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RESEARCH

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# Heterogeneity of clinical indices among the older dialysis population—a study on Japanese dialysis population

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## Abstract

**Background:** The older dialysis population is increasing, and several studies have investigated the effect of actual age on the relationship between clinical parameters or clinical practice and prognosis. There is concern that biological age does not necessarily reflect the actual effects of aging, and it is important to take heterogeneity into account when considering the older population. In this study, we investigated whether such heterogeneities exist in a large number of clinical parameters and how any disparities might be affected by the domains of clinical indices.

**Methods:** We investigated the published, summarized results of the Japanese Society for Dialysis Therapy Renal Data Registry, a nationwide survey of the Japanese dialysis population, for the year 2013.

**Results:** The potential population comprised 306,925 dialysis patients. We investigated coefficient of variations (CVs) of 25 clinical indices across age groups and compared them with the CVs of the 45–59 years age group as a reference group, using tests for homogeneity of variances. Almost all variables showed some heterogeneity by age. The domain for muscle mass or visceral protein exhibited greater heterogeneity in older patients, but surprisingly, the domain for body mass or physique exhibited less heterogeneity. The mean values of most parameters declined in the older population.

**Conclusions:** This study demonstrated that variations exist in clinical indices in the older dialysis population. Apart from biological age, we should take these heterogeneities into account when interpreting the findings of clinical studies involving older dialysis patients and in their individualized management.

**Keywords:** Aging phenotype, Biological age, Coefficient of variances, Heterogeneity, Older patients, Wasting

## Background

The dialysis population has become much older in recent years, and the proportion of elderly patients is increasing in many registries [1, 2]. There are several clinical problems to overcome in the older hemodialysis population. One of the most important involves malnutrition-related syndromes, such as sarcopenia [3], protein energy wasting [4], and frailty [5]. These syndromes are in fact associated with a worse prognosis in the dialysis population as a whole [6, 7]; these phenotypes are considered to be most important in the management of the older population.

Strategies against complications for older dialysis patients sometimes differ from those for their younger counterparts [8]. However, the definition of “older” patients varies in different reports [9–11]. The reason for this may be due to the heterogeneity among the elderly population in terms of phenotype. Some patients look younger than their actual age, while some look older. Moss et al. reported that the “surprise” question, “Would I be surprised if this patient died in the next year?” correlated well with 1 year survival [12], indicating that the phenotype, presumably wasting or malnutrition, seems important for survival.

We speculated that such phenotype of the “older” population does matter and that it is important to take the heterogeneities of such patients into account, which

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might affect the older phenotype. However, there have been no reports on the heterogeneity of the elderly population. Therefore, here, we focused on the heterogeneity of the older dialysis population and investigated which clinical indices exhibited large heterogeneity and were potentially related to a poor prognosis, using national registry data compiled by the Japanese Society for Dialysis Therapy (JSDT). It is anticipated that our results will help the clinician to undertake individualized management of older dialysis patients.

## Methods

### Population

Data from the annual Japanese Society for Dialysis Therapy Renal Data Registry (JRDR) survey run by JSDT were used for this analysis. The details of this registry have been described previously [13]. We analyzed the data collected in 2013. The summarized tables are recorded in CD-ROM or are reported on the internet. In this analysis, we used data that appears on JSDT's website [14].

The potential population for this study was the entire dialysis population as of December 31, 2013, namely 306,925 patients. The population was divided by 15-year age groups. We excluded patients with missing data on age ( $n = 12$ ) and patients who were younger than 15 years ( $n = 116$ ).

### Clinical indices

The following clinical indices were investigated: (1) mineral and bone disorder markers (corrected calcium and phosphate); (2) malnutrition-related factors (total cholesterol, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol, percent creatinine generation rate (%CGR) [15], normalized protein catabolic rate (nPCR) [16], and albumin); (3) body mass and volume status (body height, postdialytic body weight (BW), body mass index (BMI), BW change, and fractional BW change); (4) dialysis prescription and its consequences (dialysis duration, spKt/V [16], eqKt/V [17], blood flow rate, predialytic blood urea, and creatinine); (5) circulatory factors (systolic blood pressure, diastolic blood pressure, and pulse rate); and (6) other factors (hemoglobin (Hb) level, glycoalbumin, and HbA1c). Postdialytic BW, dialysis duration, and blood flow rate were investigated among the patients who were treated by hemodialysis, hemodiafiltration, or hemoperfusion. The values of %CGR, nPCR, BW change, fractional BW change, spKt/V, eqKt/V, and creatinine were investigated only in patients who were treated by hemodialysis, hemodiafiltration, or hemoperfusion three times weekly with a dialysis history of  $\geq 2$  years. Glycoalbumin and HbA1c were investigated among those who had history of diabetes or were on glucose-lowering therapies. Parameters other than those described above were studied in the entire dialysis population.

### Statistical analysis

This analysis consists of two parts: one is to determine the heterogeneities of age populations, and the other is to compare them with the standard of 45–59 year-old group.

The heterogeneity was measured by coefficient of variations (CV) in this analysis, because standard deviation (SD) does not necessarily express the degree of heterogeneity when the averages vary. The tables of the JRDR summarized data give the number of patients and mean values and SD for each parameter in all age groups. CVs were calculated by dividing the SD by the mean for each age category. The larger CV is more heterogenic or heteroscedastic the population can be considered.

Relative CVs were calculated by dividing the CVs of each age group by that of the 45–59 years age group. If the value is larger than one, the index is more heterogenic in older population than the younger counterpart. Relative means were also calculated as the ratio of the mean of each age group to that of the 45–59 years age group, similarly to relative CVs.

Finally, we statistically compared the heterogeneities across age groups by investigating the homogeneity of variances. In details, we calculated variances by squaring standard deviations. The tests for homogeneity of variances were performed on the squared relative CVs using Bartlett's test among overall groups and  $F$  tests for each pair of age groups. The former investigated the homogeneity of the variances by age groups as a whole. When the test indicated statistical significance, it shows that the clinical index is heterogenic across age groups. On the other hand, the latter tested statistical significance by comparing the CV of each age group with that of the reference group of ages 45–59. When a test was significant, it indicates that the clinical index is more heterogenic in that age group compared to that in the 45–59-year-old age group. Post hoc adjustment for multiple comparisons was done by Bonferroni correction. The  $p$  values less than 0.05 were considered significant. For multiple comparisons,  $p$  values less than 0.01 were considered significant because five pairs of comparisons were performed with the 45–59 years age group as the reference group. All statistical calculations and analyses were performed using Microsoft Excel 2013 (Microsoft Corporation, Redmond, WA).

### Ethical issues

This study is the secondary analyses of the summarized and published data and does not deal with any personal information. Therefore, we consider that this study is deemed exempt from the Institutional Review Board or Ethics Committee approval. This study adhered to the Declaration of Helsinki.

## Results

The demographics and characteristics of the total population who underwent dialysis therapy in 2013 are shown in Table 1 [1]. Mean age was  $67.21 \pm 12.51$  years (mean  $\pm$  SD). The age groups 15–29, 30–44, 45–59, 60–74, 75–89, and  $\geq 90$  years accounted for 0.37, 4.91, 18.56, 45.87, 28.72, and 1.54% of the total population, respectively.

Table 2 shows the number of patients and their proportion of sex, vintage, and primary diagnoses for each age category. In the older age groups, there was a higher proportion of female patients and a higher proportion of patients with the primary diagnosis of nephrosclerosis; less predominant were the proportion of patients with a long history of dialysis and the proportion with diabetes as the primary diagnosis.

Table 3 shows the SDs and means of the variables investigated as well as the number of the patients. Table 4 shows the CVs relative to those of the 45–59 years age group, which is used as the reference group. The overall differences of variances, including chi-square values and *p* values calculated with the Bartlett test, are shown, as well as *p* values for the differences of variances of the age groups, taking the variance of the 45–59 years age group as the references. For almost all variables, the variances differed by age group. However, the trends themselves differed by index. We can categorize these indices according to the relative CV for the 75–89 years age group into four categories: (1) relative CVs of more than 1.1 (indicating the most heteroscedastic indices), namely for %CGR, albumin, creatinine, fractional BW reduction, blood urea nitrogen, and diastolic blood pressure; (2)

relative CVs of 1.0–1.1 (mildly heterogeneous), namely for phosphate, total cholesterol, nPCR, body height, BW reduction, blood flow rate, systolic blood pressure, pulse rate, and Hb; (3) relative CVs of 0.9–1.0 (less heterogeneous), namely for corrected calcium, non-HDL, HDL, session duration, spKt/V, and eqKt/V; and (4) relative CVs of less than 0.9 (least heterogeneous), namely for BW, BMI, glycoalbumin, and HbA1c.

Figure 1 indicates that the disparities in representative indices between several domains differ significantly across the age groups. The relative CVs of indicators relating to the muscle mass or visceral proteins increased steadily with age, becoming more heteroscedastic. The parameters related to dietary intake showed a modest relationship across the age groups. On the other hand, indices of body mass demonstrated that the dispersion progressively decreased with the age of the population.

Figure 1 was designated to demonstrate the CVs by themselves so that the heteroscedasticity can be recognized easily. On the other hand, the CVs were calculated from the SDs and means. The means are also subjected to change by age groups, and the relative means indicate the trend of the distributions of the absolute values as a whole by age groups. Therefore, in Fig. 2, we added the information about the relative means to the results shown in Fig. 1 so that information about whether the absolute values tended to become smaller among the older population as well as the information about the heteroscedasticity. This figure indicates that the mean values of all indices included in Fig. 1 were lower in the older age groups, irrespective of relative CVs. This fact might indicate that the normal aging process accompanies universal declines in clinical indices.

**Table 1** Background characteristics of the patients

Number of patients	306,925	
Sex (male/female)	194,965/111,960	
Age (mean $\pm$ SD)	67.21 $\pm$ 12.51	
Vintage (years, number of patients, %)		
<2	68,475	(22.3)
2–4	76,589	(25.0)
5–9	77,197	(25.2)
10–14	39,490	(12.9)
15–19	20,874	(6.8)
20–24	11,421	(3.7)
25–29	6611	(2.2)
30+	6155	(2.0)
Primary diagnoses (numbers, %)		
Diabetes	115,484	(37.6)
Glomerulonephritis	99,492	(32.4)
Nephrosclerosis	26,569	(8.7)
Polycystic kidney	10,683	(3.5)
Others or unknown	54,697	(17.8)

## Discussion

Heterogeneity as determined by CV increased with age in some domains, especially that of muscle mass or visceral proteins. However, in some other domains such as body mass, the disparities seem to be diminished in the older population. This is the first study investigating the heteroscedasticity of clinical indices, using nationwide registry data.

There were differences among the domains of indices; factors related to sarcopenia or wasting were most prominently dispersed. Moreover, the mean values of these parameters declined with age. Therefore, muscle mass and albumin level generally decreases with age, but their speed of decline varies among individuals. The decrease in these parameters, as discussed above, reportedly relates to poor survival relating to wasting [6, 7]. Therefore, the heterogeneity of these clinical indices might reflect the diversity of the older population in terms of “old” phenotypes and relate to a worse prognosis. Moreover, the mean values of CGR and albumin decreased less in older population,

**Table 2** Patient characteristics by age group

Age groups	15–29	30–44	45–59	60–74	75–89	90+
Sex						
Male	749 (66.8)	10,315 (68.4)	38,610 (67.8)	91,189 (64.8)	51,997 (59.0)	2032 (42.9)
Female	372 (33.2)	4756 (31.6)	18,340 (32.2)	49,583 (35.2)	36,150 (41.0)	2704 (57.1)
Vintage (years, number of patients, %)						
<2	383 (34.2)	3556 (23.6)	11,484 (20.2)	28,358 (20.2)	23,464 (26.6)	1163 (24.6)
2–4	323 (28.8)	3756 (24.9)	12,996 (22.8)	32,734 (23.3)	25,177 (28.6)	1565 (33.1)
5–9	263 (23.5)	3564 (23.7)	13,807 (24.3)	35,296 (25.1)	22,800 (25.9)	1447 (30.6)
10–14	103 (9.2)	2134 (14.2)	7782 (13.7)	19,446 (13.8)	9598 (10.9)	425 (9.0)
15–19	34 (3.0)	1176 (7.8)	4673 (8.2)	10,882 (7.7)	4007 (4.5)	102 (2.2)
20–24	11 (1.0)	605 (4.0)	2890 (5.1)	6174 (4.4)	1715 (1.9)	26 (0.5)
25–29	4 (0.4)	206 (1.4)	1734 (3.0)	3890 (2.8)	774 (0.9)	3 (0.1)
30+	0 (0.0)	69 (0.5)	1564 (2.7)	3948 (2.8)	572 (0.6)	2 (0.0)
Primary diagnoses (numbers, %)						
Diabetes	61 (5.4)	4268 (28.3)	21,653 (38.0)	57,903 (41.1)	30,672 (34.8)	920 (19.4)
Glomerulonephritis	389 (34.7)	5635 (37.4)	20,180 (35.4)	46,654 (33.1)	25,273 (28.7)	1344 (28.4)
Nephrosclerosis	34 (3.0)	614 (4.1)	2411 (4.2)	8917 (6.3)	13,311 (15.1)	1279 (27.0)
Polycystic kidney	21 (1.9)	433 (2.9)	2738 (4.8)	5373 (3.8)	2050 (2.3)	63 (1.3)
Others or unknown	615 (54.9)	4119 (27.3)	9967 (17.5)	21,917 (15.6)	16,832 (19.1)	1130 (23.9)

The number of patients (percentage) in each age group is shown. Patients with missing or unknown values for age or background characteristics were excluded. Therefore, the sum of the numbers is not equal to the total population shown in Table 1

compared to other indices as shown in Fig. 2. This fact might reflect that CGR and albumin are less affected by aging and they could be good markers of aging phenotype. In this analysis, we investigated the disparity in muscle mass in terms of CGR. However, muscle strength is reported to relate to survival to a greater degree [6]. The concept of dynapenia has been proposed [18, 19]. Future studies investigating the heterogeneity of muscular strength and its relation to survival are required.

Albumin has been used as a marker of malnutrition, but many other factors also affect albumin levels [20]. Dietary restriction only does not decrease the albumin level and it is now regarded as a factor of wasting [20]. The 2013 annual JRDR survey, the source of the data analyzed in this study, also investigated C-reactive protein (CRP). However, the distribution of CRP does not follow a normal distribution, and its heterogeneity cannot be assessed by SD or CV as we performed on other variables because the variables that do not follow normal distribution cannot be summarized by SDs or means. Therefore, we could not investigate the heterogeneity of CPR, and we cannot draw the conclusion that the disparity of albumin relates to inflammation status.

Dietary intake is reduced in the elderly population because of reduced appetite [21]. Moreover, the degree of appetite itself relates to prognosis [21]. In this study, we used nPCR as a surrogate of dietary intake. On the other hand, phosphate is contained in foods that contain much protein [22]. Phosphate binders and dialysis

dosage, especially session length, also affect the level of phosphate [22]. It is interesting to note then that nPCR and phosphate exhibited similar trends. Intradialytic BW reduction can be related to sodium intake during interdialytic periods [23], which also followed a similar trend to that of nPCR and phosphate levels. Therefore, these clinical indices can be considered as surrogate markers of dietary intake in patients.

Surprisingly, the distribution of body mass tended to be smaller in the older population even though the disparities of muscle mass become wide among the elderly population. An inverse relationship can be observed in the dialysis population [24]; patients with larger BMI experience better survival [25]. However, in the Asian population, such relationship might be weaker than in the white or black populations [25]. Female patients tend to have better survival among the Japanese population, and the average age of female patients is higher than their male counterparts [1]. Actually, Table 2 shows that the proportion of female patients was larger among the older age groups. Obviously, female patients have a smaller physique than male patients. Therefore, the present results might be attributed to the predominance of female patients in the older age groups. On the other hand, it is possible that the findings of the smaller and relatively homogeneous physique in older patients merely reflect the trend in the general population because this study did not examine variances in the general population.

**Table 3** Details of investigated clinical indices by age group

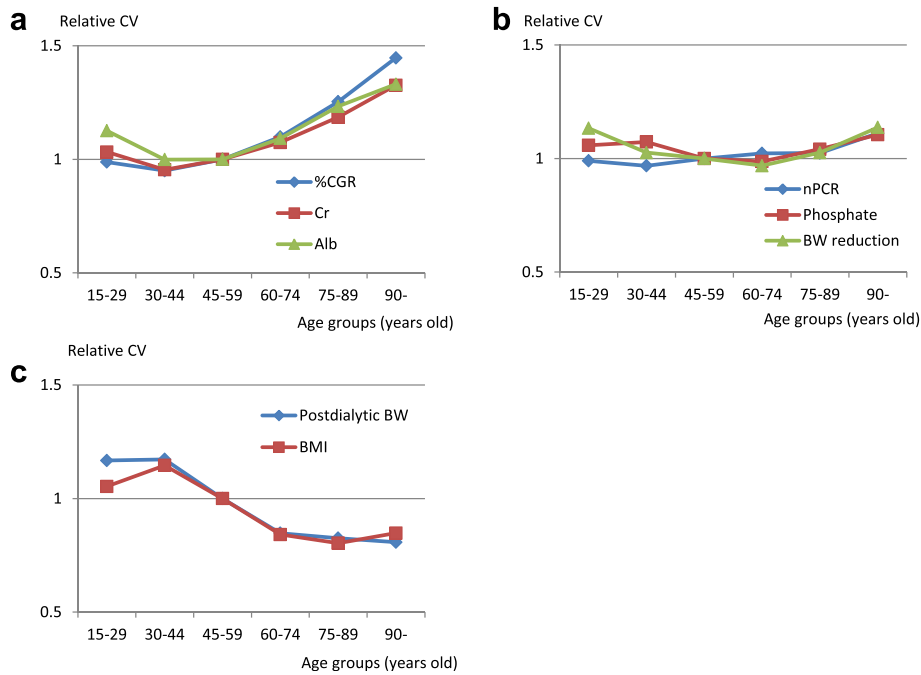
	15-29		30-44		45-59		60-74		75-89		90+							
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD						
Corrected calcium (mg/dl)	982	9.23	1.01	13,372	9.21	0.95	50,910	9.28	0.95	125,857	9.29	0.92	78,390	9.28	0.89	4159	9.32	0.88
Phosphate (mg/dl)	982	6.20	1.75	13,395	5.94	1.70	51,003	5.66	1.51	126,082	5.24	1.38	78,480	4.86	1.35	4163	4.58	1.35
Total cholesterol (mg/dl)	733	151.42	34.05	10,072	161.17	36.00	38,259	161.91	36.68	94,475	156.90	35.81	58,543	152.40	34.76	3074	152.01	34.89
Non-HDL (mg/dl)	572	98.53	30.52	8163	110.54	34.88	30,913	111.28	35.04	75,683	107.96	33.74	46,507	105.29	32.34	2386	105.10	31.91
HDL cholesterol (mg/dl)	649	51.96	15.40	9291	50.68	17.81	35,085	50.48	18.04	85,526	48.81	16.71	52,604	47.17	15.33	2707	47.06	14.59
%Creatinine generation rate (%)	576	97.84	22.30	9279	102.51	22.47	37,051	101.84	23.50	92,017	100.60	25.51	52,501	96.04	27.78	2763	89.88	30.00
Normalized protein catabolic rate (g/kg/day)	576	0.96	0.19	9283	0.93	0.18	37,071	0.90	0.18	92,080	0.88	0.18	52,547	0.83	0.17	2768	0.81	0.18
Albumin (g/dl)	957	3.94	0.46	13,123	3.86	0.40	49,868	3.76	0.39	123,713	3.62	0.41	77,239	3.44	0.44	4082	3.26	0.45
Body height (cm)	951	160.35	12.28	12,879	165.28	9.76	49,316	164.41	9.00	121,116	160.36	8.77	74,553	155.74	8.97	3895	150.46	9.31
Postdialytic body weight (kg)	904	55.07	15.10	12,921	64.44	17.75	49,320	62.10	14.59	123,611	55.35	11.02	77,661	49.86	9.67	4130	43.68	8.29
Body mass index (kg/m <sup>2</sup> )	907	20.96	4.33	12,468	23.40	5.26	47,739	22.89	4.49	117,550	21.51	3.55	72,249	20.56	3.24	3751	19.36	3.22
Body weight reduction (kg)	598	2.84	1.20	9692	3.19	1.22	38,748	2.95	1.10	96,978	2.52	0.91	55,482	2.17	0.83	2954	1.84	0.78
Fractional body weight reduction (%)	588	5.23	1.75	9627	5.09	1.67	38,616	4.83	1.57	96,725	4.61	1.56	55,325	4.41	1.61	2945	4.26	1.70
Session duration (h)	928	4.11	0.60	13,153	4.15	0.61	50,237	4.11	0.56	125,686	4.00	0.50	79,179	3.84	0.51	4228	3.68	0.54
spKt/V	576	1.55	0.33	9260	1.47	0.32	36,997	1.47	0.31	91,943	1.50	0.29	52,461	1.48	0.30	2759	1.45	0.31
eqKt/V	576	1.35	0.30	9270	1.29	0.30	37,018	1.29	0.28	91,982	1.31	0.27	52,478	1.29	0.27	2762	1.25	0.29
Blood flow rate (ml/min)	910	215.90	40.58	12,992	223.89	39.60	49,599	218.83	37.45	124,081	206.67	34.32	78,016	192.68	33.07	4149	179.45	32.49
Predialytic blood urea (mg/dl)	601	69.22	16.40	9729	67.31	15.90	38,895	64.89	15.54	97,289	62.47	15.51	55,647	58.45	15.43	2956	56.73	15.77
Creatinine (mg/dl)	601	13.83	3.12	9727	13.38	2.79	38,905	11.99	2.62	97,292	10.48	2.46	55,646	8.88	2.30	2955	7.42	2.15
Systolic blood pressure (torr)	844	147.58	22.58	11,584	152.31	24.84	43,661	153.49	24.07	108,150	152.08	23.81	67,379	148.93	24.16	3586	145.85	25.04
Diastolic blood pressure (torr)	843	87.65	16.31	11,557	88.44	15.51	43,545	84.86	14.03	107,857	77.84	13.33	67,193	72.10	13.14	3576	68.01	13.34
Pulse rate (/min)	785	80.69	13.35	11,009	81.29	12.92	41,376	78.50	12.58	102,757	74.40	12.46	64,244	72.38	12.63	3396	71.16	12.49
Hemoglobin (g/dl)	971	10.83	1.31	13,204	10.90	1.27	50,256	10.85	1.26	124,487	10.70	1.24	77,553	10.52	1.27	4096	10.37	1.25
Glycoalbumin (%)	25	21.38	7.09	1692	21.41	7.01	8742	20.82	5.82	23,723	21.24	5.21	13,001	21.35	4.93	420	21.41	5.31
A1c (%)	39	6.34	1.51	2363	6.64	1.51	12,166	6.40	1.29	32,540	6.18	1.12	17,481	6.00	1.05	544	5.83	0.99

HDL high-density lipoproteins, spKt/V single pool Kt/V, eqKt/V equilibrated Kt/V, HbA1c hemoglobin A1c, n number of patients, SD standard deviations

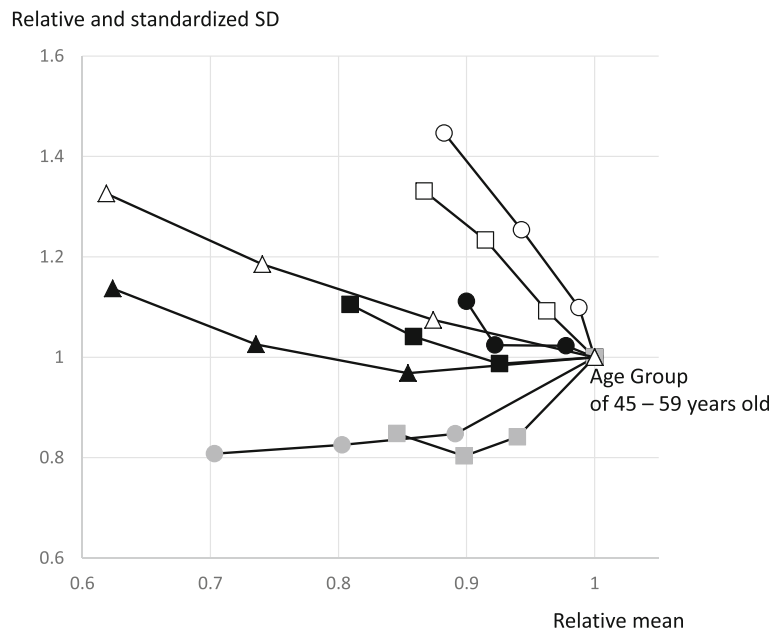
**Table 4** Trends in relative and standardized standard deviations of all clinical indices by age group

Age groups	15–29		30–44		45–59		60–74		75–89		90+		Trend analysis	
	Relative CV	p value	Relative CV	p value	Relative CV	p value	Relative CV	p value	Relative CV	p value	Relative CV	p value	Chi-square values	p value
Corrected calcium (mg/dl)	1.069	0.001	1.008	0.134	1	Ref	0.967	<0.001	0.937	<0.001	0.922	<0.001	356.9	<0.001
Phosphate (mg/dl)	1.058	0.006	1.073	<0.001	1	Ref	0.987	0.000	1.041	<0.001	1.105	<0.001	463.8	<0.001
Total cholesterol (mg/dl)	0.993	0.396	0.986	0.038	1	Ref	1.007	0.042	1.007	0.073	1.013	0.160	11.3	0.080
Non-HDL (mg/dl)	0.984	0.299	1.002	0.405	1	Ref	0.993	0.057	0.975	<0.001	0.964	0.008	32.9	<0.001
HDL cholesterol (mg/dl)	0.829	<0.001	0.983	0.021	1	Ref	0.958	<0.001	0.909	<0.001	0.868	<0.001	482.4	<0.001
%creatinine generation rate (%)	0.988	0.347	0.950	<0.001	1	Ref	1.099	<0.001	1.254	<0.001	1.446	<0.001	3282.4	<0.001
Normalized protein catabolic rate (g/kg/day)	0.990	0.370	0.968	<0.001	1	Ref	1.023	<0.001	1.024	<0.001	1.111	<0.001	122.8	<0.001
Albumin (g/dl)	1.126	<0.001	0.999	0.448	1	Ref	1.092	<0.001	1.233	<0.001	1.331	<0.001	3463.1	<0.001
Body height (cm)	1.399	<0.001	1.079	<0.001	1	Ref	0.999	0.401	1.052	<0.001	1.130	<0.001	693.7	<0.001
Postdialytic body weight (kg)	1.167	<0.001	1.172	<0.001	1	Ref	0.847	<0.001	0.825	<0.001	0.808	<0.001	5473.5	<0.001
Body mass index (kg/m <sup>2</sup> )	1.053	0.013	1.146	<0.001	1	Ref	0.841	<0.001	0.803	<0.001	0.848	<0.001	5456.5	<0.001
Body weight reduction (kg)	1.133	<0.001	1.026	0.001	1	Ref	0.968	<0.001	1.026	<0.001	1.137	<0.001	401.1	<0.001
Fractional body weight reduction (%)	1.029	0.155	1.009	0.123	1	Ref	1.041	<0.001	1.123	<0.001	1.228	<0.001	884.0	<0.001
Session duration (h)	1.071	0.001	1.079	<0.001	1	Ref	0.917	<0.001	0.975	<0.001	1.077	<0.001	1243.2	<0.001
spKt/V	1.010	0.367	1.032	<0.001	1	Ref	0.917	<0.001	0.961	<0.001	1.014	0.160	604.6	<0.001
eqKt/V	1.024	0.207	1.071	<0.001	1	Ref	0.950	<0.001	0.964	<0.001	1.069	<0.001	410.3	<0.001
Blood flow rate (ml/min)	1.098	<0.001	1.034	<0.001	1	Ref	0.970	<0.001	1.003	0.239	1.058	<0.001	243.6	<0.001
Predialytic blood urea (mg/dl)	0.989	0.364	0.986	0.044	1	Ref	1.037	<0.001	1.102	<0.001	1.161	<0.001	620.9	<0.001
Creatinine (mg/dl)	1.032	0.130	0.954	<0.001	1	Ref	1.074	<0.001	1.185	<0.001	1.326	<0.001	1992.9	<0.001
Systolic blood pressure (torr)	0.976	0.164	1.040	<0.001	1	Ref	0.998	0.342	1.034	<0.001	1.095	<0.001	184.0	<0.001
Diastolic blood pressure (torr)	1.126	<0.001	1.061	<0.001	1	Ref	1.036	<0.001	1.102	<0.001	1.186	<0.001	692.0	<0.001
Pulse rate (/min)	1.032	0.100	0.992	0.139	1	Ref	1.045	<0.001	1.089	<0.001	1.095	<0.001	449.3	<0.001
Hemoglobin (g/dl)	1.042	0.035	1.003	0.315	1	Ref	0.998	0.289	1.040	<0.001	1.038	0.001	185.3	<0.001
Glycoalbumin (%)	1.186	0.089	1.171	<0.001	1	Ref	0.877	<0.001	0.826	<0.001	0.887	<0.001	703.6	<0.001
A1c (%)	1.182	0.054	1.128	<0.001	1	Ref	0.899	<0.001	0.868	<0.001	0.842	<0.001	564.6	<0.001

Indicated CVs were relative (i.e., SD of the 45–59 years age group was set as 1) CV. The p values for each age group were calculated from F tests compared with those of the 45 and 59 years age group. Trend analysis was performed using Bartlett's test; chi-square and p values are shown. HDL high-density lipoproteins, spKt/V single pool Kt/V, HbA1c hemoglobin A1c, n number of patients, SD standard deviation, ref reference



**Fig. 1** Heterogeneity of representative clinical parameters by age group. The figure shows the trends in relative coefficient of variations (CV) (i.e., the CV of the 45–59 years age group was set as 1) for the clinical parameters related to **a** muscle mass or visceral proteins, **b** dietary intake, and **c** body mass or physique. The CVs for indices of muscle mass or visceral proteins became larger among the older population, whereas the CVs for those of body mass became smaller. Indices for dietary intake tended to be dispersed in the very old population. CV coefficient of variance, %CGR percent creatinine generation ratio, a surrogate marker of muscle mass, Cr creatinine, Alb albumin, nPCR normalized protein catabolic rate, BW body weight, BMI body mass index, ref reference



**Fig. 2** Evolution of the relationship between mean and SD for representative indices among age groups  $\geq 45$  years. The relationship between the set of relative coefficients of variations (CV) and relative mean values are shown. The 45–59 years age group was set as a standard for both CV and means. The mean of all the indices decreased to a large degree in the older population. Each point indicates the age groups of 45–59, 60–74, 75–89, and  $\geq 90$  years. Open circles, %CGR; open squares, Alb; open triangles, Cr; closed circles, nPCR; closed squares, phosphate; closed triangles, body weight reduction; gray circles, body weight; and gray squares, body mass index



Moreover, there was a discrepancy in terms of heteroscedasticity between the indices regarding body mass such as BMI or BW and the indices regarding muscle mass such as %CGR or creatinine. The former showed to be less heterogenic, while the latter showed to be more heterogenic in older population. BMI is one of the simplest indices to describe the physiques. However, it cannot distinguish fat mass from muscle mass. The dialysis patients are shown to reduce muscle mass, while they often lose less amount of fat or even gain it during the course of dialysis therapy [26]. Therefore, BMI can underestimate the changes in muscle mass [27]. This point might cause the discrepancy of heteroscedasticity between body mass and muscle mass. On the other hand, body height can contribute to BMI. However, as Table 4 shows, the heterogeneity of height remained small even in the older population. Moreover, the mean values of body height were less in older population. Several recent studies demonstrated that taller dialysis patients might experience worse survival [28, 29]. Thus, the smaller and less heterogenic older population in terms of their body height might be due to the survival effects partly.

Nonetheless, we should pay attention to the clinical indices which exhibited large heterogeneity, such as creatinine generation rate, creatinine, and albumin, when we perform clinical practice on the older population. The deterioration of these indices might reflect the degree of the morbid conditions among older population. Future study will be required to investigate the relationship to the clinical outcomes, such as mortality, quality of life (QOL), and activity of daily living (ADL). After that, the interventions to the indices are warranted to improve the outcomes of the patients.

This study has several limitations. The first is its cross-sectional and observational nature. Therefore, we cannot draw any conclusions about the time course or cause-effect relationship. The second is that this study was based on results that appeared in summarized tables, and therefore, detailed investigations, such as further stratification by sex or primary diagnoses, could not be performed. The third is that the data that we used did not contain the data for clinical outcomes. Therefore, we could not investigate the effect of heterogeneity observed on mortality, QOL, or ADL. The fourth is that the JRDR data were almost exclusively derived from Japanese people. Therefore, the applicability of our findings to other ethnicities is unclear. Lastly, data was missing on some parameters in some patients. Although the number of the patients was sufficiently large, which is the most important advantage of this study, it is possible that errors exist.

Although there are several limitations in this study, the strengths of this study are the large number of patients and parameters that were examined. These results may contribute to the individualized management

of the older dialysis population. Further studies on the cause of disparities and the relationship to the prognosis of the patients are required. We anticipate that the findings of such studies will provide a better understanding of phenotypes in the older dialysis population.

## Conclusions

This is the first study to investigate heterogeneity in the older dialysis population. There were some disparities in heterogeneity across the parameters. Clinical parameters related to muscle mass or wasting exhibited larger heterogeneity, while those related to body mass or BW exhibited less heterogeneity. Individualized management for older dialysis patients with these heterogeneities might contribute to better outcomes in this population.

## Abbreviations

%CGR: Percent creatinine generation rate; ADL: Activity of daily living; BMI: Body mass index; BW: Body weight; CD-ROM: Compact disk read-only memory; CRP: C-reactive protein; CV: Coefficient of variation; eqKt/V: Equilibrated Kt/V; Hb: Hemoglobin; HbA1c: Hemoglobin A1c; HDL: High-density lipoprotein; JRDR: The Japanese Society for Dialysis Therapy Renal Data Registry; JSDT: The Japanese Society for Dialysis Therapy; nPCR: Normalized protein catabolic rate; QOL: Quality of life; SD: Standard deviation; spKt/V: Single pool Kt/V

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## Availability of data and materials

The data we used for the analysis have been already publicized by the JSDT on the web pages.

## Authors' contributions

NH conceived of the study design, analyzed the data, and wrote the manuscript. SS and MN made the critical revisions to the manuscript and helped to finalize the article. All authors read and approved the final manuscript.

## Competing interests

NH has received research consulting fees from Kyowa Hakko Kirin Co., Ltd.; lecture fees from Bayer Yakuin, Ltd., Chugai Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., and Nikkiso Co., Ltd.; and grant support from Chugai Pharmaceutical Co., Ltd. and Kyowa Hakko Kirin Co., Ltd. NH was also a member of a division that is funded by Terumo Corporation. The other authors declare that they have no competing interests.

## Consent for publication

This study does not include any individual person's data. Therefore, this point is not applicable.

## Ethics approval and consent to participate

Although this study employs the data originally derived from the patients, the data is widely available from the JSDT web pages and the data have already been anonymized. We the authors recognized that this study was not within the scope of the Ethical Guidelines for Medical and Health Research Involving Human Subject issued by the Ministry of Health, Labour and Welfare of Japan in December 2014, pursuant to the chapter 1 of part 3 of the guideline. Therefore, the ethics approval by the institutional review boards is exempted.

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