The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Original Article

J Atheroscler Thromb, 2022; 29: 1153-1165. http://doi.org/10.5551/jat.62992

Associations of Serum Insulin-Like Growth Factor 1 with New Cardiovascular Events and Subsequent Death in Hemodialysis Patients: The DREAM Cohort

Rino Nakaya[1], Tetsuo Shoji[2, 3], Yuki Nagata[2, 3], Shinya Nakatani[1], Katsuhito Mori[4], Tomoaki Morioka[1], Yoshihiro Tsujimoto[5] and Masanori Emoto[1, 3, 4]

[1]Department of Metabolism, Endocrinology and Molecular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan
[2]Department of Vascular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan
[3]Vascular Science Center for Translational Research, Osaka City University Graduate School of Medicine, Osaka, Japan
[4]Department of Nephrology, Osaka City University Graduate School of Medicine, Osaka, Japan
[5]Division of Internal Medicine, Aijinkai Healthcare Corporation Inoue Hospital, Suita, Japan

Aim: Patients with chronic kidney disease (CKD) have elevated risk of death from cardiovascular disease (CVD). A low serum insulin-like growth factor 1 (IGF-1) level is known to predict higher risk for all-cause mortality in incident dialysis patients, although it is unknown whether IGF-1 predicts cardiovascular outcomes.

Methods: This was a prospective cohort study of maintenance hemodialysis patients followed up for 5 years. Serum IGF-1 levels were measured at baseline, and patients were divided into IGF-1 tertiles. The key outcomes were all-cause mortality, a composite of new CVD, and death after new CVD events. Additional outcomes were hospitalization for infection and subsequent death. Association was analyzed using Cox proportional hazards models.

Results: In the 516 patients that were analyzed, we identified 106 all-cause deaths, 190 new CVD events, and 61 subsequent deaths. In addition, there were 169 hospitalizations for infection and 47 subsequent deaths. The risk of all-cause death was the highest in the lowest IGF-1 tertile, and this association remained significant in multivariable-adjusted models. Regarding CVD outcomes, IGF-1 was not associated with new CVD events but significantly associated with subsequent death in adjusted models. Similarly, IGF-1 was not an independent predictor of hospitalization for infection, but it predicted subsequent death.

Conclusions: A low IGF-1 level was not a significant predictor of new CVD events but an independent predictor of subsequent death in hemodialysis patients. Since similar associations with infection outcomes were observed, IGF-1 may be a biomarker of fragility or frailty in this population.

See editorial vol. 29: 1138-1139

Key words: Chronic kidney disease, Insulin-like growth factor 1, Dialysis, Cardiovascular disease, Frailty

Introduction

The risk of cardiovascular death is 10–30 times higher in patients with kidney failure undergoing hemodialysis as compared with the general population[1]. Hemodialysis patients have a higher risk not only for the incidence of cardiovascular disease (CVD) but also for death after CVD events[2]. These two factors synergistically increase the risk of cardiovascular death[3].

The elevated risk of CVD death in patients with chronic kidney disease (CKD), including those on hemodialysis, has been explained by the traditional and nontraditional risk factors[4]. Obesity is one of the

Address for correspondence: Tetsuo Shoji, Department of Vascular Medicine, Osaka City University Graduate School of Medicine; Vascular Science Center for Translational Research, Osaka City University Graduate School of Medicine, 1-4-3, Asahi-machi, Abeno-ku, Osaka 545-8585, JAPAN
E-mail: t-shoji@med.osaka-cu.ac.jp

Received: April 25, 2021 Accepted for publication: August 10, 2021

major cardiovascular risk factors in the general population. However, low body mass is the established predictor of death in patients with kidney failure[5]. Low body mass in dialysis patients is not necessarily explained by decreased nutritional intake, and there is complex pathophysiology termed protein-energy wasting (PEW) by which patients lose body protein and fat[6]. In addition to decreased intake, inflammation, and oxidative stress, some metabolic and endocrinologic abnormalities could contribute to PEW in patients with kidney failure by increasing catabolism and/or decreasing anabolism. Such metabolic and endocrinologic abnormalities, which are associated with mortality risk, include insulin resistance[7], high blood glucose levels due to insulin resistance[8], low testosterone levels[9], low adrenal androgen dehydroepiandrosterone sulfate levels[10], low free triiodothyronine levels[11], and low insulin-like growth factor 1 (IGF-1) levels[12]. Thus, these factors may be the nontraditional risk factors in this population.

Growth hormone (GH) is secreted from the anterior lobe of the pituitary and acts in the liver to produce IGF-1. IGF-1 is bound to its specific binding proteins[13] in the circulation, having a relatively stable serum level without apparent circadian rhythm unlike GH[14]. Although the action of IGF-1 on glucose uptake is less than 10% of that of insulin, IGF-1 is more potent on cell differentiation and proliferation than insulin, contributing to the growth and maintenance of the musculoskeletal system[15]. A low IGF-1 level is associated with low handgrip strength and low physical performance in the elderly people[16]. In acromegaly with elevated GH and IGF-1 levels, hypertension, diabetes, and dyslipidemia are common[17], and CVD is the main cause of death in this patient group[18]. Thus, the excess of GH and/or IGF-1 appears to increase CVD risk. Conversely, a lower IGF-1 level was also reported to be associated with acute coronary syndrome in the general population[19].

Regarding IGF-1 in patients with kidney failure, a low IGF-1 level was reported to predict all-cause mortality among patients starting treatment with hemodialysis or peritoneal dialysis[12] and patients on incident hemodialysis[20]. A low IGF-1 level was associated with low handgrip strength in hemodialysis patients[21]. So far, however, no study has examined whether IGF-1 predicts the risk of the occurrence of new CVD events or the risk of death after CVD events in patients with kidney failure. Although the risks for these two CVD outcomes are elevated in patients with kidney failure, information on the predictors of the latter outcome is quite limited. Identifying the factors associated with post-event mortality risk would enhance our understanding of the mechanism for the extremely high mortality rate in this population.

Aim

This study was started to examine the associations between serum IGF-1 concentration and the two CVD outcomes in a cohort of hemodialysis patients.

Methods

Study Design

This is a single-center prospective cohort study of patients on maintenance hemodialysis. In this analysis, the key exposure was IGF-1 serum levels. The key outcomes were all-cause mortality, new CVD events, and death after new CVD events. In additional analyses, we examined the associations of serum IGF-1 with hospitalization for infection and death after hospitalization for infection.

Study Participants

The participants of this analysis were prevalent hemodialysis patients with serum IGF-1 measurement at baseline who were selected from the 518 total participants of the DREAM cohort, which was followed up from the end of 2004 to the end of 2009. The DREAM cohort study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies by the Ministry of Health, Labor and Welfare of Japan (the original 2003 version, which was modified in 2004 and 2006). The protocol was approved by the ethics committee of Inoue Hospital (approval no. 121). All participants gave written informed consent prior to enrollment. The DREAM cohort study was registered in the University hospital Medical Information Network Clinical Trial Registry (UMIN-CTR; ID, UMIN000006168).

Serum IGF-1 Assay

Blood was taken from blood access before the start of dialysis at the beginning of the week, and serum was separated and kept frozen at −80℃. IGF-1 was measured later using fresh frozen samples with an immunoradiometric assay at Special Refence Laboratory (Tokyo, Japan). The intra- and inter-assay coefficients of variation were $<2.4\%$ and $<2.6\%$, respectively.

Outcomes

The preplanned key outcomes of this study were all-cause mortality, new CVD events, and death after CVD events. In this cohort, CVD events were defined as a composite of ischemic heart disease, stroke, peripheral arterial disease (PAD), congestive heart failure (CHF), valvular disease, and sudden death during the observation period. Death after a CVD event was defined as all-cause death after the new CVD event. The detailed definitions of CVD events were previously described[10] and available in **Supplemental Table 1**.

To interpret the results regarding the two CVD outcomes, we performed additional analyses of the associations of IGF-1 with infection outcomes. As additional outcomes, we identified hospitalization for infection and subsequent death. We defined hospitalization for infection as hospitalization for which the main reason was infectious disease observed during the study period. Death after infection was defined as all-cause death after the hospitalization for infection.

We also recorded, if any, transition from hemodialysis to peritoneal dialysis or kidney transplantation and transfer to other institutions during the 5-year observation period.

Other Variables

We collected data on major demographic factors (age, sex, diabetic kidney disease or not, duration of hemodialysis treatment, and prior CVD), traditional risk factors (current smoking, hypertension, and dyslipidemia), nontraditional risk factors related to PEW and inflammation (body mass index [BMI], serum albumin, and C-reactive protein [CRP]), mineral bone disorder (MBD) of CKD (serum calcium, phosphate, intact parathyroid hormone [PTH], and use of vitamin D receptor activator [VDRA]), and renal anemia (hematocrit, dose of erythropoiesis-stimulating agent [ESA], and use of intravenous iron). These data were obtained from medical records. Free T4 and thyroid-stimulating hormone (TSH) were also measured because hypothyroidism is known to lower serum IGF-1 levels[22].

Hypertension was defined as 140/90 mmHg or higher and/or antihypertensive medication use[23]. Dyslipidemia was defined as non-high-density lipoprotein cholesterol (Non-HDL-C) ≥ 150 mg/dL and/or high-density lipoprotein cholesterol (HDL-C) ≤ 40 mg/dL and/or statin use. These lipid levels were derived from the target levels for patients with CKD recommended by the clinical practice guideline of the Japanese Society of Atherosclerosis[24]. Hypothyroidism was defined by 1) being treated with levothyroxine replacement (treated hypothyroidism) or 2) low free T4 (<0.8 ng/dL) with high TSH (>4.0 IU/L)[25]. No patients had central hypothyroidism (low free T4 with low TSH).

Statistical Methods

The patients of this analysis were divided into IGF-1 tertiles, and the baseline characteristics were compared across IGF-1 tertiles. Categorical variables were summarized as numbers (percentages) and compared using χ^2 test. Continuous variables were summarized as medians (interquartile ranges) and compared using the Kruskal–Wallis test. Factors associated with IGF-1 were evaluated using multivariable-adjusted linear regression analysis in which serum IGF-1 level was logarithmically transformed to fit the model.

We first examined the unadjusted association of IGF-1 tertile with all-cause mortality using the Kaplan–Meier analysis with log-rank test. Then, the association was evaluated using multivariable-adjusted Cox proportional hazards models. First, the hazard ratio was calculated using an unadjusted Cox model (model 1). Then, adjustment was done for the major demographic factors (model 2). In addition to the major demographic factors, further adjustment was done for the traditional risk factors (model 3), the variables related to PEW and inflammation (model 4), the parameters of CKD-MBD (model 5), those related with renal anemia (model 6), or the presence of hypothyroidism (model 7).

To explore the association between IGF-1 and cause-specific death, all-cause mortality was divided into cardiovascular death, non-cardiovascular death, and death from unknown cause depending on the record of the direct causes of death. Non-cardiovascular causes were further divided into infection and other than infection. Because of the small numbers of these divided outcomes, IGF-1 was handled as a continuous variable, hazard ratio was expressed per 1-SD higher IGF-1, and adjustment was done only for age and sex.

The association between IGF-1 and new CVD events was analyzed similarly to the analysis of all-cause mortality using the same statistical models for adjustment.

The association between IGF-1 and death after a new CVD event was analyzed using the Kaplan–Meier method and a multivariate-adjusted Cox proportional hazards model. For this purpose, time from the first new CVD event to all-cause death was analyzed in patients who had new CVD events. Because of the limited number of deaths after CVD events, IGF-1

was handled as a continuous variable, hazard ratio was expressed per 1-SD higher IGF-1, and adjustment was done for the five major demographic factors.

As additional analysis, we also investigated the associations of IGF-1 with hospitalization for infection and death after infection. Multivariable-adjusted Cox analysis was conducted using the same approach as described for the analysis of death after a new CVD event.

A two-sided P value < 0.05 was considered statistically significant. All these analyses were performed using JMP version 14.2 (SAS Institute Japan Ltd., Tokyo, Japan).

Results

Study Participants

The patients for this analysis were selected from 518 total participants of the DREAM cohort. Because two participants were excluded because of missing data of IGF-1, the remaining 516 patients were analyzed **(Fig. 1)**. **Table 1** presents patient characteristics at baseline according to IGF-1 tertile. The patients with lower IGF-1 levels had higher age, lower BMI, lower albumin, lower phosphate levels, and higher prevalence of hypothyroidism, whereas there was no significant difference in CRP among the IGF-1 tertiles. Multivariable-adjusted linear regression analysis revealed that age, sex, the duration of dialysis, BMI, serum albumin, and the presence of hypothyroidism were independently associated with serum IGF-1 level **(Supplemental Table 2)**.

IGF-1 and All-Cause Mortality

During the 5-year observation period, 106 (21%) participants died. Based on the direct cause of death, 38 patients died from cardiovascular causes (sudden death, N=14; heart failure, N=13; stroke, N=5; ischemic heart disease, N=3; arrhythmia, N=2; and ischemic colitis, N=1) and 48 patients died from non-cardiovascular causes (infection, N=24; malignancy, N=8; respiratory failure, N=3; hepatic cirrhosis, N=2; uremia, N=2; and others, N=9), whereas the direct cause of death was unknown for 20 patients. The Kaplan–Meier analysis showed that the risk of all-cause mortality was different among the IGF-1 tertiles **(Fig. 2A)**. The association between IGF-1 and all-cause mortality was further analyzed using Cox proportional hazards models **(Table 2)**. IGF-1 was found to be associated with all-cause mortality in various models adjusted for the major demographic factors and the factors related with PEW and inflammation, parameters of CKD-MBD, variables of renal anemia, or presence of hypothyroidism. Also, adjustment for the traditional risk factors (model 3) gave a marginally significant result.

IGF-1 and Cause-Specific Death

The Kaplan–Meier curves were significantly different by tertile of IGF-1 regarding cardiovascular and non-cardiovascular death, but not for death from unknown cause **(Fig. 2B)**. The inverse associations of IGF-1 and cardiovascular and non-cardiovascular death remained significant in Cox models, in which IGF-1 was entered as a continuous variable and adjusted for age and sex. When non-cardiovascular causes were further divided into infection and other than infection, these outcomes were inversely associated with IGF-1 **(Supplemental Table 3)**.

IGF-1 and CVD Outcomes

New CVD events were recorded in 190 patients (37%). The Kaplan–Meier analysis showed that IGF-1 tertile was significantly associated with new CVD events **(Fig. 3A)**. However, this association was no longer significant when analyzed using Cox models adjusted for the major demographic factors **(Table 3)**.

Of the 190 patients who experienced new CVD events, 61 patients died after such event. Based on the direct cause of death, 38 patients died from cardiovascular causes (sudden death, N=14; heart failure, N=13; stroke, N=5; ischemic heart disease, N=3; arrhythmia, N=2; and ischemic colitis, N=1) and 14 patients died from non-cardiovascular causes (infection, N=9; respiratory failure, N=2; and others, N=3), whereas the direct cause was unknown for the remaining 9 patients. The Kaplan–Meier analysis showed that a lower IGF-1 level was significantly associated with a higher risk of death after new CVD event **(Fig. 4A)**. This association remained significant when analyzed using a Cox model adjusted for the possible confounders **(Table 4)**.

IGF-1 and Infection Outcomes

We identified 169 patients (33%) who experienced hospitalization for infection. The Kaplan–Meier analysis showed that IGF-1 tertile was significantly associated with hospitalization for infection **(Fig. 3B)**. However, this association was no longer significant when analyzed using Cox models adjusted for the major demographic factors **(Table 3)**.

Of the 169 patients with hospitalization for infection, 47 patients died after infection. Based on the direct cause of death, 13 patients died from cardiovascular causes (sudden death, N=5; heart failure, N=5; ischemic heart disease, N=2; and stroke, N=1) and 29 patients died from non-

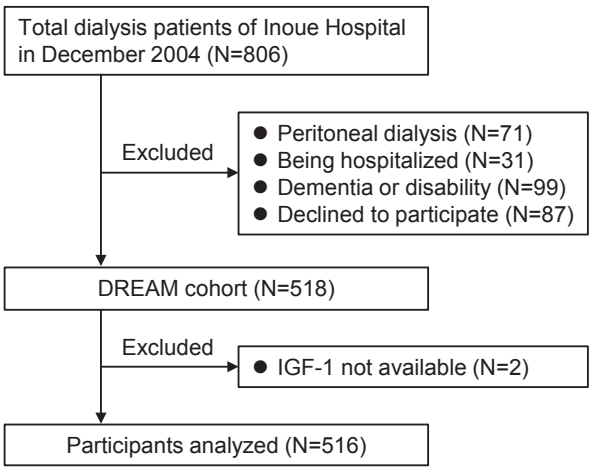

Fig. 1. Selection of participants for this analysis

Two patients were excluded due to missing data of IGF-1.
Abbreviation: IGF-1, insulin-like growth factor 1

Table 1. Baseline characteristics of the hemodialysis cohort by tertile of IGF-1

Characteristics	No. of participants with data	Overall N=516	IGF-1 tertile			
			T1 N=175	T2 N=170	T3 N=171	P across tertiles
IGF-1 (ng/mL)	516	147 (107–187)	94 (77–108)	147 (137–158)	212 (187–257)	<0.001
Age (years)	516	61 (54–68)	65 (59–72)	61 (53.8–67)	56 (51–63)	<0.001
Sex (%male)	516	63	70	55	64	0.01
Dialysis duration (year)	516	9.2 (3.8–15.9)	9.5 (3.5–17.5)	11.4 (5.5–16.9)	6.8 (3.1–12.8)	0.003
Diabetic kidney disease (%)	516	21	22	15	28	0.02
Pre-existing CVD (%)	516	33	43	27	29	0.002
Hypertension (%)	516	41	87	85	87	0.76
Smoker (%)	516	86	43	41	39	0.79
HDL-C (mg/dL)	516	44 (36–54)	46 (36–56)	45 (37–57)	41 (35–50)	0.02
Non-HDL-C (mg/dL)	516	115 (91–138)	106 (86–131)	116 (90–144)	121 (100–147)	<0.001
Dyslipidemia (%)	516	50	45	49	56	0.10
BMI (kg/m^2)	516	21.6 (19.6–23.4)	20.7 (19.1–22.5)	21.3 (19.4–23.2)	22.7 (20.8–24.4)	<0.001
Serum albumin (g/dL)	516	3.7 (3.5–3.9)	3.6 (3.4–3.8)	3.7 (3.5–3.9)	3.8 (3.6–4.0)	<0.001
CRP (mg/dL)	516	0.14 (0.05–0.41)	0.14 (0.06–0.46)	0.14 (0.05–0.41)	0.13 (0.04–0.31)	0.23
Calcium (mg/dL)	516	9.1 (8.6–9.8)	9.0 (8.3–9.7)	9.2 (8.6–9.9)	9.2 (8.6–9.8)	0.04
Phosphate (mg/dL)	516	5.8 (5–6.6)	5.5 (4.7–6.4)	5.8 (5.2–6.8)	5.9 (5.1–6.8)	<0.001
Intact PTH (pg/mL)	516	118 (41–215.8)	118 (55–194)	135 (42.8–258)	106 (34–191)	0.39
Use of VDRA (%)	516	36	42	33	34	0.18
Hematocrit (%)	516	30.7 (28.6–32.4)	30.6 (28.5–32.5)	30.3 (28.3–32.2)	31 (29–32.5)	0.18
ESA dose (units/wk)	516	9000 (7500–9000)	9000 (7500–9000)	9000 (7500–9000)	9000 (6000–9000)	0.18
Use of IV iron (%)	516	58	62	62	50	0.02
Hypothyroidism (%)	516	11	14	14	4	0.002

The table gives medians (interquartile ranges) for continuous variables and percentages for categorical variables.
P values by Kruskal-Wallis test or χ^2 test.
Abbreviations: IGF-1, insulin-like growth factor 1; T, tertile; CVD, cardiovascular disease; HDL, high-density lipoprotein; BMI, body mass index; CRP, C-reactive protein; PTH, parathyroid hormone; VDRA, vitamin D receptor activator; ESA, erythropoiesis-stimulating agent; IV-iron, intravenous iron preparation.
Conversion factors for units: HDL-C and Non-HDL-C in mg/dL to mmol/L, x 0.02586; phosphorus in mg/dL to mmol/L, x 0.3229.

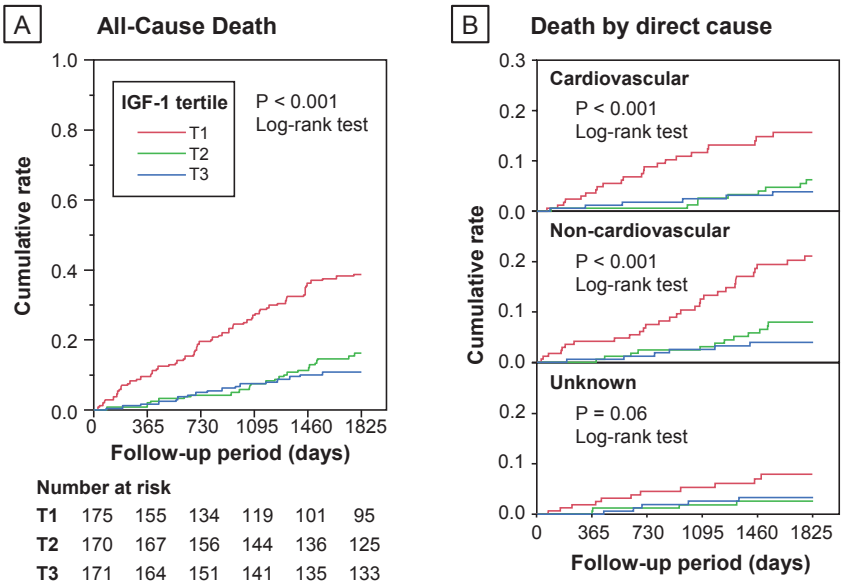

Fig. 2. Kaplan–Meier curves for the associations of IGF-1 and all-cause mortality and cause-specific mortality

The left panel (A) illustrates the Kaplan–Meier curves showing that the risk of all-cause mortality was significantly different among the IGF-1 tertiles. The right panel (B) indicates that a lower IGF-1 was associated with both cardiovascular and non-cardiovascular deaths.
Abbreviations: IGF-1, insulin-like growth factor 1; T, tertile.

Table 2. Multivariable-adjusted association of IGF-1 with all-cause mortality

Models	Adjustment	IGF-1 tertile			*P* for trend
		T1	T2	T3	
1	Unadjusted	4.32 (2.59–7.62)	1.45 (0.79–2.73)	1.00 (Referent)	<0.001
2	Age, sex, DKD or not, duration of HD, and prior CVD	2.47 (1.43–4.46)	1.12 (0.60–2.14)	1.00 (Referent)	<0.001
3	Model 2 + Hypertension, Dyslipidemia, and Smoking	1.25 (1.00–1.56)	1.00 (0.80–1.24)	1.00 (Referent)	0.07
4	Model 2 + BMI, Serum albumin, and Log CRP	2.15 (1.24–3.93)	1.08 (0.58–2.05)	1.00 (Referent)	<0.001
5	Model 2 + Calcium, Phosphate, intact PTH, and Use of VDRA	2.50 (1.44–4.56)	1.12 (0.60–2.14)	1.00 (Referent)	<0.001
6	Model 2 + Hematocrit, Dose of ESA, and Use of IV-iron	2.39 (1.38–4.33)	1.06 (0.57–2.04)	1.00 (Referent)	<0.001
7	Model 2 + Hypothyroidism	2.46 (1.43–4.46)	1.12 (0.60–2.14)	1.00 (Referent)	<0.001

P values by Wilcoxon rank sum test.
Abbreviations: IGF-1, insulin-like growth factor 1; T, tertile; DKD, diabetic kidney disease; HD, hemodialysis; CVD, cardiovascular disease; BMI, body mass index; CRP, C-reactive protein; PTH, parathyroid hormone; VDRA, vitamin D receptor activator; ESA, erythropoiesis-stimulating agent; IV-iron, intravenous iron preparation. Dyslipidemia was defined as use of statin, Non-HDL-C ≥ 150 mg/dL, and/or HDL-C ≤ 40 mg/dL, with these lipid levels being derived from the target levels for patients with chronic kidney disease recommended by the guideline of Japan Atherosclerosis Society. Conversion factors for units: phosphorus in mg/dL to mmol/L, x 0.3229.

cardiovascular causes (infection, N = 22; uremia, N = 2; and others, N = 5), whereas the direct cause was unknown for the remaining 5 patients. The Kaplan–Meier analysis showed that a lower IGF-1 level was significantly associated with a higher risk of death after infection **(Fig. 4B)**. This association remained significant when analyzed using a Cox model adjusted for the possible confounders **(Table 4)**.

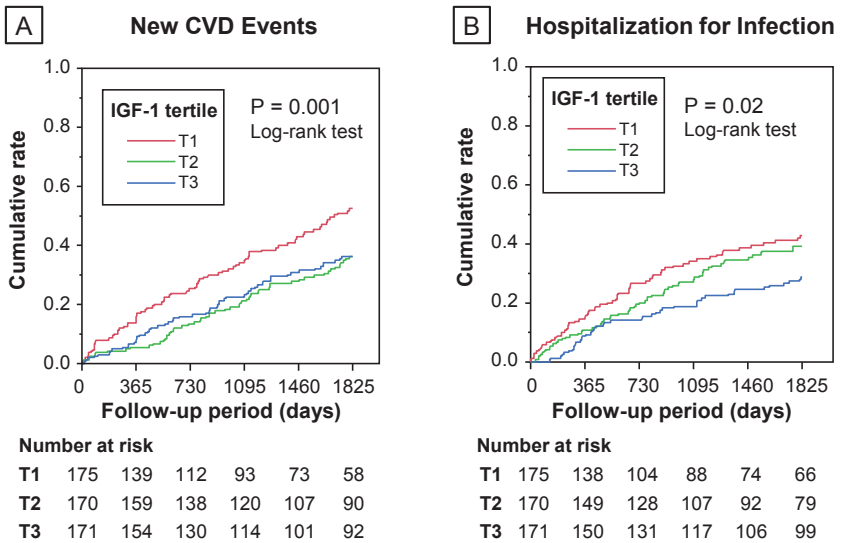

Fig. 3. Kaplan–Meier curves showing the associations of IGF-1 tertile with new CVD events and infection

The left panel (A) and right panel (B) show that the risks of occurrence of new CVD events and hospitalization for infection were different among the tertiles of IGF-1 in an unadjusted model.
Abbreviations: CVD, cardiovascular disease; IGF-1, insulin-like growth factor 1; T, tertile.

Table 3. Multivariable-adjusted association of IGF-1 with new CVD event and hospitalization for infection

Outcome	Model	Adjustment	IGF-1 tertile			*P* for trend
			T1	T2	T3	
CVD event	1	Unadjusted	1.67 (1.18–2.36)	0.96 (0.66–1.39)	1.00 (Referent)	0.005
	2	Age, sex, DKD or not, duration of HD, and prior CVD	1.07 (0.74–1.55)	0.84 (0.57–1.24)	1.00 (Referent)	0.70
	3	Model 2 + Hypertension, Smoking, and Dyslipidemia	1.03 (0.71–1.49)	0.82 (0.56–1.21)	1.00 (Referent)	0.85
	4	Model 2 + BMI, Serum albumin, and Log CRP	1.00 (0.69–1.47)	0.81 (0.55–1.19)	1.00 (Referent)	0.96
	5	Model 2 + Calcium, Phosphate, intact PTH, and Use of VDRA	1.12 (0.77–1.63)	0.86 (0.59–1.27)	1.00 (Referent)	0.54
	6	Model 2 + Hematocrit, Dose of ESA, and Use of IV-iron	1.06 (0.73–1.54)	0.84 (0.57–1.24)	1.00 (Referent)	0.71
	7	Model 2 + Hypothyroidism	1.04 (0.72–1.52)	0.83 (0.56–1.22)	1.00 (Referent)	0.78
Infection	1	Unadjusted	1.74 (1.19–2.57)	1.46 (1.00–2.17)	1.00 (Referent)	0.004
	2	Age, sex, DKD or not, duration of HD, and prior CVD	1.43 (0.95–2.17)	1.38 (0.93–2.07)	1.00 (Referent)	0.09
	3	Model 2 + Hypertension, Smoking, and Dyslipidemia	1.18 (0.90–1.56)	1.05 (0.80–1.37)	1.00 (Referent)	0.24
	4	Model 2 + BMI, Serum albumin, and Log CRP	1.32 (0.87–2.03)	1.28 (0.86–1.93)	1.00 (Referent)	0.20
	5	Model 2 + Calcium, Phosphate, intact PTH, and Use of VDRA	1.44 (0.95–2.19)	1.38 (0.93–2.06)	1.00 (Referent)	0.09
	6	Model 2 + Hematocrit, Dose of ESA, and Use of IV-iron	1.37 (0.91–2.08)	1.29 (0.86–1.95)	1.00 (Referent)	0.14
	7	Model 2 + Hypothyroidism	1.38 (0.92–2.09)	1.35 (0.91–2.01)	1.00 (Referent)	0.12

Abbreviations: IGF-1, insulin-like growth factor 1; T, tertile; CVD, cardiovascular disease; DKD, diabetic kidney disease; HD, hemodialysis; BMI, body mass index; CRP, C-reactive protein; PTH, parathyroid hormone; VDRA, vitamin D receptor activator; ESA, erythropoiesis-stimulating agent; IV-iron, intravenous iron preparation.

Discussion

We started this study to examine the associations between IGF-1 and the preplanned key outcomes, namely, all-cause mortality, new CVD events, and death after new CVD events. A low IGF-1 level was an independent predictor of all-cause death, and it also predicted cardiovascular and non-cardiovascular deaths. IGF-1 level did not have an independent association with new CVD events, whereas a lower IGF-1 was significantly associated with death after a new CVD event. Additional analyses showed that IGF-1 was not independently associated with hospitalization for infection, whereas a low IGF-1

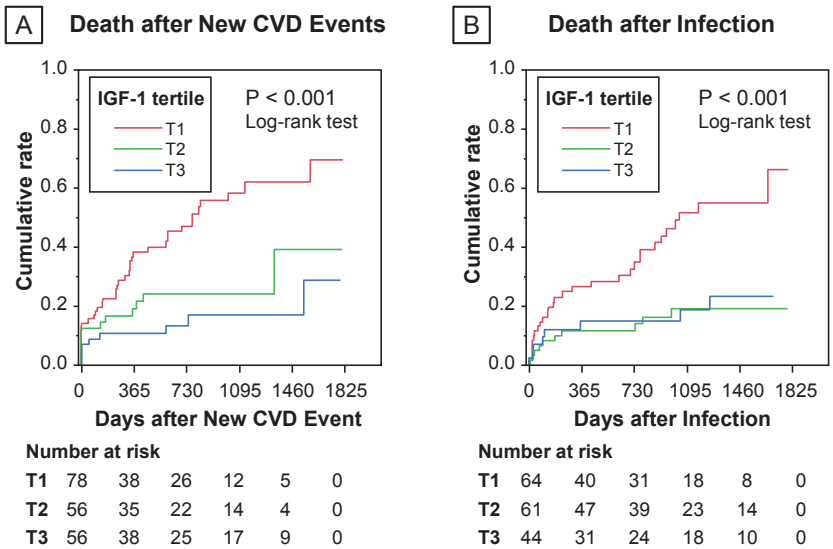

Fig. 4. Kaplan–Meier curves of death after new CVD events and death after infection

The left panel (A) shows that a lower IGF-1 level was associated with a higher risk of death after CVD events in an unadjusted model. The right panel (B) shows the similar association between IGF-1 and the risk of death after hospitalization for infection.
Abbreviations: CVD, cardiovascular disease; IGF-1, insulin-like growth factor 1; T, tertile.

Table 4. Multivariable-adjusted associations of IGF-1 with death after new CVD events and death after infection

Outcome	Models	Adjustment	HR (95%CI) per 1 SD higher IGF-1	*P* value
Death after new CVD events	1	Unadjusted	0.53 (0.38–0.73)	<0.001
	2	Age and sex	0.59 (0.41–0.82)	0.002
	3	Model 2 + DKD or not, duration of HD, and prior CVD	0.60 (0.42–0.85)	0.003
	4	Model 2 + BMI, serum albumin, and Log-CRP	0.61 (0.42–0.87)	0.006
	5	Model 2 + Hypothyroidism	0.59 (0.41–0.83)	0.002
Death after infection	1	Unadjusted	0.50 (0.33–0.74)	<0.001
	2	Age and sex	0.54 (0.35–0.81)	0.002
	3	Model 2 + DKD or not, duration of HD, and prior CVD	0.61 (0.40–0.91)	0.02
	4	Model 2 + BMI, serum albumin, and Log-CRP	0.66 (0.42–1.02)	0.06
	5	Model 2 + Hypothyroidism	0.54 (0.35–0.81)	0.002

The table gives HRs (95% CIs) per 1 SD higher IGF-1 for death after new CVD events and death after hospitalization for infection.
Abbreviations: HR, hazard ratio; 95%CI, 95% confidence interval; SD, standard deviation; IGF-1, insulin-like growth factor 1; CVD, cardiovascular disease; DKD, diabetic kidney disease; HD, hemodialysis; BMI, body mass index; and CRP, C-reactive protein.

level predicted death after hospitalization for infection. These results may indicate that a low serum IGF-1 concentration is closely related with vulnerability to fatal outcomes in the case of stressful conditions such as cardiovascular and infectious events in patients undergoing hemodialysis.

Previous studies by Jia *et al.*[12] and Nilsson *et al.*[20] reported that a lower IGF-1 level was an independent predictor of all-cause mortality in patients with kidney failure starting hemodialysis or peritoneal dialysis. These previous studies are consistent with our results in patients on maintenance hemodialysis. In our study, a lower IGF-1 predicts both cardiovascular and non-cardiovascular deaths based on the direct causes of death. Then, one may speculate that a lower IGF-1 could predict both cardiovascular and non-cardiovascular events. However, IGF-1 was not an independent predictor of either new CVD events or hospitalization for infection. Nonetheless, a lower IGF-1 was significantly predictive of shorter survival after CVD events and infection.

How can we understand these results? The relative risk of cardiovascular death in patients treated

with hemodialysis was reported in the range of 10–30 as compared with the general population[1]. Although the risks for incident acute myocardial infarction[2] and incident stroke[26] in hemodialysis patients are higher than those in the general population, the elevated risk for incident CVD events does not fully explain the extremely high risk for cardiovascular death in this population. Importantly, hemodialysis patients have a lower survival rate after myocardial infarction[2] and stroke[26]. Thus, the extremely elevated risk for cardiovascular mortality can be explained by the synergistic effects of a high risk for the occurrence of CVD events and a high risk for subsequent death[3, 27, 28]. Going back to the interpretation of our results, if we can divide the pathway to cardiovascular event-related death into two steps, namely, the occurrence of a CVD event (first step) and death after the CVD event (second step), a lower IGF-1 can be regarded as a factor preferentially associated with the second step.

At least two previous studies examined the predictors of death after incident CVD event among hemodialysis patients. These studies[29, 30] reported that a higher age, higher level of CRP, and lower BMI were among the independent factors associated with death after the composite of myocardial infarction and stroke. These reports may indicate that the so-called "malnutrition–inflammation–atherosclerosis syndrome"[31], "malnutrition–inflammation complex syndrome"[32], and PEW[33] are the factors closely related to the second step to cardiovascular death. In the present study, we showed that a lower IGF-1 was predictive of death after a new CVD event independent of age, sex, dialysis duration, diabetic kidney disease or not, and prior CVD history. When adjustment was done for BMI, serum albumin, and CRP, the association between IGF-1 and death after CVD events remained significant. Thus, a lower IGF-1 appears to represent risk of poor survival after CVD events independent of PEW.

We found that a lower IGF-1 level was independently associated with not only death after new CVD events but also death after infection. Taken together, a lower IGF-1 level could represent vulnerability to fatal outcomes when the patient is exposed to some stressful conditions. According to Fried *et al.*[34], "geriatricians define frailty as a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes." Therefore, a lower IGF-1 can be regarded as a biomarker of frailty by this definition. In the absence of a gold standard criteria for frailty, it is usually diagnosed using the phenotypes including shrinking, weakness, self-reported exhaustion, slowness, and low physical activity level[34]. In the elderly general population, IGF-1 was associated with muscle weakness[35], decreased tongue pressure[36], and functional deterioration after hospitalization[37]. Also, in patients treated with hemodialysis, a lower IGF-1 was associated with a lower muscle strength[21]. Taken these findings into consideration, a lower serum IGF-1 level may serve as a biomarker of frailty in hemodialysis patients, although we did not have information for the phenotypic criteria for frailty in this study.

What is the relationship between low IGF-1, PEW, and frailty? In this study, a low IGF-1 level was associated with all-cause mortality independent of the PEW-related factors (BMI, serum albumin, and CRP). In the same model, these PEW-related factors were also significant predictors of all-cause mortality (data not shown), suggesting that both low IGF-1 and PEW were associated with vulnerability to adverse outcomes. Similarly, a lower IGF-1 level was associated with death after a new CVD event and death after hospitalization for infection independent of these PEW-related factors. Presumably, IGF-1 and PEW play different roles in the pathogenesis of vulnerable clinical course. IGF-1 is a growth factor that promotes cell proliferation and tissue repair, whereas protein-energy store is used for tissue repair processes. Therefore, we interpret our data to indicate that both sufficient IGF-1 and protein-energy store are required for better survival after a stressful condition, such as CVD and infection. In other words, the results suggest that a low IGF-1 level, in addition to PEW, is a key factor that predisposes patients to frailty.

Then, what causes decreased IGF-1 levels in these patients? First, since hepatic IGF-1 secretion is stimulated by GH, the suppression of GH secretion from the pituitary gland can be one of the reasons. Metabolic acidosis in kidney failure was shown to suppress GH secretion[38]. Second, hepatic dysfunction may cause low IGF-1. Because hepatitis C viral (HCV) hepatitis was highly prevalent among hemodialysis patients in 1990s[39], we looked for HCV antibody data in 2004 in medical records; however, it was only available for the 284 patients of this cohort, and 14% of these patients were HCV(+). Thus, the role of HCV(+) in low IGF-1 cannot be ruled out. Third, endocrine disorders other than pituitary hormones may affect IGF-1 level. Among these, hypothyroidism is known to be causally related to low IGF-1 level[22]. In our patients, the presence of hypothyroidism was found to be an independent factor associated with a lower IGF-1 level **(Supplemental Table 2)**. Finally, a higher age is the

most powerful factor associated with a lower IGF-1 level **(Supplemental Table 2)**. Importantly, however, the inverse associations of low IGF-1 with all-cause mortality, death after CVD event, and death after infection remained significant when the models were adjusted for confounding factors, including hypothyroidism and age **(Tables 2, 3, 4)**.

This study has several limitations. First, because this study included only patients undergoing maintenance hemodialysis in Japan, we are not sure that the results of this study are applicable to other populations. Second, because the results of this study were based on a single measurement of serum IGF-1, the associations between IGF-1 and clinical outcomes may be underestimated or overestimated. Third, due to lack of data for the phenotypic criteria for frailty, we were unable to examine the possible relationship between serum IGF-1 and frailty as assessed by the commonly used phenotypic criteria. Fourth, although IGF-1 promotes cell proliferation and a higher level of IGF-1 is known to be associated with increased risk of some cancers such as breast cancer[40, 41], we have no data on the prevalence of cancer at baseline. However, it is difficult to explain the observed inverse association between IGF-1 and mortality risk by cancer risk associated with high IGF-1. Finally, because of the observational nature of this study, the observed associations do not necessarily indicate causality.

Conclusion

In conclusion, a lower IGF-1 level was an independent predictor of all-cause mortality, and it also predicted poor survival after new CVD events and infection in a cohort of hemodialysis patients. These findings may indicate serum IGF-1 as a biomarker of frailty in this population. Clearly, further studies are needed to confirm our observations in other settings and test the value of IGF-1 with the simultaneous assessment of frailty using widely used criteria.

Acknowledgements

Preliminary results of this study were presented as a poster (FP-705) at the 56th Annual Meeting of the ERA-EDAT in Budapest, Hungary (June 13-16, 2019), and abstract was published. Also, part of this study was presented as a poster (2-P-2-1) at the 52nd Annual Meeting of the Japan Atherosclerosis Society in Nagoya, Japan (Web version; June 17-31, 2020).

This study was partly supported by a grant for TS from the Japan Dialysis Outcome Research Foundation, Tokyo, Japan (No. 002). The funder played no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflict of Interest Statement

All authors declared no competing interests relevant to this study.

References

1) Foley RN, Parfrey PS and Sarnak MJ: Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis, 1998; 32: S112-119
2) Iseki K and Fukiyama K: Long-term prognosis and incidence of acute myocardial infarction in patients on chronic hemodialysis. The Okinawa Dialysis Study Group. Am J Kidney Dis, 2000; 36: 820-825
3) Wanner C, Amann K and Shoji T: The heart and vascular system in dialysis. Lancet, 2016; 388: 276-284
4) Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW, American Heart Association Councils on Kidney in Cardiovascular Disease HBPRCC, Epidemiology and Prevention: Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation, 2003; 108: 2154-2169
5) Kalantar-Zadeh K: Causes and consequences of the reverse epidemiology of body mass index in dialysis patients. J Ren Nutr, 2005; 15: 142-147
6) Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, Franch H, Guarnieri G, Ikizler TA, Kaysen G, Lindholm B, Massy Z, Mitch W, Pineda E, Stenvinkel P, Trevino-Becerra A and Wanner C: A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int, 2008; 73: 391-398
7) Morioka T, Emoto M, Tabata T, Shoji T, Tahara H, Kishimoto H, Ishimura E and Nishizawa Y: Glycemic control is a predictor of survival for diabetic patients on hemodialysis. Diabetes Care, 2001; 24: 909-913
8) Shinohara K, Shoji T, Emoto M, Tahara H, Koyama H, Ishimura E, Miki T, Tabata T and Nishizawa Y: Insulin resistance as an independent predictor of cardiovascular mortality in patients with end-stage renal disease. J Am Soc Nephrol, 2002; 13: 1894-1900
9) Carrero JJ, Qureshi AR, Parini P, Arver S, Lindholm B, Barany P, Heimburger O and Stenvinkel P: Low serum testosterone increases mortality risk among male dialysis patients. J Am Soc Nephrol, 2009; 20: 613-620
10) Kakiya R, Shoji T, Hayashi T, Tatsumi-Shimomura N, Tsujimoto Y, Tabata T, Shima H, Mori K, Fukumoto S, Tahara H, Koyama H, Emoto M, Ishimura E, Nishizawa

Y and Inaba M: Decreased serum adrenal androgen dehydroepiandrosterone sulfate and mortality in hemodialysis patients. Nephrol Dial Transplant, 2012; 27: 3915-3922
11) Zoccali C, Tripepi G, Cutrupi S, Pizzini P and Mallamaci F: Low triiodothyronine: a new facet of inflammation in end-stage renal disease. J Am Soc Nephrol, 2005; 16: 2789-2795
12) Jia T, Gama Axelsson T, Heimburger O, Barany P, Lindholm B, Stenvinkel P and Qureshi AR: IGF-1 and survival in ESRD. Clin J Am Soc Nephrol, 2014; 9: 120-127
13) Cohick WS and Clemmons DR: The insulin-like growth factors. Annu Rev Physiol, 1993; 55: 131-153
14) Daughaday WH and Rotwein P: Insulin-like growth factors I and II. Peptide, messenger ribonucleic acid and gene structures, serum, and tissue concentrations. Endocr Rev, 1989; 10: 68-91
15) Isojima T, Shimatsu A, Yokoya S, Chihara K, Tanaka T, Hizuka N, Teramoto A, Tatsumi KI, Tachibana K, Katsumata N and Horikawa R: Standardized centile curves and reference intervals of serum insulin-like growth factor-I (IGF-I) levels in a normal Japanese population using the LMS method. Endocr J, 2012; 59: 771-780
16) van Nieuwpoort IC, Vlot MC, Schaap LA, Lips P and Drent ML: The relationship between serum IGF-1, handgrip strength, physical performance and falls in elderly men and women. Eur J Endocrinol, 2018; 179: 73-84
17) Petrossians P, Daly AF, Natchev E, Maione L, Blijdorp K, Sahnoun-Fathallah M, Auriemma R, Diallo AM, Hulting AL, Ferone D, Hana V, Jr., Filipponi S, Sievers C, Nogueira C, Fajardo-Montanana C, Carvalho D, Hana V, Stalla GK, Jaffrain-Rea ML, Delemer B, Colao A, Brue T, Neggers S, Zacharieva S, Chanson P and Beckers A: Acromegaly at diagnosis in 3173 patients from the Liege Acromegaly Survey (LAS) Database. Endocr Relat Cancer, 2017; 24: 505-518
18) Orme SM, McNally RJ, Cartwright RA and Belchetz PE: Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. J Clin Endocrinol Metab, 1998; 83: 2730-2734
19) Ruidavets JB, Luc G, Machez E, Genoux AL, Kee F, Arveiler D, Morange P, Woodside JV, Amouyel P, Evans A, Ducimetiere P, Bingham A, Ferrieres J and Perret B: Effects of insulin-like growth factor 1 in preventing acute coronary syndromes: the PRIME study. Atherosclerosis, 2011; 218: 464-469
20) Nilsson E, Carrero JJ, Heimburger O, Hellberg O, Lindholm B and Stenvinkel P: A cohort study of insulin-like growth factor 1 and mortality in haemodialysis patients. Clin Kidney J, 2016; 9: 148-152
21) Delanaye P, Bataille S, Quinonez K, Buckinx F, Warling X, Krzesinski JM, Pottel H, Burtey S, Bruyere O and Cavalier E: Myostatin and Insulin-Like Growth Factor 1 Are Biomarkers of Muscle Strength, Muscle Mass, and Mortality in Patients on Hemodialysis. J Ren Nutr, 2019; 29: 511-520
22) Miell JP, Taylor AM, Zini M, Maheshwari HG, Ross RJ and Valcavi R: Effects of hypothyroidism and hyperthyroidism on insulin-like growth factors (IGFs) and growth hormone- and IGF-binding proteins. J Clin Endocrinol Metab, 1993; 76: 950-955
23) Umemura S, Arima H, Arima S, Asayama K, Dohi Y, Hirooka Y, Horio T, Hoshide S, Ikeda S, Ishimitsu T, Ito M, Ito S, Iwashima Y, Kai H, Kamide K, Kanno Y, Kashihara N, Kawano Y, Kikuchi T, Kitamura K, Kitazono T, Kohara K, Kudo M, Kumagai H, Matsumura K, Matsuura H, Miura K, Mukoyama M, Nakamura S, Ohkubo T, Ohya Y, Okura T, Rakugi H, Saitoh S, Shibata H, Shimosawa T, Suzuki H, Takahashi S, Tamura K, Tomiyama H, Tsuchihashi T, Ueda S, Uehara Y, Urata H and Hirawa N: The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019). Hypertens Res, 2019; 42: 1235-1481
24) Kinoshita M, Yokote K, Arai H, Iida M, Ishigaki Y, Ishibashi S, Umemoto S, Egusa G, Ohmura H, Okamura T, Kihara S, Koba S, Saito I, Shoji T, Daida H, Tsukamoto K, Deguchi J, Dohi S, Dobashi K, Hamaguchi H, Hara M, Hiro T, Biro S, Fujioka Y, Maruyama C, Miyamoto Y, Murakami Y, Yokode M, Yoshida H, Rakugi H, Wakatsuki A, Yamashita S, Committee for E and Clinical Management of A: Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017. J Atheroscler Thromb, 2018; 25: 846-984
25) Yamazaki Y, Shoji T, Miyashima M, Nagata Y, Kakutani Y, Ochi A, Morioka T, Nakatani S, Mori K, Tsujimoto Y and Emoto M: Low Free Triiodothyronine Level as a Predictor of Cardiovascular Events and All-Cause Mortality in Patients Undergoing Hemodialysis: The DREAM Cohort. J Atheroscler Thromb, 2021; 28: 1071-1082
26) Iseki K, Fukiyama K and Okawa Dialysis Study G: Clinical demographics and long-term prognosis after stroke in patients on chronic haemodialysis. The Okinawa Dialysis Study (OKIDS) Group. Nephrol Dial Transplant, 2000; 15: 1808-1813
27) Nishizawa Y, Shoji T, Ishimura E, Inaba M and Morii H: Paradox of risk factors for cardiovascular mortality in uremia: is a higher cholesterol level better for atherosclerosis in uremia? Am J Kidney Dis, 2001; 38: S4-7
28) Shoji T and Nishizawa Y: Chronic kidney disease as a metabolic syndrome with malnutrition--need for strict control of risk factors. Intern Med, 2005; 44: 179-187
29) Shoji T, Masakane I, Watanabe Y, Iseki K and Tsubakihara Y: Elevated non-high-density lipoprotein cholesterol (non-HDL-C) predicts atherosclerotic cardiovascular events in hemodialysis patients. Clin J Am Soc Nephrol, 2011; 6: 1112-1120
30) Shoji T, Marubayashi S, Shigematsu T, Iseki K and Tsubakihara Y: Use of vitamin D receptor activator, incident cardiovascular disease and death in a cohort of hemodialysis patients. Ther Apher Dial, 2015; 19: 235-244
31) Stenvinkel P, Heimburger O, Lindholm B, Kaysen GA and Bergstrom J: Are there two types of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation and atherosclerosis (MIA syndrome). Nephrol Dial Transplant, 2000; 15: 953-960

32) Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM and Kopple JD: Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. Am J Kidney Dis, 2003; 42: 864-881
33) Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, Franch H, Guarnieri G, Ikizler TA, Kaysen G, Lindholm B, Massy Z, Mitch W, Pineda E, Stenvinkel P, Treviño-Becerra A and Wanner C: A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int, 2008; 73: 391-398
34) Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G and McBurnie MA: Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci, 2001; 56: M146-156
35) Chew J, Tay L, Lim JP, Leung BP, Yeo A, Yew S, Ding YY and Lim WS: Serum Myostatin and IGF-1 as Gender-Specific Biomarkers of Frailty and Low Muscle Mass in Community-Dwelling Older Adults. J Nutr Health Aging, 2019; 23: 979-986
36) Shimizu Y, Yamanashi H, Noguchi Y, Koyamatsu J, Higashi M, Fukui S, Kawashiri SY, Arima K, Takamura N and Maeda T: Insulin-Like Growth Factor-1 (IGF-1) and Reduced Tongue Pressure in Relation to Atherosclerosis Among Community-Dwelling Elderly Japanese Men: A Cross-Sectional Study. Dysphagia, 2020; 35: 948-954
37) de Saint-Hubert M, Jamart J, Morrhaye G, Martens HJ, Geenen V, Duy Vo TK, Toussaint O and Swine C: Serum IL-6 and IGF-1 improve clinical prediction of functional decline after hospitalization in older patients. Aging Clin Exp Res, 2011; 23: 106-111
38) Brungger M, Hulter HN and Krapf R: Effect of chronic metabolic acidosis on the growth hormone/IGF-1 endocrine axis: new cause of growth hormone insensitivity in humans. Kidney Int, 1997; 51: 216-221
39) Hayashi J, Nakashima K, Kajiyama W, Noguchi A, Morofuji M, Maeda Y and Kashiwagi S: Prevalence of antibody to hepatitis C virus in hemodialysis patients. Am J Epidemiol, 1991; 134: 651-657
40) Monson KR, Goldberg M, Wu HC, Santella RM, Chung WK and Terry MB: Circulating growth factor concentrations and breast cancer risk: a nested case-control study of IGF-1, IGFBP-3, and breast cancer in a family-based cohort. Breast Cancer Res, 2020; 22: 109
41) Rigiracciolo DC, Nohata N, Lappano R, Cirillo F, Talia M, Scordamaglia D, Gutkind JS and Maggiolini M: IGF-1/IGF-1R/FAK/YAP Transduction Signaling Prompts Growth Effects in Triple-Negative Breast Cancer (TNBC) Cells. Cells, 2020; 9: 1010

Supplemental Table 1. Definitions of CVD events in the DREAM cohort

CVD event	Definition
Ischemic heart disease (IHD)	IHD included myocardial infarction, percutaneous coronary intervention, and coronary artery bypass grafting. Angina pectoris was included in IHD only when myocardial ischemia was evident by electrocardiogram and/or stress myocardial scintigraphy.
Stroke	Stroke denoted symptomatic stroke with sudden onset of neurological deficit confirmed by magnetic resonance imaging (MRI) and/or X-ray computed tomography (CT) of the brain. Based on available information, stroke was classified into ischemic stroke, hemorrhagic stroke, and unspecified. Transient ischemic attack was not included in stroke.
Peripheral artery disease (PAD)	PAD was diagnosed when the patient had history of amputation of lower limb, percutaneous transluminal angioplasty, and/or bypass grafting due to ischemic limb. We did not include intermittent claudication, leg pain at rest, or foot ulceration in PAD if none of the above-mentioned treatment was performed.
Congestive heart failure (CHF)	CHF was defined by severe pulmonary edema requiring hospitalization, excluding pneumonia, but not excluding non-cardiac circulatory failure.
Valve disease	Valve disease was diagnosed when the patient had valve replacement.

Sudden deaths are considered as fatal CVD events.
Abbreviations: MRI, magnetic resonance imaging; CT, computed tomography.

Supplemental Table 2. Factors associated with IGF-1 levels

Factors	Standardized coefficient (ß)	*P* value
Age	–0.299	<0.001
Sex (male=1, female=0)	–0.131	<0.001
Diabetic kidney disease (yes=1, no=0)	–0.027	0.53
Dialysis duration	–0.152	<0.001
Pre-existing cardiovascular disease (yes=1, no=0)	–0.006	0.89
Body mass index	0.168	<0.001
Serum albumin	0.182	<0.001
Log C-reactive protein	0.012	0.77
Hypothyroidism (yes=1, no=0)	–0.078	0.046

Factors associated with IGF-1 levels were examined by a multivariable-adjusted linear regression model. Logarithmically transformed IGF-1 was entered in the model so that the residual was deemed to have normal distribution. Hypothyroidism was defined in the text.

Supplemental Table 3. Associations of IGF-1 with death by direct cause

Direct cause of death	Number of cases	Unadjusted HR (per 1 SD higher IGF-1)	HR adjusted for age and sex (per 1 SD higher IGF-1)
Cardiovascular	38	0.49 (0.31–0.74) *P*<0.001	0.62 (0.38–0.95) *P*=0.04
Non-cardiovascular	48	0.30 (0.19–0.47) *P*<0.001	0.36 (0.22–0.57) *P*<0.001
Infection	24	0.28 (0.14–0.51) *P*<0.001	0.30 (0.15–0.57) *P*< 0.001
Other than infection	24	0.33 (0.17–0.59) *P*<0.001	0.44 (0.22–0.81) *P*=0.01
Unknown	20	0.58 (0.31–0.97) *P*=0.04	0.74 (0.39–1.28) *P*=0.31

All-cause deaths were classified into cardiovascular death and non-cardiovascular death based on direct cause of death. The direct cause of death was unknown for 20 cases. Non-cardiovascular causes (48 cases) were further divided into infection (24 cases) and other than infection (24 cases).