR), as defined by the ratio between waist circumference to hip circumference, was used to assess central adiposity. Waist circumference was measured at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest, while the hip circumference was measured around the widest portion of the buttocks. Central obesity was defined as WHR more than or equals sex-specific sample median (females 0.92, males 0.98).

We used the multi-frequency bioimpedance spectroscopy device (Body Composition Monitor [BCM], Fresenius Medical Care, Germany), which was validated in dialysis patients [14, 15]. Briefly, electrodes were attached to one hand and one foot with the patient in a supine position. The following parameters were computed: extracellular water (ECW), lean tissue mass (LTM), adipose tissue mass (ATM), and volume of overhydration (OH).

Anthropometric and body composition assessments were performed with empty abdomen (before infusion of dialysate) by the same trained research nurse with at the time of recruitment.

Pulse wave velocity

Pulse wave velocity (PWV) is a simple, non-invasive technique of assessing arterial stiffness. High levels of PWV analysis are indicative of increased rigidity and low distensibility of

vascular walls, along with poor vascular function [16]. PWV was measured by Vicorder device (SMT Medical GmbH&Co.), an automatic computerised recorder. The results were analyzed by the Complior Analyse program (Artech Medical, Pantin, France). Pressure-sensitive transducers will be placed over neck (carotid artery), wrist (radial artery), and groin (femoral artery), with the patient in the supine position. PWV of the carotid-femoral (CF-PWV) and carotid-radial (CR-PWV) territories will be calculated by dividing the distance between the sensors by the time corresponding to the period separating the start of the rising phase of the carotid pulse wave and that of the femoral and also the radial pulse waves. Measurements were performed at the beginning of study, and 1 year after recruitment.

Outcome measures

All patients were followed for 2 years. Primary outcome measures were all-cause mortality and cardiovascular mortality. Secondary outcome measures were number of all-cause hospital admission, number of cardiovascular event-related hospitalization, and total length of hospital stay within study period. Cardiovascular mortality is defined by death due to peripheral vascular disease, myocardial infarction, heart failure, stroke and sudden cardiac death. In this analysis, receiving kidney transplantation, transferal to hemodialysis, transferal to another center and death from non-cardiovascular causes were considered as competing events.

Statistical analysis

Statistical analysis was performed by SPSS for Windows software version 24 (SPSS Inc., Chicago). Descriptive data were presented as mean \pm SD if normally distributed, or median (inter-quartile range) otherwise. Patients were grouped according to presence of physical frailty as defined above for analysis. Clinical parameters were compared by Student's t-test or one way analysis of variance (ANOVA) for continuous variables, and Chi-square test for categorical variables. $P < 0.05$ was considered to be statistically significant in this study. All probabilities were two-tailed.

The number and duration of hospitalization were compared between non-frail and frail individuals. Age, dialysis vintage, Charlson Comorbidity Index, serum albumin, total Kt/V, normalised protein nitrogen appearance (NPNA) and residual glomerular filtration rate (GFR), which were potential confounding factors shown in previous studies [3, 17, 18], were added to linear regression model for adjustment. Backward stepwise elimination was used to determine the independent predictor of hospitalization.

Kaplan Meier plots were constructed for patient and cardiovascular survival rates. Log-rank test was used to compare between survival curves. Receiving kidney transplantation, transferal to hemodialysis, and transferal to another center were considered as competing events. Multivariate Cox regression models were constructed to further identify independent predictors of survival after adjustment of potential confounders with P values below 0.1 with univariate analysis. Backward stepwise analysis was used to remove insignificant variables. $P < 0.05$ was considered to be statistically significant in this study. All probabilities were two-tailed.

Results

Baseline demographic characteristics

A total of 267 PD patients were recruited. Their baseline clinical and demographic data are summarized in [Table 1](#) and [S1 Table](#). Among them, 120 patients (44.9%) were physically frail ([Fig 1](#)). As compared to those without frailty, frail PD patients were older, more often required helper assistance in performing PD, had higher CCI, and worse nutritional state. Frail PD

Table 1. Baseline clinical and demographic data.

	Not frail	Frail
No. of patients	147	120
Age (year)	61.1 ± 11.8	64.2 ± 12.2
Sex (M:F)	75: 72	56: 64
Duration of dialysis (months)	44.3 ± 46.9	51.8 ± 57.4
Blood pressure (mmHg)		
Systolic	142.8 ± 18.9	142.6 ± 20.9
Diastolic	75.8 ± 12.4	73.4 ± 12.7
Renal Diagnosis, no of cases. (%)		
Glomerulonephritis	51 (34.7%)	33 (27.5%)
Diabetic nephropathy	42 (28.6%)	56 (46.7%)
HTN	18 (12.2%)	12 (10%)
Polycystic kidney	5 (3.4%)	3 (2.5%)
Urological disease	9 (6.1%)	2 (1.7%)
Other / unknown	22 (15%)	14 (11.6%)
Comorbid disease, no of cases (%)		
DM	55 (37.4%)	66 (55.0%)
IHD	19 (12.9%)	19 (15.8%)
CVA	16 (10.9%)	31 (25.8%)
Charlson Comorbidity Index	5.1 ± 2.2	5.6 ± 2.2
Nutritional Status		
MIS	6.57 ± 3.13	9.00 ± 3.46
SGA	5.38 ± 0.83	4.84 ± 0.92
Total weekly Kt/V	1.88 ± 0.49	1.76 ± 0.40
Residual GFR (ml/min/1.73m ²)	1.70 ± 2.02	1.04 ± 1.74
NPNA (g/kg/day)	1.07 ± 0.25	1.03 ± 0.30
Biochemical parameters		
Hemoglobin (g/dL)	9.72 ± 1.31	9.25 ± 1.26
Albumin (g/L)	34.10 ± 4.15	33.46 ± 4.16
Pulse Wave Velocity (m/sec)		
CF-PWV	10.93 ± 2.38	11.19 ± 2.40
CR-PWV	10.34 ± 1.75	10.48 ± 1.80
Peritoneal Transport State- 4-hour dialysate/plasma creatinine	0.64 ± 0.13	0.65 ± 0.12
Helper-assisted PD, no of cases (%)	8 (5.4%)	24 (20.0%)
Type of peritoneal dialysis, no of cases (%)		
CAPD	127 (86.4%)	106 (88.3%)
CCPD	4 (2.7%)	2 (1.7%)
NIPD	16 (10.9%)	12 (10.0%)
Icodextrin dialysate use, no of cases (%)	39 (26.5%)	34 (28.3%)
Concomitant medications, no of cases (%)		
Aspirin	35 (23.8%)	42 (35.0%)
Beta blocker	99 (67.3%)	72 (60.0%)
RAS blocking agent	79 (53.7%)	77 (64.2%)
Calcium channel blocker	125 (85.0%)	90 (75.0%)
Statin	64 (43.5%)	62 (51.7%)
Calcium containing phosphate binder	115 (78.2%)	84 (70.0%)
Vitamin D supplement	64 (43.5%)	62 (51.7%)

(Continued)

Table 1. (Continued)

	Not frail	Frail
Erythropoiesis-stimulating agents	112 (76.2%)	82 (68.3%)

Data are expressed as mean \pm standard deviation.

HTN, hypertensive nephrosclerosis; DM, diabetes mellitus; IHD, ischemic heart disease; CVA, cerebrovascular accident; MIS, Malnutrition Inflammation Score; SGA, Subjective Global Assessment; GFR, glomerular filtration rate; NPNA, normalized protein nitrogen appearance; CF-PWV, carotid-femoral pulse wave velocity; CR-PWV, carotid-radial pulse wave velocity; PD, peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; CCPD, continuous cycler peritoneal dialysis; NIPD, nocturnal intermittent peritoneal dialysis; RAS blocking agent, renin angiotensin system-blocking agent.

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patients were also more likely to be diabetic, had lower residual renal function and hemoglobin level.

The body composition of patients with and without frailty are summarized and compared in Table 2. Frail patients had significantly higher WHR, and marginally higher BMI, than those without frailty, although the latter was not statistically significant. Among frail patients, the prevalence of central obesity and general obesity was 60.0% and 13.3% respectively, whereas among non-frail patients, the prevalence was 46.9% and 10.2% respectively. Frail patients had marginally higher adipose tissue mass than non-frail patients by bioimpedance spectroscopy, although the difference was not statistically significant. Frail patients also had significantly a higher overhydration volume than those without frailty, but their lean tissue mass was similar.

There was no significant difference in baseline CF-PWV and CR-PWV between patients with and without frailty. After 1 year of PD, CF-PWV increased from 11.04 ± 2.39 to 12.19 ± 3.17 m/sec (paired Student's t test, $p = 0.003$), whereas there was no significant change in CR-PWV (from 10.40 ± 1.77 to 10.73 ± 2.14 m/sec, paired Student's t test, $p = 0.8$). The baseline frailty score did not correlate with the change in CF-PWV ($r = 0.145$, $p = 0.3$) or CR-PWV ($r = 0.081$, $p = 0.6$) over one year. In central obese patients, there was a modest correlation between physical frailty and the change in CF-PWV although it did not reach statistical significance ($r = 0.359$, $p = 0.08$). There was no correlation between physical frailty and change in CR-PWV ($r = 0.001$, $p = 0.9$).

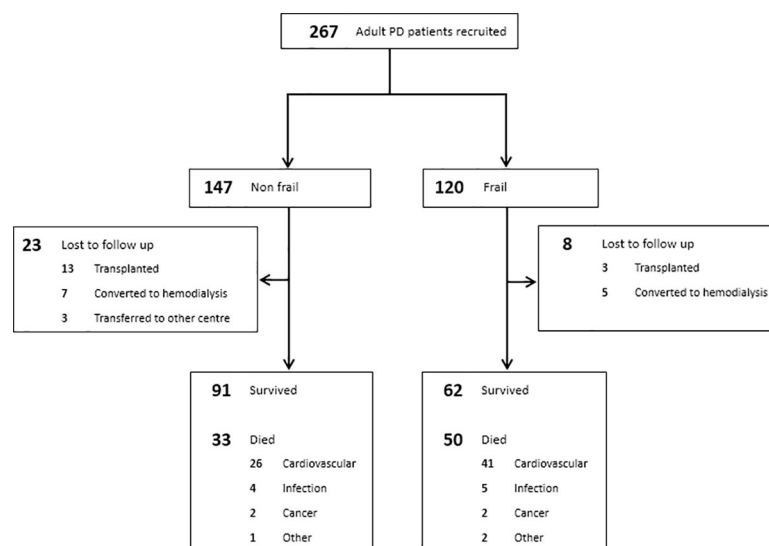


Fig 1. Flow diagram of subjects' inclusion and their outcomes.

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Table 2. Body anthropometry and composition by bioimpedance spectroscopy.

	Not frail	Frail	P value
No. of patients	147	120	
Body weight (kg)	64.2 ± 12.9	66.3 ± 12.5	p = 0.2
Body height (cm)	161.0 ± 7.5	160.0 ± 8.3	p = 0.2
Body mass index (kg/m ²)	25.7 ± 4.1	26.0 ± 4.3	p = 0.07
Waist hip ratio (WHR)	0.95 ± 0.07	0.99 ± 0.11	p < 0.001
Overhydration (OH)			
Volume (L)	2.90 ± 3.09	3.62 ± 2.99	p = 0.08
>1 L, no. of case (%)	101 (72.7%)	96 (87.3%)	p = 0.005
Adipose tissue mass (kg)	21.1 ± 11.6	23.1 ± 11.0	p = 0.16
Lean tissue mass (kg)	38.0 ± 9.66	36.7 ± 9.67	p = 0.3

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Patient survival

During the study period, 83 patients (31.1%) died. During this period, 16 patients (6.0%) underwent kidney transplantation, 12 (4.5%) were switched to chronic hemodialysis, and 3 (1.1%) were transferred to other renal center. The 2-year overall survival rate was 58.3% in frail and 77.6% in non-frail patients (log-rank test, p = 0.001). The 2-year cardiovascular survival was 65.8% in frail and 82.3% in non-frail individuals (log-rank test, p < 0.001). After adjusting for potential confounding factors by multivariate Cox regression analysis (Table 3), physical frailty remained a significant predictor for all-cause mortality and cardiovascular mortality. In these models, other significant predictive factors of all-cause mortality included age, CCI and serum albumin level. For cardiovascular mortality, CCI was the only other independent predictor.

Interaction with WHR on survival

Neither WHR nor BMI predicted overall survival or cardiovascular survival. However, there was a significant interaction between central obesity and frailty on patient survival and

Table 3. Univariate and multivariate Cox regression analysis.

(A) Patient survival				
Factors	Univariate analysis		Multivariate analysis	
	AHR (95% CI)	P value	AHR (95% CI)	P value
Physical frailty	2.126 (1.369–3.330)	p = 0.001	1.793 (1.094–2.939)	p = 0.021
CCI	1.350 (1.246–1.464)	p < 0.001	1.131 (1.015–1.259)	p = 0.025
Age	1.067 (1.043–1.091)	p < 0.001	1.069 (1.034–1.104)	p < 0.001
Albumin	0.881 (0.837–0.927)	p < 0.001	0.915 (0.859–0.975)	p = 0.006
CF-PWV	1.172 (1.070–1.284)	p = 0.001		
Overhydration	1.085 (1.019–1.156)	p = 0.011		
(B) Cardiovascular survival				
Factors	Univariate analysis		Multivariate analysis	
	AHR (95% CI)	P value	AHR (95% CI)	P value
Physical frailty	2.959 (1.277–6.860)	p = 0.011	2.652 (1.134–6.200)	p = 0.024
CCI	1.282 (1.111–1.479)	p = 0.001	1.294 (1.109–1.509)	p = 0.001
Age	1.052 (1.011–1.095)	p = 0.012		
Albumin	0.921 (0.839–1.011)	p = 0.085		

CCI, Charlson Comorbidity Index; CF-PWV, carotid-femoral pulse wave velocity; BMI, body mass index; AHR, adjusted hazard ratio; CI, confidence interval; CV, cardiovascular.

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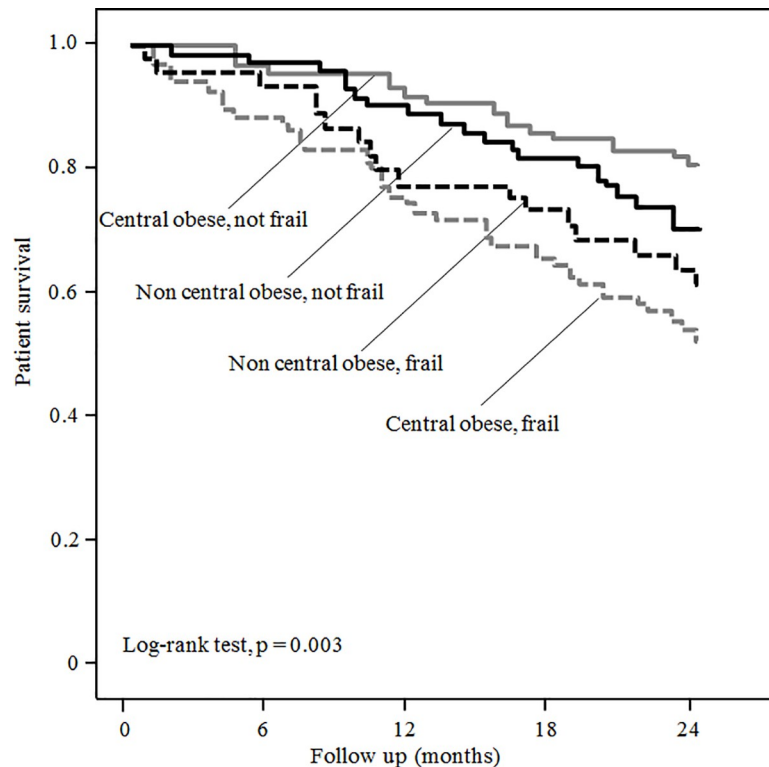


Fig 2. Kaplan-Meier plot of patient survival according to the frailty state and central obesity.

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cardiovascular survival ($p = 0.002$ and $p = 0.038$, respectively, for interaction), while the interaction between general obesity and frailty on survival did not reach statistical significance (overall survival, $p = 0.057$ and cardiovascular survival, $p = 0.156$, respectively, for interaction). The 2-year patient survival of patients with central obesity was marginally lower than those without central obesity for the frail group (54.2% vs 64.6%, $p = 0.3$), but marginally higher than those without central obesity for the non-frail group (81.2% vs 74.4%, $p = 0.2$), although neither of the difference was statistically significant (Fig 2). Similarly, the 2-year cardiovascular survival of patients with central obesity was similar to those without central obesity for the frail group (64.6% vs 66.7%, $p = 0.6$), but significantly higher than those without central obesity for the non-frail group (91.3% vs 74.4%, $p = 0.002$).

Further subgroup analysis on 2-year patient survival was performed for patients on short duration of peritoneal dialysis (less than 1 year use). In short, the survival rate was higher among non-frail individuals, which is in line with the results of our whole cohort. Non-frail, central obese individuals had the best survival rate while frail, central obese individuals had the worst survival rate. The survival rates decreased in a stepwise manner, from 100% for non-frail central obese, 82.4% for non-frail non-central obese, 76.9% for frail non-central obese, to 61.5% for non-frail non-central obese (S1 Fig) though the difference did not reach significance (log-rank test, $p = 0.069$).

Hospitalization

After 2 years of follow up, there were in total 984 episodes of hospital admission for a total of 10,695 days in our cohort; 45 patients (16.8%) did not require any hospitalization during the study period (Table 4). Among all, 88 episodes of hospitalization admission for a total of 1,190

Table 4. Relation between physical frailty and hospitalization.

	Not frail	Frail	P value
Number of patients	147	120	
Without hospitalization, no. of patients (%)	24 (16.3%)	21 (17.5%)	p = 0.799 ^a
Number of hospitalization			
All-cause	3.13 ± 3.51	4.37 ± 4.27	p = 0.025 ^b
Cardiovascular event	0.24 ± 0.59	0.44 ± 0.92	p = 0.049 ^b
Total duration of hospitalization (days)	31.05 ± 42.48	51.08 ± 68.99	p = 0.068 ^b

Data are compared by

^aChi-square test and

^bMann Whitney U test.

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days had cardiovascular events as the primary diagnosis. In short, frailty score had modest correlations with the number of hospitalization for all-cause ($r = 0.158$, $p = 0.025$) or cardiovascular event ($r = 0.133$, $p = 0.049$), total duration of hospitalization ($r = 0.176$, $p = 0.068$), although the last correlation did not reach statistical significance. In contrast, WHR did not correlate with number of hospitalization for all-cause ($p = 0.4$) or cardiovascular-event ($p = 0.7$), or the duration of hospitalization ($p = 0.4$). By using linear regression model after log transformation to adjust for potential confounders, frailty score remained an independent factor associated with the number of hospital admission for all-cause and total duration of hospitalization (Table 5).

We further performed subgroup analysis on hospitalization data according to physical frailty. In short, general obese patients were hospitalized more frequently with a longer hospitalization period, while central obese patients were hospitalized less frequently with a shorter period (Table 6). In non-frail patients, those with general obesity had more than a doubled number and duration of cardiovascular-event related hospitalization as compared to those without general obesity, while those with central obesity had halved number and duration of cardiovascular-event related hospitalization as compared to those without central obesity. A similar trend was also observed in frail patients, but the difference was not significant (S2 Table).

Table 5. Multivariate linear regression analysis of hospitalization after log transformation.

(A) Number of hospitalization			
Factors	Unstandardized B	95% CI	P value
Physical frailty	0.998	0.024–1.971	p = 0.045
CCI	0.372	0.101–0.644	p = 0.007
GFR	-0.348	-0.602 – -0.094	p = 0.007
(B) Number of cardiovascular event-related hospitalization			
Factors	Unstandardized B	95% CI	P value
CCI	0.060	0.017–0.104	p = 0.007
Kt/V	-0.191	-0.355 – -0.027	p = 0.022
(C) Total duration of hospitalization			
Factors	Unstandardized B	95% CI	P value
Physical frailty	14.295	0.032–28.558	p = 0.049
CCI	4.090	0.954–7.227	p = 0.011
Kt/V	-14.483	-26.696 – -2.270	p = 0.020

CI, confidence interval; CCI, Charlson Comorbidity Index; GFR, glomerular filtration rate.

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Table 6. Relation between hospitalization and general versus central obesity in non-frail patients.

	No central obesity	Central obesity	P value*	No general obesity	General obesity	P value*
Number of patients	78	69		132	15	
Number of hospitalization						
All-cause	3.37 ± 3.94	2.86 ± 2.95	p = 0.5	3.08 ± 3.59	3.60 ± 2.75	p = 0.189
Cardiovascular event	0.34 ± 0.72	0.12 ± 0.37	p = 0.030	0.20 ± 0.56	0.60 ± 0.74	p = 0.002
Duration of hospitalization (days)						
All-cause	35.22 ± 51.53	26.34 ± 28.70	p = 0.9	29.67 ± 41.73	43.27 ± 48.39	p = 0.076
Cardiovascular event	3.54 ± 9.16	1.45 ± 5.38	p = 0.040	1.92 ± 7.04	8.13 ± 10.62	p = 0.001

*Data are compared by Mann Whitney U test.

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Discussion

The present study identified frailty is prevalent among PD patients, and it is an independent predictor of adverse outcomes including a higher hospitalization rate, a longer duration of hospitalization, as well as a worse survival with higher all-cause and cardiovascular mortality rates. Our results also showed presence of significant interactions between central obesity and frailty in terms of hospitalization and survival in PD patients.

Physical frailty is traditionally regarded as a geriatric disease as it primarily affects elderly patients. As predicted, frail individuals are generally older in our cohort as shown in [Table 1](#). When compared to HD, performing PD is relatively simpler and it does not require as much technical support as in HD. PD also does not require vascular access creation, and it offers a better cardiovascular stability [19–21]. PD is therefore commonly regarded as a better dialysis option over HD in elderlies. More than 30% to 75% of elderlies preferred PD over HD in different countries [22, 23]. Assisted PD is particularly more preferred to hemodialysis as assisted PD provides a better quality of life to frail elderly on dialysis [24–26]. Therefore, it is important to recognize and quantify the impact of physical frailty in PD patients. In fact, routine frailty screening has been suggested to be part of assessment for and maintenance care on PD [27]. However, most of the currently available literature in the field of physical frailty in dialysis population involved either HD [28] or a mixture of HD and PD cases [29]. This evidence are unable to reflect the burden of physical frailty in PD population, and cannot be applied to certain countries like Hong Kong, Taiwan, Thailand, Vietnam, as well as New Zealand and Australia, which have a relatively higher PD to HD case ratio compared to other western countries like the USA and Canada [30].

Patients with chronic kidney disease have a different body composition compared with the general population [31, 32]. The causes are multifold. Firstly, uremia, defects in homeostasis and metabolic derangements in chronic kidney disease cause anorexia, which results in malnutrition and protein energy wasting [33]. Secondly, dialysis treatment also induces protein loss and muscle catabolism [34, 35]. In particular, PD causes central obesity [10, 36] due to the exposure to glucose-containing dialysate fluid. On the other hand, physical frailty itself is also associated with similar change in body composition i.e. development of obesity with a reduction in muscle mass [7–9]. The overall combined effect on body composition by renal failure, dialysis treatment and physical frailty in PD patients were uncertain. Our study demonstrated a comparable total adipose tissue mass between frail and non-frail PD patients. It is worth to note that despite the total adipose tissue was similar between two groups, when comparing between general and central obesity, frail individuals were more central obese but not general obese. This observation highlights frail individual had a different fat composition, with a relatively higher visceral fat to subcutaneous fat ratio when compared to non-frail PD patients.

This may be the potential cause for an inferior survival in frail PD patients, which will be further elaborated.

In contrast to general obesity, central obesity correlates with a worse survival in ESRD and HD patients [11, 37]. There were only a few published data in PD patients [11, 38, 39], with limited power due to small sample size. One Korean study [40] advocated the use of Sagittal Abdominal Diameter (SAD) measured by X-ray, and found correlation of central obesity with all-cause and cardiovascular mortality. However, its use is limited by the need of a dedicated X-ray machine and it involves additional radiation exposure, which may not be feasible in a clinic setting. Two small scaled studies by Canadian group [38] with 22 subjects, and Korean group [11] with 84 subjects showed controversial mortality risk from central obesity in PD patients. Another study with a larger sample size from Brazil [39] showed a worse short-term 1-year survival in central obese PD patients. However, the long-term survival could not be assessed due to limited study period. In our study, we recruited 267 subjects, which represented the largest scaled study compared to other studies in same field. Our results reflected neither general nor central obesity predicted 2-year all-cause and cardiovascular disease-related mortality in PD patients.

Central obesity has been reported to have synergistic effect on mortality with physical frailty in HD patients [41]. However, such effect is not yet explored in PD patients. Our study is the first study to prove an additive effect on mortality by physical frailty and central obesity in PD patients. The underlying pathophysiology is probably related to the potentiation of pro-inflammatory state by certain cytokines. Visceral fat in central obese patients secretes numerous pro-inflammatory cytokines including C-reactive protein (CRP), tumor necrosis factor (TNF)-alpha and interleukin (IL)-6 [42, 43]. These cytokines modulate lipid and carbohydrate metabolism [44], and orchestrate the inflammatory pathway by stimulation of T cell proliferation, B cell-related immunoglobulin production and hepatic synthesis of acute phase protein [42]. At the same time, physical frailty is associated with an inflammatory state with high levels of CRP and IL-6. Study has shown elevated CRP and IL-6 levels predict mortality, cardiovascular events and composite outcomes in dialysis patients [42]. Although vascular calcification and arterial stiffening, which could be secondary to chronic inflammation, play a prognostic role on survival of PD patients [45], the cross linkage between frailty, central obesity and mortality appears to be independent from arterial stiffening as reflected by a similar CF-PWV and CR-PWV between frail and non-frail individuals (Table 1, S1 Table), and a lack of correlation between progression of the two parameters with time between frail and non-frail individuals, both in central and non-central obese subgroups. Activation of the inflammatory cascade can also lead to impairment of immune response [46] and subsequent activation of coagulation system causing a higher thrombotic tendency and cardiovascular risk [47]. This may explain why physical frailty had a much higher hazard ratio on all-cause and cardiovascular disease-related mortality in central obese PD patients when compared to all PD patients. It is worthwhile to note that from our result, physical frailty did not cause a worse survival in non-central obese PD patients. The underlying cause remains to be elucidated and further studies should be undertaken in the future to clarify the mechanism.

On top of the proven 1-year mortality risk from frailty in PD patients [5], this study illustrated a longer term mortality risk from frailty in PD patients. However, physical frailty not only confers mortality risk to PD patients, but also imposes a huge burden to the economy and healthcare system as frail individuals are often high users of healthcare resources. In our cohort, frail PD patients were more often required helper assistance in performing dialysis. They also tend to hospitalize more frequent and longer than non-frail individuals, which is in line with other published studies [28, 29, 48]. Notably, frail central obese PD patients required nearly twice as many hospital admissions than non-frail central obese PD patients, and their

total hospital length of stay was also nearly twice in our study. Aside from physical frailty, obesity may also influence clinical outcome in terms of hospitalization in dialysis patients. Patients with higher BMI were associated with a higher incidence of peritonitis-related hospitalization but not in non-peritonitis-related hospitalization [49]. Similarly, central obesity was also identified to be a predictor for cardiovascular events, all-cause hospitalization and mortality [37, 39]. Our data is the first published result both evaluating and comparing the impact of both general and central obesity, as well as identifying the potential interaction with physical frailty on hospitalization parameters in PD patients. In contrast to previous study [37, 39], we identified central obesity as a protective factor associated with a fewer hospital admission and higher survival rate in non-frail PD patients. Similar findings have been reported in patients with stable coronary artery disease patients [50], and heart failure patients especially those with reduced ejection fraction [51, 52]. The proposed mechanisms are related to the extra energy reserve provided by visceral fat [51], and the anti-inflammatory and endotoxin-neutralizing effects mediated by a raised lipoprotein level [52]. In addition, central obese individuals also seek medical attention at the earlier stage of acute illnesses as they tend to be more symptomatic, and their renin-angiotensin-aldosterone system is more attenuated, leading to a higher blood pressure and a better tolerance to cardioprotective medications [52]. On the other hand, general obesity in non-frail PD patients were hospitalized more frequently with a longer duration, regardless of the cause of hospitalization. While most of the available literature focused on recognition of frailty and the associated adverse outcomes in PD patients, our result addressed the impact of body composition in non-frail group and this should not be overlooked. Identification of mechanism underlying such difference between general and central obesity is beyond our scope, but this should be evaluated in future study.

Our study has several limitations. Our data collection is retrospective in nature from a single center with a limited number of study subjects, which may lead to the concern on generalizability. We believe our cohort is a good representation of a Chinese PD cohort as our centre is one of the largest tertiary-care and university-affiliated medical centres. It is also part of the public healthcare system which takes care of 94% of dialysis patients in Hong Kong [53]. We also included both incident and prevalent PD patients, which can lead to a few concerns. Firstly, body composition, fat mass and waist circumference can be altered by the long duration of peritoneal dialysis due to exposure of glucose-containing dialysate [10] and that may have prognostic implications too [39]. However, the marker of central obesity we used i.e. WHR takes both waist and hip circumference into account. Whether there is any change with time depends on the proportion of difference in both parameters. Moreover, univariate analysis reflected PD duration did not predict hospitalization ($p = 0.364$) and mortality ($p = 0.210$). All other results reported in this study were adjusted with the duration on PD in their corresponding statistical analyses. On the other hand, we also performed subgroup analysis on patients who were on short PD duration of less than 1 year with a shorter exposure time to glucose-containing dialysate. The survival rate trend is the same as the trend in our whole cohort (S1 Fig) though the difference in survival rates of the 4 groups in subgroup analysis did not reach statistical significance. Together with the other insignificant or barely significant results we presented, this can be attributed to the relatively small sample size in our cohort, which may raise the issue regarding the weight that this study can give. Despite so, our results, as the first published data in this aspect, still give valuable information regarding potential interaction between central obesity, frailty and their association with adverse outcomes in PD patients. Base on this, we suggest future research with a larger sample size to identify any significant interaction and association with the outcomes that we investigated. Secondly, there will also be potential lead-time bias and selection bias favoring surviving patients. However, this can be strength of our study as it can be applied more universally. Moreover, the duration

of follow-up may not be long enough to detect the effect of physical frailty and body composition in survival. Furthermore, our measurement of frailty and body composition is a one-off measurement performed at the recruitment period. These results may also be transiently affected by acute illnesses. Serial measurements of these parameters may provide a better assessment in corresponding aspects. The cross-sectional nature of our data can only allow us to establish association rather than causal relationship. Although we have sufficient power to identify the independent association between two factors, these results do not have sufficient data to analyse the aspect of effect modification.

In summary, we found that physical frailty is prevalent in Chinese PD patients. Frail PD patients were usually older and they often had higher comorbidity loads and poorer nutritional state. They are also more central obese. Physical frailty was an independent predictor for adverse outcomes in PD patients, in terms of a higher hospitalization rate and longer duration of hospitalization, as well as a worse survival with higher all-cause and cardiovascular mortality rates. In subgroup analysis, central and general obesity caused a differential effect on hospitalization parameters in non-frail PD patients. Furthermore, central obesity conferred a numerically but statistically non-significant inferior patient's survival and cardiovascular survival in frail PD patients. On the contrary, central obesity conferred a significantly superior cardiovascular survival in non-frail PD patients. We suggest routine screening of physical frailty and central obesity in PD patients, so as to achieve risk stratification by identification of the high-risk group. Further prospective study is urgently needed to explore on potential interventional measures that can be done to these high-risk individuals to improve their clinical outcomes and survival.

Supporting information

S1 Checklist.

(DOCX)

S1 Fig. Kaplan-Meier plot of patient survival among patients on peritoneal dialysis for less than 1 year according to the frailty state and central obesity.

(TIF)

S1 Table. Baseline clinical and demographic data, statistical tests results.

(DOCX)

S2 Table. Relation between hospitalization and general versus central obesity in frail patients.

(DOCX)

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References

1. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; 56:M146–M156. <https://doi.org/10.1093/gerona/56.3.m146> PMID: 11253156
2. Johansen KL, Chertow GM, Jin C, Kutner NG. Significance of frailty among dialysis patients. *J Am Soc Nephrol* 2007; 18(11):2960–7. <https://doi.org/10.1681/ASN.2007020221> PMID: 17942958
3. Ng JK, Kwan BC, Chow KM, Cheng PM, Law MC, Pang WF, et al. Frailty in Chinese Peritoneal Dialysis Patients: Prevalence and Prognostic Significance. *Kidney Blood Press Res* 2016; 41: 736–745. <https://doi.org/10.1159/000450563> PMID: 27771713
4. Pugh J, Aggett J, Goodland A, Prichard A, Thomas N, Donovan K, et al. Frailty and comorbidity are independent predictors of outcome in patients referred for pre-dialysis education. *Clin Kidney J.* 2016 Apr; 9(2):324–9. <https://doi.org/10.1093/ckj/sfv150> PMID: 26985387
5. Chan GC, Ng JK, Chow KM, et al. Depression Does Not Predict Clinical Outcome of Chinese Peritoneal Dialysis Patients After Adjusting for the Degree of Frailty. *BMC Nephrol* 21, 329 (2020). <https://doi.org/10.1186/s12882-020-01994-4> PMID: 32758180
6. Johansen KL, Dalrymple L, Delgado C, Kaysen G, Kornak J, Grimes B, et al. Association between body composition and frailty among prevalent hemodialysis patients: A US renal data system special study. *J Am Soc Nephrol* 2014; 5(2):381–389.
7. Crow RS, Lohman MC, Titus AJ, et al. Association of Obesity and Frailty in Older Adults: NHANES 1999–2004. *J Nutr Health Aging.* 2019; 23(2):138–144. <https://doi.org/10.1007/s12603-018-1138-x> PMID: 30697622
8. Buch A, Carmeli E, Boker LK, et al. Muscle function and fat content in relation to sarcopenia, obesity and frailty of old age—An overview. *Exp Gerontol.* 2016; 76:25–32. <https://doi.org/10.1016/j.exger.2016.01.008> PMID: 26785313
9. Hubbard RE, Lang IA, Llewellyn DJ, Rockwood K. Frailty, body mass index, and abdominal obesity in older people. *J Gerontol A Biol Sci Med Sci.* 2010; 65(4):377–381. <https://doi.org/10.1093/gerona/glp186> PMID: 19942592
10. Kim JK, Park HC, Song YR, Kim HJ, Moon SJ, Kim SG. Effects of Excessive Body Fat Accumulation on Long-Term Outcomes During Peritoneal Dialysis. *Perit Dial Int.* 2019; 39(3):268–275. <https://doi.org/10.3747/pdi.2018.00164> PMID: 30846607
11. Jin H, Shin JY, Lee SH, Song JH, Kim MJ, Lee SW. Abdominal obesity and mortality in continuous ambulatory peritoneal dialysis patients. *Electrolytes & Blood Pressure.* 2015 Jun 1; 13(1):22–9.
12. Afşar B, Sezer S, Ozdemir FN, Celik H, Elsurer R, Haberal M. Malnutrition-inflammation score is a useful tool in peritoneal dialysis patients. *Perit Dial Int.* 2006; 26(6):705–711. PMID: 17047239
13. Kiebalo T, Holotka J, Habura I, Pawlaczyk K. Nutritional Status in Peritoneal Dialysis: Nutritional Guidelines, Adequacy and the Management of Malnutrition. *Nutrients.* 2020; 12(6):1715.
14. Kwan BC, Szeto CC, Chow KM, Law MC, Cheng MS, Leung CB, et al. Bioimpedance spectroscopy for the detection of fluid overload in Chinese peritoneal dialysis patients. *Perit Dial Int* 2014; 34: 409–416. <https://doi.org/10.3747/pdi.2013.00066> PMID: 24385329
15. O'Lone EL, Visser A, Finney H, Fan SL. Clinical significance of multi-frequency bioimpedance spectroscopy in peritoneal dialysis patients: independent predictor of patient survival. *Nephrol Dial Transplant.* 2014; 29(7):1430–1437. <https://doi.org/10.1093/ndt/gfu049> PMID: 24598280
16. Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR, et al. American Heart Association Council on Hypertension. Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness: A Scientific Statement From the American Heart Association. *Hypertension* 2015; 66(3):698–722. <https://doi.org/10.1161/HYP.000000000000033> PMID: 26160955

17. Kumar VA, Sidell MA, Yang WT, Jones JP. Predictors of peritonitis, hospital days, and technique survival for peritoneal dialysis patients in a managed care setting. *Perit Dial Int*. 2014 Mar-Apr; 34(2):171–8. <https://doi.org/10.3747/pdi.2012.00165> PMID: 24084841
18. Szeto CC, Wong TY, Chow KM, Leung CB, Law MC, Wang AY, et al. Impact of dialysis adequacy on the mortality and morbidity of anuric Chinese patients receiving continuous ambulatory peritoneal dialysis. *J Am Soc Nephrol*. 2010 Feb; 12(2):355–60.
19. Segall L, Nistor I, Van Biesen W, Brown EA, Heaf JG, Lindley E, et al. Dialysis modality choice in elderly patients with end-stage renal disease: a narrative review of the available evidence. *Nephrology Dialysis Transplantation*. 2015 Dec 15; 32(1):41–9.
20. Franco MR, Fernandes NM. Dialysis in the elderly patient: a challenge of the XXI century—narrative review. *J Bras Nefrol* 2013; 35: 132–141. <https://doi.org/10.5935/0101-2800.20130022> PMID: 23812571
21. Brown EA, Johansson L, Farrington K, Gallagher H, Sensky T, Gordon F, et al. Broadening Options for Long-term Dialysis in the Elderly (BOLDE): differences in quality of life on peritoneal dialysis compared to haemodialysis for older patients. *Nephrol Dial Transplant* 2010; 25: 3755–3763. <https://doi.org/10.1093/ndt/gfq212> PMID: 20400451
22. Brown EA, Finkelstein FO, Iyasere OU, Kliger AS. Peritoneal or hemodialysis for the frail elderly patient, the choice of 2 evils? *Kidney Int*. 2017; 91(2):294–303. <https://doi.org/10.1016/j.kint.2016.08.026> PMID: 27773426
23. Li PK, Law MC, Chow KM, Leung CB, Kwan BC, Chung KY, et al. Good patient and technique survival in elderly patients on continuous ambulatory peritoneal dialysis. *Perit Dial Int* 2007; 27:S196–S201. PMID: 17556304
24. Iyasere OU, Brown EA, Johansson L, et al. Quality of Life and Physical Function in Older Patients on Dialysis: A Comparison of Assisted Peritoneal Dialysis with Hemodialysis. *Clin J Am Soc Nephrol*. 2016; 11(3):423–430. <https://doi.org/10.2215/CJN.01050115> PMID: 26712808
25. Iyasere O, Brown E, Gordon F, et al. Longitudinal Trends in Quality of Life and Physical Function in Frail Older Dialysis Patients: A Comparison of Assisted Peritoneal Dialysis and In-Center Hemodialysis. *Perit Dial Int*. 2019; 39(2):112–118. <https://doi.org/10.3747/pdi.2018.00086> PMID: 30661007
26. Iyasere O, Brown EA, Johansson L, et al. Quality of life with conservative care compared with assisted peritoneal dialysis and haemodialysis. *Clin Kidney J*. 2018; 12(2):262–268. <https://doi.org/10.1093/ckj/sfy059> PMID: 30976407
27. Brown EA, Hurst H. Delivering peritoneal dialysis for the multimorbid, frail and palliative patient. *Perit Dial Int*. 2020; 40(3):327–332.
28. McAdams-DeMarco MA, Law A, Salter ML, et al. Frailty as a novel predictor of mortality and hospitalization in individuals of all ages undergoing hemodialysis. *J Am Geriatr Soc*. 2013; 61(6):896–901. <https://doi.org/10.1111/jgs.12266> PMID: 23711111
29. Lee SY, Yang DH, Hwang E, et al. The Prevalence, Association, and Clinical Outcomes of Frailty in Maintenance Dialysis Patients. *J Ren Nutr*. 2017; 27(2):106–112. <https://doi.org/10.1053/j.jrn.2016.11.003> PMID: 28065454
30. Kwong VW, Li PK. Peritoneal dialysis in Asia. *Kidney Diseases*, 2015; 1(3):147–156. <https://doi.org/10.1159/000439193> PMID: 27536675
31. Johansen KL, Lee C. Body composition in chronic kidney disease. *Curr Opin Nephrol Hypertens*. 2015 May; 24(3):268–75. <https://doi.org/10.1097/MNH.0000000000000120> PMID: 25887900
32. Lu JL, Kalantar-Zadeh K, Ma JZ, Quarles LD, Kovesdy CP. Association of body mass index with outcomes in patients with CKD. *J Am Soc Nephrol*. 2014; 25:2088–2096. <https://doi.org/10.1681/ASN.2013070754> PMID: 24652789
33. Cobo G, Lindholm B, Stenvinkel P. Chronic inflammation in end-stage renal disease and dialysis. *Nephrol Dial Transplant*. 2018; 33(suppl_3):iii35–iii40. <https://doi.org/10.1093/ndt/gfy175> PMID: 30281126
34. Sabatino A, Regolisti G, Karupiah T, et al. Protein-energy wasting and nutritional supplementation in patients with end-stage renal disease on hemodialysis. *Clin Nutr*. 2017; 36(3):663–671. <https://doi.org/10.1016/j.clnu.2016.06.007> PMID: 27371993
35. Guedes AM. Peritoneal Protein Loss, Leakage or Clearance In Peritoneal Dialysis, Where Do We Stand?. *Perit Dial Int*. 2019; 39(3):201–209. <https://doi.org/10.3747/pdi.2018.00138> PMID: 31088933
36. Choi SJ, Kim NR, Hong SA, Lee WB, Park MY, Kim JK, et al. Changes in body fat mass in patients after starting peritoneal dialysis. *Perit Dial Int*. 2011 Jan-Feb; 31(1):67–73. <https://doi.org/10.3747/pdi.2009.00131> PMID: 20448238

37. Wu CC, Liou HH, Su PF, Chang MY, Wang HH, Chen MJ, et al. Abdominal obesity is the most significant metabolic syndrome component predictive of cardiovascular events in chronic hemodialysis patients. *Nephrology Dialysis Transplantation*. 2011 Feb 28; 26(11):3689–95.
38. Su WS, Clase CM, Brimble KS, Margetts PJ, Wilkieson TJ, Gangji AS. Waist-to-hip ratio, cardiovascular outcomes, and death in peritoneal dialysis patients. *International journal of nephrology*. 2010; 2010:831243. <https://doi.org/10.4061/2010/831243> PMID: 21188241
39. Castro AC, Bazanelli AP, Nerbass FB, Cuppari L, Kamimura MA. Waist circumference as a predictor of mortality in peritoneal dialysis patients: a follow-up study of 48 months. *British Journal of Nutrition*. 2017 May; 117(9):1299–303. <https://doi.org/10.1017/S0007114517001179> PMID: 28583215
40. Lee MJ, Shin DH, Kim SJ, Yoo DE, Ko KI, Koo HM, et al. Sagittal abdominal diameter is an independent predictor of all-cause and cardiovascular mortality in incident peritoneal dialysis patients. *PloS one*. 2013 Oct 22; 8(10):e77082. <https://doi.org/10.1371/journal.pone.0077082> PMID: 24167560
41. Fitzpatrick J, Sozio SM, Jaar BG, Estrella MM, Segev DL, Parekh RS, et al. Frailty, body composition and the risk of mortality in incident hemodialysis patients: the Predictors of Arrhythmic and Cardiovascular Risk in End Stage Renal Disease study. *Nephrology Dialysis Transplantation*, 2018; 34(2):346–354.
42. Li PK, Ng JK, McIntyre CW. Inflammation and peritoneal dialysis. In *Seminars in Nephrology* 2017 Jan 1 (Vol. 37, No. 1, pp. 54–65). WB Saunders.
43. Soysal P, Stubbs B, Lucato P, Luchini C, Solmi M, Peluso R, et al. Inflammation and frailty in the elderly: a systematic review and meta-analysis. *Ageing research reviews*, 2016, 31: 1–8. <https://doi.org/10.1016/j.arr.2016.08.006> PMID: 27592340
44. Avila-Carrasco L, Pavone MA, González E, et al. Abnormalities in Glucose Metabolism, Appetite-Related Peptide Release, and Pro-inflammatory Cytokines Play a Central Role in Appetite Disorders in Peritoneal Dialysis. *Front Physiol*. 2019; 10:630. <https://doi.org/10.3389/fphys.2019.00630> PMID: 31191339
45. Szeto CC, Kwan BC, Chow KM, Leung CB, Law MC, Li PK. Prognostic value of arterial pulse wave velocity in peritoneal dialysis patients. *Am J Nephrol*. 2012; 35(2):127–133. <https://doi.org/10.1159/000335580> PMID: 22236995
46. Li H, Manwani B, Leng SX. Frailty, inflammation, and immunity. *Aging and disease*. 2011 Dec; 2(6):466. PMID: 22396895
47. Wang Z, Nakayama T. Inflammation, a link between obesity and cardiovascular disease. *Mediators Inflamm*. 2010; 2010:535918. <https://doi.org/10.1155/2010/535918> PMID: 20847813
48. Alfaadhel TA, Soroka SD, Kiberd BA, Landry D, Moorhouse P, Tennankore KK. Frailty and mortality in dialysis: evaluation of a clinical frailty scale. *Clin J Am Soc Nephrol*. 2015; 10(5):832–840. <https://doi.org/10.2215/CJN.07760814> PMID: 25739851
49. Obi Y, Streja E, Mehrotra R, Rivara MB, Rhee CM, Soohoo M, et al. Impact of Obesity on Modality Longevity, Residual Kidney Function, Peritonitis, and Survival Among Incident Peritoneal Dialysis Patients. *Am J Kidney Dis*. 2018 Jun; 71(6):802–813. <https://doi.org/10.1053/j.ajkd.2017.09.010> PMID: 29223620
50. Lavie CJ, De Schutter A, Patel DA, Romero-Corral A, Artham SM, Milani RV. Body composition and survival in stable coronary heart disease: impact of lean mass index and body fat in the "obesity paradox". *J Am Coll Cardiol*. 2012 Oct 9; 60(15):1374–80. <https://doi.org/10.1016/j.jacc.2012.05.037> PMID: 22958953
51. Clark AL, Fonarow GC, Horwich TB. Waist circumference, body mass index, and survival in systolic heart failure: the obesity paradox revisited. *J Card Fail*. 2011 May; 17(5):374–80. <https://doi.org/10.1016/j.cardfail.2011.01.009> PMID: 21549293
52. Horwich TB, Fonarow GC, Clark AL. Obesity and the Obesity Paradox in Heart Failure. *Prog Cardiovasc Dis*. 2018 Jul-Aug; 61(2):151–156. <https://doi.org/10.1016/j.pcad.2018.05.005> PMID: 29852198
53. Tang SCW, Yu X, Chen HC, et al. Dialysis Care and Dialysis Funding in Asia. *Am J Kidney Dis*. 2020; 75(5):772–781. <https://doi.org/10.1053/j.ajkd.2019.08.005> PMID: 31699518