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Association between geriatric nutritional risk index and stroke risk in hemodialysis patients: 10-Years outcome of the Q-Cohort study

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ABSTRACT

Backgrounds and aims: The geriatric nutritional risk index (GNRI), which is calculated using the serum albumin level and body mass index, is a nutritional marker associated with an increased risk of cardiovascular events in patients who are receiving hemodialysis. However, no studies have examined the association between the GNRI level and the incidence of stroke in this population.

Methods: Three thousand forty-five patients were registered in the Q-Cohort Study, which is a multicenter, observational cohort of hemodialysis patients. The main outcomes were brain infarction and brain hemorrhage. The main exposure was GNRI levels at baseline. Patients were divided into quartiles on the basis of baseline GNRI levels: Q1, <90.7; Q2, 90.7–95.5; Q3, 95.6–99.8; Q4, >99.8. The risk of brain infarction or hemorrhage was estimated using the multivariable-adjusted Cox proportional hazard risk models and restricted cubic spline analyses.

Results: During the 10-year follow-up period, 326 patients developed brain infarction and 149 patients developed brain hemorrhage. Cox proportional hazard risk models showed that the risk of brain infarction and hemorrhage in Q1 was significantly higher than that in Q4 group. The hazard ratios [95% confidence intervals] were 1.49 [1.05–2.12] and 1.89 [1.11–3.20], respectively. Restricted cubic spline curves showed that a lower GNRI was incrementally associated with an increased risk for both brain infarction and brain hemorrhage.

Conclusions: Our results suggest that a lower GNRI is an independent risk factor for both brain infarction and hemorrhage in patients who are receiving maintenance hemodialysis.

1. Introduction

Patients with end-stage kidney disease have a five to ten-fold increased risk of developing stroke compared with the general population [1]. The mortality rate by stroke in patients who are undergoing hemodialysis is three-times higher than that in patients who are not undergoing dialysis [2]. To date, various risk factors for stroke have been identified [3–5]. However, the incidence rate of stroke and its related mortality remain extremely high in patients who are receiving maintenance hemodialysis [6]. Therefore, there is an urgent need to identify modifiable risk factors for stroke in this population.

Malnutrition is highly prevalent in patients with end-stage kidney disease, and it increases the risk of mortality [7–9]. Appropriate tools to assess the nutritional status are needed to improve hemodialysis patient longevity. Among a variety of surrogate markers for malnutrition, both serum albumin level and body mass index (BMI) are frequently used to evaluate the nutritional status [9]. In the general population, hypoalbuminemia increases the risk of developing stroke [10], while a higher BMI is associated a higher risk of stroke [11]. In dialysis patients, lower BMI and hypoalbuminemia have been reported to be independent risk factors for stroke [12]. The geriatric nutritional risk index (GNRI), which is calculated based on the serum albumin and BMI levels, is a relatively

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new assessment tool for evaluating the nutritional status in older patients [13], and has been reported to correlate well with the malnutrition–inflammation score [14], which is the gold standard for nutritional evaluation in hemodialysis patients [15]. Previous research has demonstrated that GNRI is associated with all-cause, cardiovascular, and infection-related mortality, even in patients who are receiving hemodialysis [16–18]. GNRI was also reported to be associated with the risk of composite outcome in various cardiovascular diseases (CVDs) in dialysis patients [19,20]. However, the association of GNRI levels with the development of stroke has not been documented.

The purpose of the present study was to investigate the association between GNRI and the risk of developing brain infarction and hemorrhage individually, using the dataset in the Q-Cohort Study, which is a multicenter, observational study comprising Japanese patients who are receiving maintenance hemodialysis [3,21].

2. Materials and methods

2.1. Study design and population

The Q-Cohort Study is a multicenter, longitudinal, observational study designed to identify the risk factors for morbidity and mortality in patients undergoing hemodialysis. The details of the Q-Cohort Study are described elsewhere [22]. Briefly, we recruited 3598 outpatients aged 18 years or older who underwent hemodialysis between 31 December 2006 and 31 December 2007, in 39 dialysis facilities in Fukuoka and Saga Prefectures in Japan. All the patients were followed-up until 31 December 2016. We excluded 90 participants because of missing data on either baseline characteristics or outcomes, and 463 participants whose baseline BMI was not available. The remaining 3045 patients were used for the present analysis. The present study was performed in accordance with the Ethics of Clinical Research (Declaration of Helsinki). It was approved by the Clinical Research Ethics Committee of the Institutional Review Board at Kyushu University (Approval Number 20–31) and all participating institutions. Written informed consent was provided from all the patients before participation in the study. The ethics committee at all participant institutions waived the requirement for written informed consent for the additional follow-up surveys from 2011 to 2016 because of the retrospective nature of this study (Clinical Trial Registration: University Hospital Medical Information Network (UMIN) clinical trial registry, UMIN ID: 000000556).

2.2. Definition of GNRI

GNRI was calculated as previously reported [13], and is presented as follows:

GNRI = [14.89 × serum albumin (g/dL)] + [41.7 × body weight/ideal body weight].

Body weight/ideal body weight was set to 1 when the patient's body weight exceeded the ideal body weight. Instead of using the Lorentz formula in the original GNRI equation [13], the ideal body weight in the present study was defined as the value calculated from the height and a BMI of 22 kg/m^2, as previously reported [14].

2.3. Outcomes and covariates

The primary outcome was the first-ever incidence of brain infarction and brain hemorrhage. Stroke was defined as a sudden-onset neurological impairment lasting ≥24 h. Stroke types were confirmed by brain imaging, including computed tomography and magnetic resonance imaging, and they were classified as either brain infarction or hemorrhage by the attending physician. The patients were classified as having developed the first type of stroke and were censored for the subsequent stroke.

The main exposure was GNRI value at baseline. Potential confounding factors were age; sex; presence of diabetic nephropathy; history of CVDs; history of stroke; hemodialysis vintage; hemodialysis time (<5 h or ≥5 h); systolic blood pressure; cardiothoracic ratio (CTR); Kt/V for urea; normalized protein catabolism rate (nPCR); blood hemoglobin; serum creatinine, C-reactive protein (CRP), total cholesterol, corrected calcium (Ca), phosphate, and alkaline phosphatase (ALP) levels; and use of antihypertensive agents and erythropoiesis-stimulating agents (ESAs). Height and body weight were measured when the patient wore light clothing without shoes, and BMI (kg/m^2) was then calculated. History of CVDs included coronary artery disease, congestive heart failure, and peripheral arterial disease, whereas stroke was excluded. Blood samples were collected before starting hemodialysis on the first dialysis day of the week (i.e., Monday or Tuesday). The biochemical parameters were measured in different laboratories using an automated analyzer with standard procedures. The corrected serum Ca concentration was calculated using Payne's formula: corrected Ca (mg/dL) = observed total Ca (mg/dL) + [4.0 − serum albumin concentration (g/dL)] [23]. Single-pool Kt/V for urea on the basis of Daugirdas [24] was used as the index of adequacy of hemodialysis and was calculated without accounting for residual renal function.

2.4. Statistical analysis

Data are presented as the mean ± standard deviation, median (interquartile range) for continuous variables and number (percentage) for categorical variables. The patients were divided to quartiles on the basis of the GNRI at baseline as follows: quartile 1 (Q1): <90.7; Q2: 90.7–95.5; Q3: 95.6–99.8; and Q4: >99.8. The distribution of baseline characteristics across GNRI levels was compared using the following trend analyses: the Jonckheere–Terpstra test was used for continuous values and the Cochran–Armitage test was used for categorical values. Kaplan–Meier curves and log-rank tests were used to evaluate the event-free survival rate for brain infarction and brain hemorrhage on the basis of the GNRI levels.

Unadjusted, age- and sex-adjusted, and multivariable-adjusted Cox proportional hazards risk models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the outcome on the basis of the baseline GNRI levels. The assumption of the proportional hazards analysis was confirmed graphically using log cumulative hazard plots for each outcome, stratified on the basis of the GNRI levels, and tested using an analysis of Schoenfeld residuals. The multivariable-adjusted restricted cubic spline model was also used to determine whether there was a non-linear association between the GNRI level and the risk of brain infarction and brain hemorrhage. Restricted cubic spline curves were plotted using four knots that were located at the 5th, 35th, 65th, and 95th percentiles of GNRI. The median GNRI level (95.6) was chosen as the reference for each spline plot. All the multivariable-adjusted models included the following confounding factors that were selected based on previous clinical judgment, as follows: age; sex; presence of diabetic nephropathy; history of CVDs; history of stroke; hemodialysis vintage; hemodialysis time; systolic blood pressure; CTR; Kt/V for urea; nPCR; blood hemoglobin; serum creatinine, CRP, total cholesterol, corrected Ca, phosphate, and ALP levels; and use of antihypertensive agents and ESAs. Hemodialysis vintage and serum CRP, total cholesterol, and ALP levels were transformed logarithmically. As a sensitivity analysis, Fine–Gray proportional subdistribution hazards models were applied by treating all-cause mortality as a competing risk. As an additional analysis, the association between the baseline serum albumin levels and the incidence of brain infarction or hemorrhage, and the association between the baseline BMI levels and their incidence were separately analyzed using Cox proportional hazards risk models and restricted cubic spline analyses.

To test whether there were effect modifications regarding the association between GNRI levels and the risk of stroke, subgroup analyses that were stratified on the basis of the baseline characteristics were performed. Thus, patients were divided into binary data on the basis of the baseline characteristics. Median values were used as the cut-off

values for the continuous baseline data. The HR (95%CI) for the risk of lower GNRI levels, which was determined by using the median value of 95.6 as the cut-off value, were calculated using Cox proportional hazard models that were adjusted for the relevant multiple covariates. The *P* for heterogeneity was tested by adding the interaction term in the multivariable models, and for the *p*-value for the interaction term, a two-trailed *p*-value of <0.1 was considered to be statistically significant.

A two-tailed *p*-value of <0.05 was considered to be statistically significant in all analyses except for the interaction term in the subgroup analyses. All statistical analyses were performed using JMP Pro version 14.1.0 (SAS Institute, Cary, NC, USA), R version 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria), and SAS software, version 9.4 (SAS Institute).

3. Results

3.1. Baseline characteristics stratified by the GNRI quartiles

Patients' baseline characteristics based on GNRI quartile are shown in Table 1. The patients with lower GNRI levels were significantly older, with a higher proportion of women, and a higher prevalence of history of CVDs and stroke ($p < 0.05$). The mean hemodialysis time, systolic blood pressure, BMI, nPCR, blood hemoglobin level, and serum albumin, creatinine, and phosphate levels were significantly lower in patients with lower GNRI levels ($p < 0.05$). However, mean CTR, single-pool Kt/V for urea, serum CRP, corrected Ca, and ALP levels were significantly higher in patients with lower GNRI levels ($p < 0.05$).

3.2. Association between GNRI and the incidence of brain infarction and brain hemorrhage

During a median observational period of 8.8 years (interquartile range: 4.1–10.0 years), 326 (10.7%) and 149 (4.9%) patients developed brain infarction and brain hemorrhage, respectively. Kaplan–Meier curves showed that patients in a lower GNRI category had a higher incidence rate of both brain infarction and brain hemorrhage than patients in a higher GNRI category (log-rank $p < 0.001$ for brain infarction and log-rank $p = 0.038$ for brain hemorrhage; Fig. 1).

In the multivariable-adjusted Cox proportional hazards risk models, the incidence of brain infarction and brain hemorrhage increased significantly with lower GNRI levels (Tables 2 and 3). Compared with Q4 (which is the reference), the incidence of both brain infarction (multivariable-adjusted HR: 1.49, 95% CI: 1.05–2.12) and brain hemorrhage (multivariable-adjusted HR: 1.89, 95% CI: 1.11–3.20) was significantly higher in Q1. In the multivariable-adjusted analyses, HR for the incidence of brain infarction and brain hemorrhage increased as GNRI decreased. The multivariable-adjusted restricted cubic spline curve showed that HRs for brain infarction and brain hemorrhage increased gradually with a decrease in GNRI levels (Fig. 2).

As a sensitivity analysis, we performed the Fine–Gray subdistribution hazards model, with all-cause mortality as a competing risk (Supplementary Tables 1 and 2). Competing risk models showed that lower GNRI levels were not significantly associated with an elevated risk of brain infarction, but were significantly associated with an elevated risk of brain hemorrhage (HRs [95%CIs] for brain infarction and brain hemorrhage by every ten-unit increase in GNRI levels were 1.08 [0.91–1.28] ($p = 0.37$) and 1.31 [1.02–1.67] ($p = 0.031$), respectively).

Furthermore, we investigated the association between baseline albumin levels and incidence of brain infarction or hemorrhage, and the

Table 1
Baseline characteristics on the basis of the baseline GNRI quartile values.

	GNRI quartiles				*p* for trend
	Q1 (<90.7)	Q2 (90.7–95.5)	Q3 (95.6–99.8)	Q4 (>99.8)	
	(*n* = 757)	(*n* = 762)	(*n* = 780)	(*n* = 746)	
Basic information					
Age, years	68.9 (12.3)	64.7 (12.6)	62.2 (11.9)	58.3 (12.4)	<0.001
Sex, male	385 (50.9)	417 (54.7)	486 (62.3)	520 (69.7)	<0.001
Presence of diabetic nephropathy	203 (26.8)	216 (28.4)	236 (30.3)	222 (29.8)	0.144
History of CVDs	207 (27.3)	169 (22.2)	167 (21.4)	155 (20.8)	0.003
History of stroke	153 (20.2)	117 (15.3)	104 (13.3)	109 (14.6)	0.002
Hemodialysis vintage, years	4.8 (1.7–11.6)	5 (1.9–12)	5.8 (2.1–11.9)	5.7 (2.8–10.1)	0.633
Hemodialysis time, hours	4.5 (4–5)	5 (4–5)	5 (4.5–5)	5 (5–5)	<0.001
Systolic blood pressure, mmHg	149 (26)	153 (22)	155 (23)	157 (23)	<0.001
Cardiothoracic ratio, %	51.9 (5.9)	50.5 (5.2)	50.1 (5.4)	50.0 (5.2)	<0.001
BMI, kg/m^2	18.6 (2.6)	21.0 (3.1)	22.0 (3.1)	22.8 (2.9)	<0.001
nPCR, g/kg/day	0.92 (0.21)	0.96 (0.20)	0.97 (0.20)	0.96 (0.17)	<0.001
Single–pool Kt/V for urea	1.62 (0.31)	1.61 (0.30)	1.58 (0.27)	1.51 (0.24)	<0.001
Blood hemoglobin, g/dL	10.2 (1.3)	10.5 (1.1)	10.6 (1.1)	10.8 (1.0)	<0.001
Blood tests					
Serum albumin, g/dL	3.3 (0.4)	3.7 (0.2)	3.9 (0.2)	4.3 (0.3)	<0.001
Serum C-reactive protein, mg/dL	0.20 (0.08–0.68)	0.13 (0.07–0.32)	0.12 (0.05–0.23)	0.11 (0.05–0.2)	<0.001
Serum total cholesterol, mg/dL	146 (122–170)	151 (132–181)	156 (132–181)	156 (134–182)	0.151
Serum creatinine, mg/dL	8.7 (2.3)	10.1 (2.5)	10.9 (2.5)	11.5 (2.6)	<0.001
Serum corrected calcium, mg/dL	9.6 (0.9)	9.4 (0.8)	9.3 (0.7)	9.3 (0.7)	<0.001
Serum phosphate, mg/dL	4.7 (1.3)	4.9 (1.2)	5.0 (1.1)	5.2 (1.1)	<0.001
Serum alkaline phosphatase, U/L	255 (203–345)	244 (189–316)	228 (175–303)	212 (165–280)	<0.001
Medications					
Use of antihypertensive agents	471 (62.2)	494 (64.8)	499 (64.0)	483 (64.8)	0.391
Use of ESAs	678 (89.6)	656 (86.1)	637 (81.7)	588 (78.8)	<0.001
Use of VDRAs	460 (60.8)	560 (73.5)	562 (72.1)	573 (76.8)	<0.001
Use of phosphate binders	510 (67.4)	628 (82.4)	671 (86.0)	675 (90.5)	<0.001

Baseline data are presented as the mean (standard deviation) or median (interquartile range) for continuous variables and as the number (percentage) for categorical variables. Trend tests were performed to determine if there was a trend across the GNRI quartiles. The Jonckheere–Terpstra test was used for continuous values and the Cochran–Armitage test was used for categorical values. A two-tailed *p*-value <0.05 was considered to be statistically significant.
BMI, body mass index; CVDs, cardiovascular diseases; ESAs, erythropoiesis-stimulating agents; GNRI, geriatric nutritional risk index; nPCR, normalized protein catabolic rate; Q, quartiles by the baseline GNRI values; VDRAs, vitamin D receptor activators.

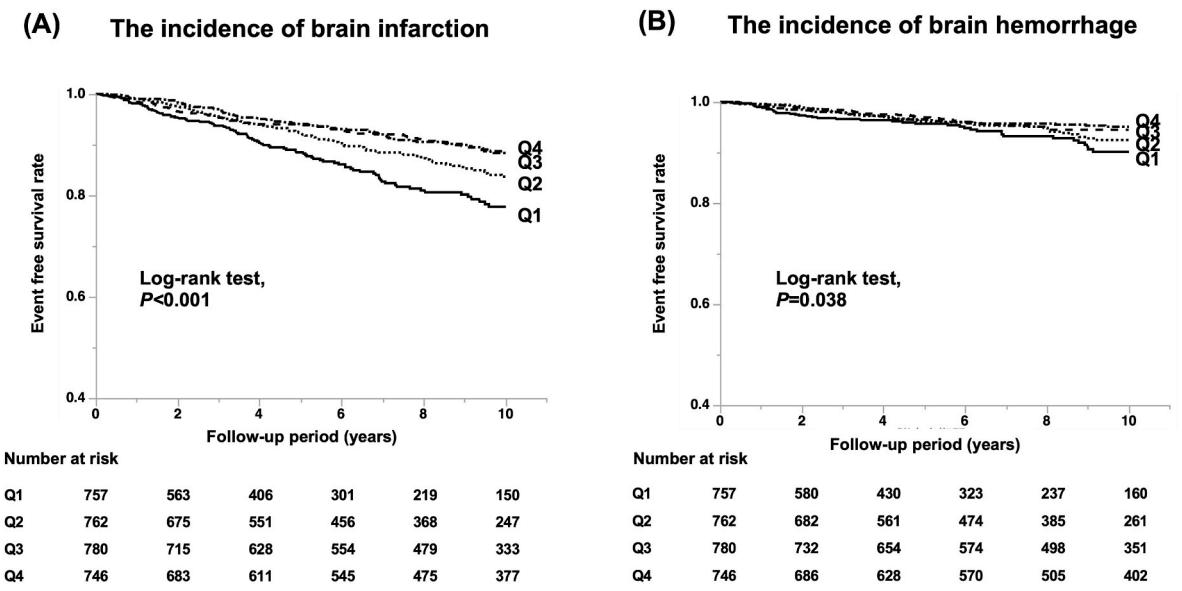

Fig. 1. Kaplan–Meier curves for the incidence of stroke on the basis of the GNRI levels at baseline during the 10-year observational period.
(A) Brain infarction, (B) brain hemorrhage. Log-rank tests were used to compare the incidence rate across quartiles of GNRI at baseline. A two-tailed *p*-value <0.05 was considered to be statistically significant. GNRI, geriatric nutritional index.

Table 2
Hazard ratios for the incidence of brain infarction using the Cox proportional hazard risk model on the basis of the GNRI quartiles at baseline.

GNRI quartiles	No. of events/ No. of patients	Unadjusted model			Age- and sex-adjusted model			Multivariable-adjusted model		
		HR (95% CI)	*p*-value	*p* for trend	HR (95% CI)	*p*-value	*p* for trend	HR (95% CI)	*p*-value	*p* for trend
Q1 (<90.7)	96/757	2.06 (1.51–2.81)	<0.001	<0.001	1.48 (1.07–2.05)	0.017	0.008	1.49 (1.05–2.12)	0.027	0.023
Q2 (90.7–95.5)	88/762	1.42 (1.03–1.94)	0.030		1.14 (0.82–1.56)	0.436		1.18 (0.85–1.64)	0.333	
Q3 (95.6–99.8)	72/780	1.01 (0.73–1.40)	0.957		0.87 (0.63–1.21)	0.415		0.90 (0.64–1.26)	0.531	
Q4 (>99.8)	70/746	1.00 (reference)			1.00 (reference)			1.00 (reference)		
Every 10–unit decrease in GNRI		1.46 (1.27–1.69)	<0.001		1.24 (1.06–1.45)	0.006		1.23 (1.03–1.47)	0.019	

HRs (95%CIs) were calculated using the Cox proportional hazard risk models. A multivariable-adjusted model was adjusted for age; sex; presence of diabetic nephropathy; hemodialysis vintage history of CVDs; history of stroke; hemodialysis time (<5 h or ≥5 h); systolic blood pressure; cardiothoracic ratio; Kt/V for urea; nPCR; blood hemoglobin; serum creatinine, serum C-reactive protein, total cholesterol, corrected calcium, phosphate, and alkaline phosphatase levels; and use of antihypertensive agents and ESAs. Hemodialysis vintage and serum C-reactive protein, total cholesterol, and alkaline phosphatase levels were transformed logarithmically. A two-tailed p-value <0.05 was considered to be statistically significant.
CI, confidence interval; CVDs, cardiovascular diseases; ESAs, erythropoiesis-stimulating agents; GNRI, geriatric nutritional risk index; HR, hazard ratio; nPCR, normalized protein catabolic rate.

association between baseline BMI levels and their incidence using Cox proportional hazards risk models. Although similar trends between low albumin or low BMI levels and these outcomes were observed, statistical significance was found only in a few categories (Supplementary Tables 3, 4, 5, and 6). The multivariable-adjusted restricted cubic spline curve showed similar results (Supplementary Figs. 1 and 2).

3.3. Subgroup analysis by baseline characteristics

The association of GNRI levels with the risk of brain infarction was significantly enhanced in female patients and in patients without a history of stroke ($p < 0.1$; Supplementary Fig. 3). The association of GNRI levels with the risk of brain hemorrhage was significantly augmented in patients with a history of stroke ($p < 0.1$; Supplementary Fig. 4). The other baseline characteristics showed no significant interactions with GNRI levels ($p = 0.111$–0.915).

4. Discussion

In the present study, we showed for the first time that a lower GNRI was associated with an increased risk of both brain infarction and brain hemorrhage in patients receiving maintenance hemodialysis. Restricted cubic spline analysis also confirmed that the association between GNRI levels and the risk of stroke was linear. In the sensitivity analysis, competing risk models also showed a similar association between GNRI levels and the risk of stroke. Subgroup analysis showed that some of the baseline characteristics exert effect modifications with the GNRI regarding mortality. Our data suggest that GNRI, which is a simple index that is easily calculated using the routinely measured clinical parameters, is a useful tool to stratify hemodialysis patients who are at an increased risk of stroke.

For the association between GNRI and the risk of developing CVDs in hemodialysis patients, conflicting results have been reported. Panichi et al. reported that lower GNRI levels predicted all-cause mortality, but did not predict the onset of CVDs [25], whereas Beberashvili et al. reported that lower GNRI levels were associated with an increased risk of CVDs and all-cause mortality [19]. In these reports, CVDs were evaluated as a composite event of coronary disease, peripheral vascular disease, and stroke, and thus, stroke was not evaluated alone. Ours was the first study to examine the association between GNRI levels and the

Table 3
Hazard ratios for the incidence of brain hemorrhage using the Cox proportional hazard risk model on the basis of the GNRI quartiles at baseline.

GNRI quartiles	No. of events/ No. of patients	Unadjusted model			Age- and sex-adjusted model			Multivariable-adjusted model		
		HR (95% CI)	*p*-value	*p* for trend	HR (95% CI)	*p*-value	*p* for trend	HR (95% CI)	*p*-value	*p* for trend
Q1 (<90.7)	41/757	1.84 (1.16–2.93)	<0.010	0.039	1.90 (1.17–3.09)	0.009	0.038	1.89 (1.11–3.20)	0.018	0.071
Q2 (90.7–95.5)	40/762	1.40 (0.88–2.22)	0.159		1.43 (0.89–2.30)	0.159		1.44 (0.88–2.34)	0.147	
Q3 (95.6–99.8)	36/780	1.09 (0.68–1.76)	0.711		1.10 (0.68–1.78)	0.686		1.08 (0.67–1.76)	0.749	
Q4 (>99.8)	32/746	1.00 (reference)			1.00 (reference)			1.00 (reference)		
Every 10–unit decrease in GNRI		1.43 (1.15–1.77)	0.001		1.45 (1.16–1.81)	0.001		1.49 (1.15–1.92)	0.003	

HRs (95%CIs) were calculated using the Cox proportional hazard risk models. A multivariable-adjusted model was adjusted for age; sex; presence of diabetic nephropathy; hemodialysis vintage; history of CVDs; history of stroke; hemodialysis time (<5 h or ≥5 h); systolic blood pressure; cardiothoracic ratio; Kt/V for urea; nPCR; blood hemoglobin; serum creatinine, serum C-reactive protein, total cholesterol, corrected calcium, phosphate, and alkaline phosphatase levels; and use of antihypertensive agents and ESAs. Hemodialysis vintage and serum C-reactive protein, total cholesterol, and alkaline phosphatase levels were transformed logarithmically. A two-tailed *p*-value <0.05 was considered to be statistically significant.
CI, confidence interval; CVDs, cardiovascular diseases; ESAs, erythropoiesis-stimulating agents; GNRI, geriatric nutritional risk index; HR, hazard ratio; nPCR, normalized protein catabolic rate.

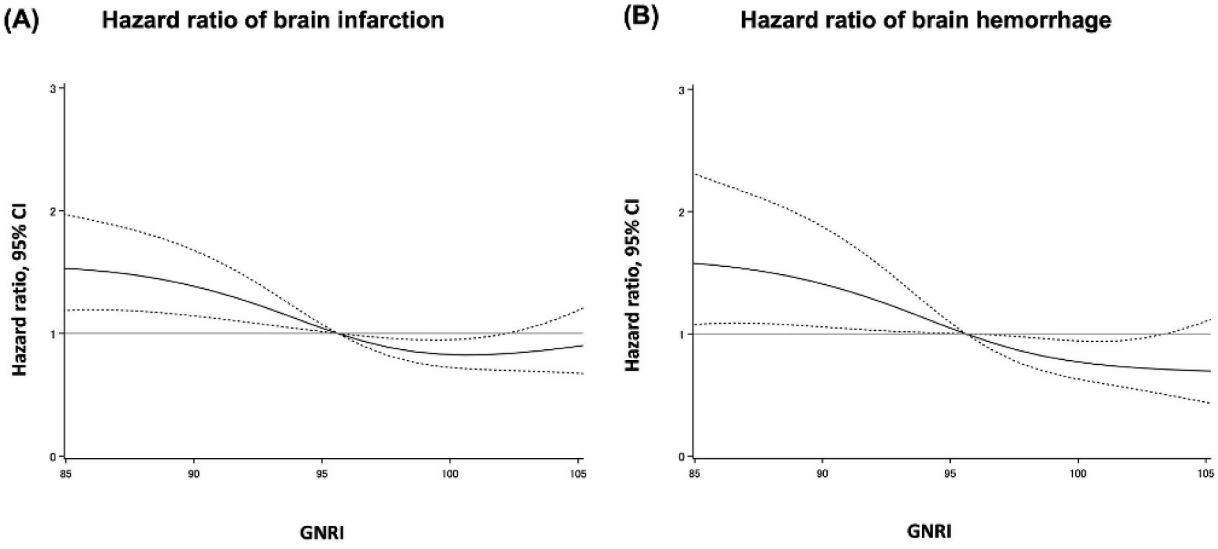

Fig. 2. Multivariable-adjusted restricted cubic spline curves for the hazard ratio for stroke on the basis of the GNRI levels at baseline.
(A) Brain infarction, (B) brain hemorrhage. The solid line represents the HR, the dotted lines represent the 95% confidence intervals, and the horizontal gray line corresponds to an HR of 1.0. The multivariable-adjusted model was adjusted for the covariates as described in the Methods section. A two-tailed *p*-value <0.05 was considered to be statistically significant. GNRI, geriatric nutritional index; HR, hazard ratio.

incidence of brain infarction and hemorrhage separately, and we demonstrated that lower GNRI levels were associated with an increased risk of both brain infarction and brain hemorrhage. Considering that the pathogenesis and the risks of CVDs including brain infarction and hemorrhage are diverse and complex, our results were of great importance in determining the differential impact of GNRI on the risk of brain infarction and hemorrhage.

The underlying mechanism for the association between low GNRI and an increased risk of stroke remains poorly understood, although lower GNRI may reflect malnutrition–inflammation–atherosclerosis (MIA) syndrome [26]. One study in hemodialysis patients reported that a low GNRI was associated with an increase in the abdominal aortic calcification index assessed using computed tomographic scanning [27]. This report confirmed a tight link between malnutrition and arteriosclerosis, which may explain why the incidence of either brain infarction or brain hemorrhage increases in patients with lower GNRI levels. Several studies have evaluated the association between inflammation and the incidence of stroke. In a meta-analysis of non-dialysis patients, high serum CRP levels were associated with brain infarction [28]. Thus, inflammation as part of the MIA syndrome may help explain the increased risk of stroke, but GNRI was an independent predictor of stroke in this study even after adjusting for serum CRP. Thus, further studies are required to clarify the mechanism that can explain the association between GNRI and the risk of stroke in patients receiving hemodialysis.

Serum albumin, which is one component of GNRI, retains antioxidant and inflammatory properties [29] and works as a carrier of anti-oxidative stress substances such as nitric oxide and bilirubin [30]. It is reasonable to think that attenuation of these functions by albumin may cause arteriosclerosis. Hypoalbuminemia was reported to be associated with carotid atherosclerosis [31]. Hypoalbuminemia was also associated with an increased risk of atrial fibrillation [32], which supports a report that serum albumin levels are associated with cardioembolic ischemic stroke [10]. Additionally, albumin has anti-platelet/anti-coagulation activity, which is a cause of increased brain infarction due to hypoalbuminemia [33]. However, infusion of

25% human albumin in the acute phase of ischemic stroke did not contribute to improving neurological prognosis [34]. Thus, it remains unclear whether improving hypoalbuminemia reduces the risk of developing stroke, and further studies are needed.

Previous studies have shown that a higher BMI is associated an increased risk of developing stroke in the general population [11]. Conversely, a lower BMI is reported to be associated with an elevated risk of stroke in hemodialysis patients [12]. Although the mechanism of these relationships remains poorly understood, it is probable that the impact of BMI on the stroke incidence may differ between the general population and patients who are receiving hemodialysis. The association between a higher BMI and better survival in patients receiving hemodialysis is recognized as reverse epidemiology [35]. A low BMI does not necessarily mean malnutrition in non-dialysis patients, whereas subjects with a lower BMI may be more frequently associated with malnutrition in patients receiving hemodialysis.

As mentioned above, the association between lower serum albumin levels or lower BMI levels and the risk of developing stroke has been reported [10,12]. However, in our additional analyses, we did not find an association between each of the serum albumin levels, or BMI levels, and the risk of developing stroke except for the association between lower BMI levels and an increased risk of brain hemorrhage. This result might be derived from a lack of statistical power, study design, or other factors such as differences in baseline characteristics. However, a trend between low serum albumin or low BMI and the risk of brain infarction or brain hemorrhage was observed, but it was not statistically significant. GNRI is calculated based on serum albumin and BMI, and it has a linear relationship with each factor. Thus, the predictive value for GNRI would be synergistically higher than that of serum albumin or BMI in our study. We believe that GNRI may be a useful nutrition assessment tool to predict the risk of stroke in clinical settings.

Several studies have reported the association between changes in GNRI and various prognoses. The increase of GNRI levels during the first year was associated with a lower risk of all-cause mortality in patients who are undergoing hemodialysis [36]. In another study, the risk of developing CVDs was lower in the group with increased GNRI levels 12 months after starting peritoneal dialysis [37]. However, it remains to be clarified whether increasing GNRI reduces the risk of stroke, and further studies are required.

The results of the subgroup analyses should be explained. For brain infarction, female patients and subjects with no history of stroke have more risk factors for stroke. Male sex [5] and a history of stroke are associated with a high risk of developing brain infarction. The impact of lower GNRI was greater in patients who appeared to have a lower risk of brain infarction with these baseline characteristics. For brain hemorrhage, in contrast to brain infarction, the impact of a lower GNRI was greater in patients with a history of stroke. Patients with a history of stroke often take antiplatelet or anticoagulant medications, which may render them more susceptible to lower GNRI levels for brain hemorrhage. The significance of our subgroup analysis provided opportunities to focus on the potential effect modification regarding the association between GNRI level and risk of stroke. Thus, further studies are required to determine whether some baseline backgrounds, including the potential effect modifiers that were observed in our subgroup analysis, were present in other hemodialysis populations.

Our study has some strengths. First, ours was the first study to show the association between GNRI levels and the incidence of stroke in a longitudinal cohort study with a large number of patients who were undergoing hemodialysis. Second, we determined the association between GNRI levels and brain infarction or hemorrhage separately because the pathogenesis of brain infarction and hemorrhage is different, and the impact may not be identical.

The present study had several limitations. First, the data including serum albumin level and BMI were measured once at baseline, and the trajectory of GNRI was not considered. Thus, some patients might have been misclassified and our current observation might be biased. In future studies, time-average or time-varying models should be considered. Second, although we rigorously adjusted for the baseline clinical characteristics, our observations may be affected by unmeasured and unknown confounding factors such as smoking, a history of atrial fibrillation, and use of antiplatelet/anticoagulant medicines, lipid-lowering drugs or serum uric acid-lowering drugs. Third, we were unable to classify brain infarction into cardioembolic and non-cardioembolic infarction. Because the pathogenesis of these two types of brain infarction is different, we were unable to provide reasonable mechanistic speculations for the association between lower GNRI levels and the higher incidence of brain infarction. Despite these limitations, we believe that our study provides a better understating of the pathogenesis of stroke and some clues about preventing stroke in patients who are receiving maintenance hemodialysis.

In conclusion, we showed that lower GNRI levels were associated with an increased risk of both brain infarction and brain hemorrhage in patients who are undergoing maintenance hemodialysis, independent of the baseline characteristics. Further studies are necessary to determine whether interventions to increase GNRI could effectively lower the risk of stroke among hemodialysis patients.

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Author contributions

Research idea and study design: ST, YM, SY, TN; data acquisition: HH, MT, KT; data analysis and interpretation: ST, YM, YK, SY; statistical analysis: ST, YM, YK, SY, HK; supervision or mentorship: ST, TN, KT, TK. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. TN ensures that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

CRediT authorship contribution statement

Shoji Tsuneyoshi: Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization. **Yuta Matsukuma:** Conceptualization, Formal analysis, Writing – review & editing. **Yasuhiro Kawai:** Methodology, Formal analysis. **Hiroto Hiyamuta:** Data aquisition, Writing – review & editing. **Shunsuke Yamada:** Conceptualization, Formal analysis, Validation, Writing – review & editing. **Hiromasa Kitamura:** Formal analysis, Writing – review & editing. **Shigeru Tanaka:** Writing – review & editing. **Masatomo Taniguchi:** Data aquisition, Writing – review & editing. **Kazuhiko Tsuruya:** Supervision. **Toshiaki Nakano:** Project administration, Writing – review & editing. **Takanari Kitazono:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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