ORIGINAL RESEARCH

Nutritional Disorder Evaluated by the Geriatric Nutritional Risk Index Predicts Death After Hospitalization for Infection in Patients Undergoing Maintenance Hemodialysis

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Objective: Infection is related to a higher rate of hospitalization and subsequent death in patients undergoing hemodialysis. Limited data are available about factors associated with death after hospitalization for infection. Nutritional disorder also known as protein energy wasting is profoundly associated with poor consequences. The Geriatric Nutritional Risk Index (GNRI) is a simple but useful nutritional screening tool to predict mortality. We examined whether the GNRI could predict hospitalization for infection and subsequent death.

Design and Methods: This was a prospective cohort study on patients undergoing hemodialysis. The predictor was the GNRI. The patients were divided into tertiles of the GNRI (T1 to T3), with the highest tertile of T3 as the referent. The outcomes of interest were all-cause mortality, hospitalization for infection, and subsequent death.

Results: Of 518 patients, 107 patients died (median follow-up period: 5.0 years; interquartile range: 3.6-5.0) and 169 patients experienced new hospitalization for infection (median follow-up period: 4.5 years; interquartile range: 3.4-5.0) during the follow-up period from December 2004 to December 2009. A lower GNRI was a significant predictor for all-cause mortality in multivariable Cox models (hazard ratio [HR]: 2.9, 95% confidential interval [CI]: 1.5-5.5, $P < .001$ for T1 vs. T3). However, the GNRI was not associated with hospitalization for infection in multivariable Fine-Gray models with death as a competing risk (subdistributional HR: 1.5, 95% CI: 1.0-2.3, $P = .056$ for T1 vs. T3). After hospitalization for infection, 38 patients died during the subsequent 2.5-year follow-up period. The GNRI was a significant predictor of death after hospitalization for infection in multivariable Cox models (HR: 2.7, 95% CI: 1.3-5.6, $P = .006$ for T1 vs. T2+T3).

Conclusions: A lower GNRI predicted a higher risk of all-cause mortality but not hospitalization for infection. However, a lower GNRI was significantly associated with a higher risk of mortality after hospitalization for infection. These findings suggest that long-term mortality after hospitalization for infection was predicted by nutritional disorder evaluated by the GNRI.

Keywords: geriatric nutritional risk index (GNRI); protein-energy wasting (PEW); infection; mortality; hospitalization; hemodialysis

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Study information: The "DREAM" (Dialysis-Related Endocrine And Metabolic changes affecting cardiovascular disease) prospective cohort study was conducted from December 2004 to December 2009. This study has been approved by the ethics committee at the Inoue Hospital (Approval No. 121) and was registered at UMIN-CTR (ID UMIN0000006168, http://www.umin.ac.jp/ctr/index.htm).

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Introduction

INFECTION IS A common cause of death in patients undergoing dialysis.[1,2] Although infection is also related to a higher rate of hospitalization,[3,4] limited data are available to examine the outcomes after hospitalization for infection in patients undergoing hemodialysis. In the HEMO (Hemodialysis) study, 58% of patients with a first hospitalization for infection had severe outcomes including intensive care unit stay, prolonged hospitalization, and death.[5] A retrospective cohort study using the US Renal Data System showed very high rates of 30-day readmission and death after initial hospitalization for infection.[6] However, factors associated with the long-term mortality after hospitalization for infection are largely unknown.

Nutritional disorder in patients undergoing hemodialysis is characterized by loss of muscle mass and fuel reserves. The International Society of Renal Nutrition and Metabolism proposed the concept of protein energy wasting (PEW) to express adverse changes in nutrition and body composition.[7] PEW is closely related to poor consequences including frailty, sarcopenia, infection, cardiovascular disease (CVD), and resultant death.[8] As a potential tool for the assessment of PEW, the International Society of Renal Nutrition and Metabolism referred to the Malnutrition-Inflammation Score (MIS),[9] which is a comprehensive scoring system but is required for subjective assessment by a well-trained examiner.[7] In contrast, the Geriatric Nutritional Risk Index (GNRI) is a simple screening tool, which is easily calculated only by body weight, height, and serum albumin.[10] Among 5 candidates for nutritional screening tool, the GNRI was most correlated to the MIS in patients undergoing hemodialysis.[10] It has been reported that the GNRI was a significant predictor of all-cause,[11,12] CVD-related,[13] and infection-related mortality[14] in patients undergoing hemodialysis. However, it is not clear whether a lower GNRI was associated with the onset of infection or subsequent death.

The aim of this study was to examine the association of the GNRI with all-cause mortality and hospitalization for infection in a prospective cohort of Japanese patients undergoing maintenance hemodialysis. In addition, we investigated whether the GNRI could predict death after hospitalization for infection.

Methods

Study Design and Participants

The "DREAM" (Dialysis-Related Endocrine And Metabolic changes affecting cardiovascular disease) prospective cohort study was conducted from December 2004 to December 2009. Some results have been published.[15-18]

Table 1. Clinical Characteristics of 518 Patients by Tertiles of the GNRI

		GNRI			
	All	T1 (≤92.3)	T2 (>92.3 to ≤ 96.8)	T3 (>96.8)	*P*
Number of participants (%)	518	183 (35.3)	170 (32.8)	165 (31.9)	
GNRI	95.2 (90.8-98.3)	89.6 (86.9-90.9)	95.3 (93.8-96.0)	99.8 (98.3-101.6)	<.001
Age (y)	61.0 (54.0-68.0)	66.0 (60.0-72.0)	61.0 (54.0-67.0)	57.0 (50.0-62.0)	<.001
Male (%)	326 (62.9)	107 (58.5)	105 (61.8)	114 (69.1)	.114
Duration of hemodialysis (y)	9.2 (3.8-15.9)	11.4 (4.3-20.0)	9.1 (3.7-15.0)	8.0 (3.8-13.1)	.006
CKD with diabetes (%)	110 (21.2)	30 (16.4)	38 (22.4)	42 (25.5)	.108
Pre-existing CVD (%)	173 (33.4)	73 (39.9)	57 (33.5)	43 (26.1)	.024
Calcium (mg/dL)	9.1 (8.6-9.8)	9.0 (8.3-9.6)	9.2 (8.6-9.8)	9.3 (8.9-9.9)	.002
Phosphate (mg/dL)	5.8 (5.0-6.6)	5.5 (4.7-6.3)	5.9 (5.2-6.6)	5.9 (5.2-6.8)	<.001
Intact PTH (pg/mL)	118.0 (41.0-214.8)	101.0 (28.0-197.5)	131.0 (54.5-232.5)	121.0 (43.0-210.0)	.157
Use of VDRA (%)	230 (44.4)	73 (39.9)	87 (51.2)	70 (42.4)	.085
Potassium (mEq/L)	5.2 (4.8-5.6)	5.1 (4.7-5.5)	5.2 (4.8-5.6)	5.3 (4.9-5.8)	.004
Hematocrit (%)	30.7 (28.6-32.4)	30.6 (28.2-32.2)	30.9 (28.8-32.5)	30.6 (28.9-32.6)	.216
ESA dose (x1,000 U/week)	9.0 (7.5-9.0)	9.0 (7.5-9.0)	9.0 (7.5-9.0)	9.0 (7.5-9.0)	.503
Use of IV iron (%)	301 (58.1)	119 (65.0)	102 (60.0)	80 (48.5)	.006
Hypertension (%)	447(86.3)	145 (79.2)	151 (88.8)	151(91.5)	.002
Smoker (%)	213 (41.1)	73 (39.9)	57 (33.5)	83 (50.3)	.007
HDL-C (mg/dL)	44.2 (36.0-54.2)	44.6 (36.3-53.5)	46.2 (36.6-56.9)	41.2 (35.3-52.4)	.154
Non-HDL-C (mg/dL)	114.7 (91.1-138.0)	106.8 (89.6-128.8)	119.2 (95.4-143.3)	118.7 (90.3-144.6)	.019
Serum creatinine (mg/dL)	11.6 (10.0-13.5)	10.2 (9.0-12.0)	11.5 (10.2-13.3)	13.0 (11.3-15.1)	<.001
BMI (kg/m^2)	21.6 (19.6-23.5)	19.5 (18.4-21.5)	21.7 (20.4-23.8)	22.9 (21.8-24.2)	<.001
Serum albumin (g/dL)	3.7 (3.5-3.9)	3.4 (3.3-3.6)	3.7 (3.6-3.8)	4.0 (3.9-4.1)	<.001
CRP (mg/dL)	0.14 (0.05-0.41)	0.16 (0.06-0.53)	0.17 (0.05-0.45)	0.08 (0.04-0.22)	<.001

Data are expressed as numbers, percentages, or median (interquartile range). *P* values were by χ^2 test or by Kruskal-Wallis test.

BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; ESA, erythropoiesis-stimulating agent; GNRI, Geriatric Nutritional Risk Index; HDL-C, high-density-lipoprotein cholesterol; IV iron, intravenous iron preparation; PTH, parathyroid hormone; VDRA, vitamin D receptor activator.

Table 2. Association of the GNRI With All-Cause Mortality

		Tertiles of the GNRI			
		T1	T2	T3	
Number of cases		64	30	13	
Patient-years		682	725	742	
Crude rate (cases per 1,000 patient-years)		94	41	18	
Model	Adjustment	Hazard ratio (95% confidential interval)			*P* for trend
1	Unadjusted	5.4 (3.0-9.8)‡	2.4 (1.2-4.6)†	1.0 (reference)	<.001
2	Age, sex, duration of hemodialysis, CKD with diabetes, pre-existing CVD	2.9 (1.5-5.5)‡	1.9 (1.0-3.6)	1.0 (reference)	<.001
3	Model 2 + calcium, phosphate, intact PTH, any use of VDRA	3.1 (1.6-5.9)‡	1.9 (1.0-3.6)	1.0 (reference)	<.001
4	Model 2 + hematocrit, dose of ESA, use of IV iron	2.8 (1.5-5.2)†	1.8 (0.9-3.5)	1.0 (reference)	.001
5	Model 2 + hypertension, smoking, HDL-C, non-HDL-C	2.9 (1.5-5.6)†	2.0 (1.0-3.9)*	1.0 (reference)	.002
6	Model 2 + log CRP	2.6 (1.4-5.0)†	1.7 (0.9-3.3)	1.0 (reference)	.002

(Cox models).

CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; ESA, erythropoiesis-stimulating agent; GNRI, Geriatric Nutritional Risk Index; HDL-C, high-density-lipoprotein cholesterol; IV iron, intravenous iron preparation; PTH, parathyroid hormone; VDRA, vitamin D receptor activator.

*$P < .05$.

†$P < .01$.

‡$P < .001$.

In the longitudinal analysis using the DREAM cohort, we examined whether the GNRI could predict all-cause mortality, hospitalization for infection, and subsequent death.

Data Source and Clinical Parameters

Demographic, anthropometric, and routine laboratory data were obtained from medical records of participants. Blood samples were taken from an arteriovenous fistula before hemodialysis sessions after 2-day interval (Monday or Tuesday). We recorded age, sex, the presence of chronic kidney disease (CKD) with diabetes, duration of hemodialysis, and pre-existing CVD as demographic factors. We documented serum calcium, phosphate, intact parathyroid hormone (PTH), and use of vitamin D receptor activator as factors related to CKD-mineral and bone disorder (CKD-MBD). As factors related to anemia in CKD, we included hematocrit, dose of erythropoiesis-stimulating agent, and use of intravenous iron injection. As traditional risk factors, current smoking, high-density-lipoprotein cholesterol, non–high-density-lipoprotein cholesterol, and the presence of hypertension were collected. We defined hypertension as blood pressure of 140/90 mmHg or higher and/or use of antihypertensive medication.[19] C-reactive protein was recognized as an inflammation-associated factor.

Geriatric Nutritional Risk Index

The GNRI was calculated from the baseline data using the following formula[10-14]:

GNRI = [14.89 × serum albumin (g/dL)] + [41.7 × (body weight {BW}/ideal body weight {IBW})]

BW/IBW was set to 1 when a participant's actual BW was equal to or above the IBW. The IBW was defined as the value calculated from the height and a body mass index (BMI) of 22.

Outcomes

The outcomes of interest were all-cause mortality, hospitalization for infection, and subsequent death during the follow-up period. The hospitalization for infection was defined as admission to the hospital for infectious diseases. Among patients who experienced the first hospitalization for infection during follow-up, death after the hospitalization was examined.

Statistics

The participants were divided into tertiles of the GNRI. Baseline characteristics were shown as numbers (percentages) for categorical variables and medians (interquartile range [IQR]) for continuous variables. Differences in categorical and continuous values across the GNRI tertiles were examined by χ^2 test and Kruskal-Wallis test, respectively.

The association of GNRI tertiles with all-cause mortality was examined by the Kaplan-Meier method and log-rank test. The Cox proportional hazard model was used to estimate unadjusted and multivariable-adjusted hazard ratios (HRs) and 95% confidential intervals (CIs), with the highest tertile of the GNRI (T3) as the referent. HRs (95% CIs) of GNRI tertiles with all-cause mortality were calculated with unadjusted Cox model (Model 1) and then adjusted for the five demographic factors (Model 2). Further adjustment was performed for factors related to

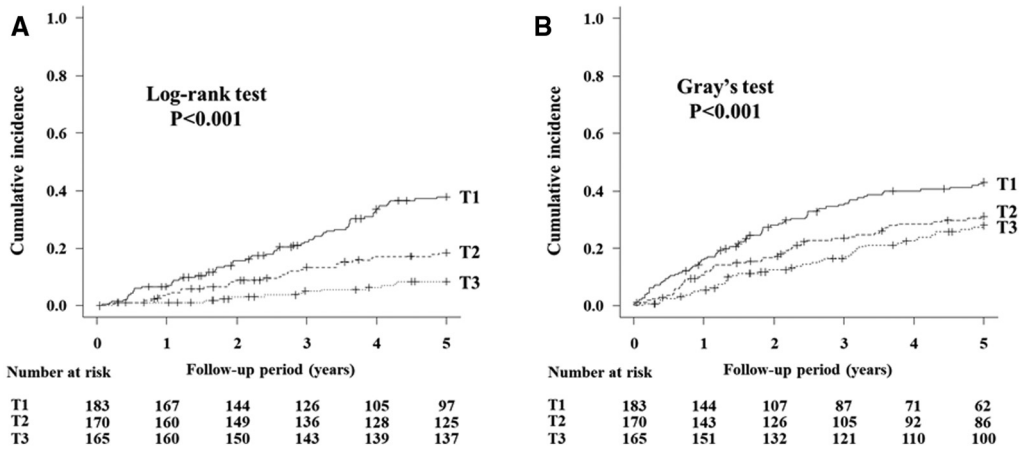

Figure 1. (A) Cumulative incidences of all-cause mortality. (B) Cumulative incidences of hospitalization for infection.

CKD-MBD (Model 3), factors related to anemia in CKD (Model 4), traditional risk factors (Model 5), and inflammation-related factor (Model 6).

Next, we analyzed the unadjusted and multivariable-adjusted associations of GNRI tertiles with hospitalization for infection by Gray's test and Fine-Gray models with death as a competing risk.[20,21] Subdistribution HRs (95% CIs) of GNRI tertiles with hospitalization for infection were calculated with unadjusted (Model 1) and adjusted models for various factors (Model 2 to 6) as described earlier.

Finally, the association of the GNRI with death after hospitalization for infection was examined. Time from the first hospitalization for infection to all-cause death was analyzed with the Kaplan-Meier method and Cox proportional hazard model in patients who experienced hospitalization for infection with follow-up period for 2.5 years. Because the number of deaths after hospitalization for infection was limited, and because the T2 and T3 showed similar incidence rates, we combined the T2 and T3 as T2 + T3 and comparison was made between T1 and T2 + T3. Also, the model was adjusted for age and sex (Model 2), Model 2 + duration of hemodialysis (Model 3), Model 2 + the presence of CKD with diabetes (Model 4), and Model 2 + pre-existing CVD (Model 5).

These statistical calculations were performed with EZR[22] (version 1.54) developed by Dr. Kanda, Saitama Medical Center, Jichi Medical University, Saitama, Japan, which is graphical interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R computer designed to add statistical functions frequently used in biostatics. A P value $< .05$ by two-sided test was considered statistically significant.

Results

Characteristics of Study Participants

The study participant selection process is shown in Figure S1. A total of 518 participants undergoing hemodialysis from the DREAM cohort were analyzed in this study. Baseline characteristics according to GNRI tertiles is shown in Table 1. The patients with a lower GNRI showed higher age, longer duration of hemodialysis, higher rate of pre-existing CVD, lower calcium, lower phosphate, lower potassium, higher rate of use of intravenous iron injection, lower rate of hypertension, lower serum creatinine, lower BMI, and lower serum albumin.

GNRI and All-Cause Mortality

We recorded 107 all-cause deaths during the follow-up period (median follow-up period: 5.0 years; IQR: 3.6-5.0). GNRI tertiles were inversely associated with cumulative incidence of death (Figure 1A). The GNRI showed significant association with all-cause mortality in unadjusted and all adjusted Cox hazard models (Table 2).

GNRI and Hospitalization for Infection

Hospitalization for infection was recorded in 169 patients (median follow-up period: 4.5 years; IQR: 3.4-5.0). Figure 1B shows cumulative incidence function for hospitalization for infection considering the competing risk of death according to GNRI tertiles by Gray's test. A lower GNRI was a significant predictor of a higher risk of hospitalization for infection in unadjusted Fine and Gray models (Table 3). However, this association was no longer significant in all adjusted models except for a model adjusted for traditional risk factors (Model 5).

GNRI and Death after Hospitalization for Infection

Finally, we focused on the death in 169 patients who were recorded as the first hospitalization for infection. During the subsequent 2.5-year follow-up period, 38 patients died. T1 showed a significantly higher mortality than T2 + T3 (Figure 2). The association was significant in unadjusted Cox model (Model 1) and adjusted models for age and sex (Model 2), Model 2 + duration of hemodialysis (Model 3), Model 2 + the presence of CKD with

Table 3. Association of the GNRI With Hospitalization for Infection

		Tertiles of GNRI			
		T1	T2	T3	
Number of cases		75	51	43	
Patient-years		526	595	643	
Crude rate (cases per 1,000 patient-years)		143	86	67	
Model	Adjustment	Subdistribution hazard ratio (95% confidential interval)			*P* for trend
1	Unadjusted	1.8 (1.3-2.7)†	1.2 (0.8-1.8)	1.0 (reference)	<.001
2	Age, sex, duration of hemodialysis, CKD with diabetes, pre-existing CVD	1.5 (1.0-2.3)	1.1 (0.7-1.7)	1.0 (reference)	.028
3	Model 2 + calcium, phosphate, intact PTH, any use of VDRA	1.4 (0.9-2.2)	1.1 (0.7-1.7)	1.0 (reference)	.053
4	Model 2 + hematocrit, dose of ESA, use of IV iron	1.5 (1.0-2.3)	1.1 (0.7-1.6)	1.0 (reference)	.048
5	Model 2 +hypertension, smoking, HDL-C, non-HDL-C	1.6 (1.1-2.5)*	1.2 (0.8-1.8)	1.0 (reference)	.012
6	Model 2 + log CRP	1.4 (0.9-2.1)	1.0 (0.7-1.5)	1.0 (reference)	.042

(death as a competing risk) (Fine-Gray models).

CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; ESA, erythropoiesis-stimulating agent; GNRI, Geriatric Nutritional Risk Index; HDL-C, high-density-lipoprotein cholesterol; IV iron, intravenous iron preparation; PTH, parathyroid hormone; VDRA, vitamin D receptor activator.

*$P < .05$.

†$P < .01$.

diabetes (Model 4), and Model 2 + pre-existing CVD (Model 5) (Table 4).

Discussion

In the present study, a lower GNRI was significantly associated with all-cause mortality but not hospitalization for infection. However, a lower GNRI was an independent risk factor for death after hospitalization for infection during the subsequent 2.5-year follow-up period. These findings suggest that nutritional disorder evaluated by the GNRI could predict long-term death after infection as well as mortality.

Although the GNRI is a simple and objective tool with no need of special equipment and technique, it seems to be equivalent to other nutritional scoring systems such as the MIS,[10] which is recognized to be a comprehensive standard tool for assessment of PEW.[7,23] Previous studies reported that the GNRI was a predictor of all-cause mortality in patients undergoing hemodialysis.[11,12] The GNRI was also associated with CVD mortality in patients undergoing incident hemodialysis.[13] A recent report showed that the GNRI was a significant predictor of infection-related mortality as well as all-cause mortality in patients undergoing hemodialysis.[14] To our knowledge, this is the first study to show that the GNRI can predict not only mortality but also death after hospitalization for infection.

Two studies reported short-term morbidity and mortality after hospitalization for infection and factors associated with these poor outcomes in patients undergoing hemodialysis. Allon et al reported the poor outcomes after hospitalization for infection in analyses of secondary endpoints in the HEMO study.[5] Among 783 patients with the first hospitalization for infection, 224 (28.6%) were hospitalized longer than 7 days, 120 (15.3%) were treated in the intensive care unit, and 108 (13.8%) died. Advanced age and low albumin level were associated with these worse outcomes. On the other hand, Dalrymple et al focused on 30-day outcomes after discharge using the US Renal Data System.[6] Of patients who survived the initial hospitalization (n = 54,996), 15,113 (27%) were readmitted and survived the 30 days, 1,624 (3%) were readmitted and then died within 30 days of discharge, and 2,425 (4%) died without hospital readmission. They found that lower albumin level, lower BMI, physical inability, absence of nephrology care prior to dialysis, and non-Hispanic ethnicity were associated with readmission and death without readmission. Thus, poor nutritional status as indicated by low albumin level was a common risk factor for short-term prognosis in these previous reports. In this study, we followed up patients after the first hospitalization for infection during relatively longer period (2.5 years). Our results indicate that poor nutritional status evaluated by the GNRI could predict longer-term mortality after hospitalization for infection.

Table 4. Association of the GNRI With Death After Hospitalization for Infection

	Tertiles of GNRI		
	T1	T2	T3
Number of cases	26	6	6
Patient-years	158	127	98
Crude rate (cases per 1,000 patient-years)	164	47	61

		T1	T2 + T3	
Model	Adjustment	Hazard ratio (95% confidential interval)		*P*
1	Unadjusted	2.9 (1.5-5.8)†	1.0 (reference)	.002
2	Age, sex	2.7 (1.3-5.6)†	1.0 (reference)	.006
3	Model 2 + duration of hemodialysis	2.3 (1.1-4.7)*	1.0 (reference)	.032
4	Model 2 + CKD with diabetes	2.8 (1.4-5.9)†	1.0 (reference)	.005
5	Model 2 + pre-existing CVD	2.7 (1.3-5.6)†	1.0 (reference)	.007

(Cox models).
CKD, chronic kidney disease; CVD, cardiovascular disease; GNRI, Geriatric Nutritional Risk Index.
*$P < .05$.
†$P < .01$.

Recent works focus on the long-term management after sepsis rather than acute-phase treatment. Medical progress has improved in-hospital and 28-day mortality,[24] whereas long-term mortality remains considerably high in patients with chronic critical illness (CCI) including survivors from sepsis.[24-26] The patients with CCI suffer from recurrent infections, organ dysfunction, malnutrition, weakness, and resultant death.[24,26] Although there is no established treatment for CCI, nutritional support is one of the approaches for optimal outcomes.[24,27] It is likely that the GNRI is useful for the detection of high-risk patients undergoing hemodialysis and that early nutritional intervention may lead to favorable long-term outcomes in patients after hospitalization for infection.

Our study has several limitations. First, we evaluated the GNRI at baseline. The single evaluation of the GNRI might fail to detect the true association with the outcomes. Second, since this was a single-center study which consisted of only Japanese participants, the generalizability of our findings was limited. Larger, multicenter studies are necessary to confirm our findings in different ethnic groups. Third, we did not compare the GNRI with other nutritional screening tools such as the MIS. Finally, we did not know the detailed information about causes and types of infection as well as the severity of infection, that is, sepsis or not. On the other hand, it was one of the strengths of this study that we had a unique outcome variable, namely the death after hospitalization for infection. The association between nutritional status and the death after hospitalization could not have been analyzed in studies which recorded only the dates and causes of all-cause deaths.

In conclusion, we found the significant association of the GNRI with all-cause mortality but not hospitalization for infection. Importantly, the GNRI was significantly associated with death after hospitalization for infection. These findings suggest that baseline nutritional disorder evaluated by the GNRI could predict not only mortality but also long-term death after hospitalization for infection in patients undergoing hemodialysis.

Practical Application

The GNRI may be suitable as a screening tool of nutritional disorder since it could predict long-term death after hospitalization for infection in patients undergoing hemodialysis. Easy and objective detection of high-risk patients by the GNRI may lead to favorable long-term outcomes after hospitalization for infection through early nutritional intervention. Routine and repeated assessment of nutritional status using the GNRI will be helpful in individualized nutritional care.

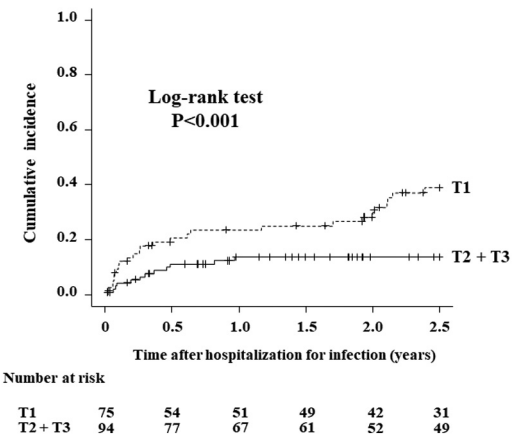

Figure 2. Cumulative incidences of death after hospitalization for infection.

CRediT authorship contribution statement

Yuri Machiba: Conceptualization, Formal analysis, Visualization, Writing – original draft. **Katsuhito Mori:** Conceptualization, Writing – original draft, Formal analysis. **Tetsuo Shoji:** Conceptualization, Data curation, Writing – review & editing. **Yuki Nagata:** Writing – review & editing. **Hideki Uedono:** Writing – review & editing. **Shinya Nakatani:** Writing – review & editing. **Akinobu Ochi:** Writing – review & editing. **Akihiro Tsuda:** Writing – review & editing. **Tomoaki Morioka:** Writing – review & editing. **Hisako Yoshida:** Formal analysis, Writing – review & editing. **Yoshihiro Tsujimoto:** Writing – review & editing. **Masanori Emoto:** Supervision, Writing – review & editing.

Supplementary Data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1053/j.jrn.2022.01.008.

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