CASE REPORT

Nutrition-related risk and severe hypoglycemia in older adult outpatients with and without diabetes

Yoshinobu Kimura^{1,2} 💿 | Naoya Kimura² | Manabu Akazawa¹ 💿

¹Department of Public Health and Epidemiology, Meiji Pharmaceutical University, Kiyose, Japan

²Department of Pharmacy, Soka Municipal Hospital, Soka, Japan

Correspondence

Manabu Akazawa, Department of Public Health and Epidemiology, Meiji Pharmaceutical University, 2-522-1 Noshio, Kiyose, Tokyo 204-8588, Japan. Email: makazawa@my-pharm.ac.jp

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Abstract

In this study, 17 patients with severe hypoglycemia were assessed for nutritionrelated risk using the Geriatric Nutritional Risk Index (GNRI). The results showed that 13 of the 17 patients had nutrition-related risk. Hypoglycemia should be noted in patients with problems on GNRI, with or without diabetes.

KEYWORDS

geriatric nutritional risk index, GNRI, hypoglycemia, nutrition-related risk

1 **INTRODUCTION**

In patients with diabetes, hypoglycemia is a barrier to treatment. Severe hypoglycemia has been associated with increased risk of premature mortality, cardiovascular disease, and fatal arrhythmias.^{1,2} In addition, the risk of dementia has been reported to increase with the number of severe hypoglycemia episodes.³ In patients without diabetes, severe hypoglycemia may indicate a serious clinical condition; in fact, it has been associated with abnormal QT prolongation⁴ and increased risk of premature death.⁵ Thus, hypoglycemia needs to be prevented or promptly addressed in all patients.

Risk factors for hypoglycemia include treatment with insulin or sulfonylurea, older age, chronic kidney disease (CKD), liver failure, dementia, and tight glycemic control. In the association between nutritional status and hypoglycemia, a previous study that assessed nutritional status using the Nutritional Risk Screening-2002 (NRS-2002)⁶ recently found that malnutrition in hospitalized patients

without diabetes increases the risk of hypoglycemia. Our previous study, which focused on older adults vulnerable to hypoglycemia, used the Geriatric Nutritional Risk Index (GNRI) to assess the nutritional status of hospitalized older adults with diabetes and showed that the risk of hypoglycemia was increased in malnourished cases in this patient group.⁷

The GNRI helps to assess the risk of complications (aspiration pneumonia and pressure ulcers) and mortality associated with malnutrition.⁸ However, it is not clear whether nutrition-related risk assessed by the GNRI is associated with hypoglycemia in outpatients. Initially, the GNRI was developed for use in sub-acute medical settings, but it has been found to be suitable for a variety of settings, including acute and outpatient.⁹⁻¹¹ For these reasons, the use of the GNRI is expanding. The strength of the GNRI that it is based on serum albumin levels, current and ideal body weight values, and is more objective and easier to use than other nutritional assessment methods, even for those who are not familiar with nutritional assessment.

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If an association is identified between this nutritional assessment and outpatients, it could be used to screen more patients for hypoglycemic risk, not just inpatients.

In this study, we investigated the association between severe hypoglycemia and nutrition-related risk in outpatients.

2 | MATERIALS AND METHODS

This study investigated the nutritional status of outpatients with severe hypoglycemia who presented at the emergency department of the Soka Municipal Hospital, a secondary care institution in Japan. This was a singlecenter study in which cases were descriptively summarized by retrospective observation using electronic medical records. Outpatients aged ≥ 65 years presenting with severe hypoglycemia between September 1, 2018, and June 15, 2021, were eligible for this study. Patients with missing data on height, weight, or serum albumin levels, precluding GNRI calculations were excluded.

2.1 | Definitions of variables

Nutrition-related risk was assessed using the GNRI formula and classified into four risk categories, based on previous studies⁸: major (GNRI of <82), moderate (GNRI in the range of 82–92), low (GNRI in the range of 92–98), and no (GNRI of >98) risk. The GNRI was calculated using height, current body weight, and serum albumin levels, based on the following formula: Liver failure, dementia, and sepsis were determined from medical records.

2.2 | Nutrition-related risk assessment

We assessed nutrition-related risk on the day of severe hypoglycemia onset and examined the patients' clinical characteristics and trends. Data required for calculating the GNRI were serum albumin levels obtained at the time of severe hypoglycemia onset, height values obtained 5 years before and after severe hypoglycemia, and weight values obtained 1 month before and after severe hypoglycemia onset. The value obtained closest to the date of severe hypoglycemia onset was used. The observation period was from the date of hypoglycemia onset to the date of discharge from the hospital or death. The follow-up period was 90 days from the date of hypoglycemia onset.

Next, we examined the association between past nutrition-related risk factors and severe hypoglycemia onset, using data from a subset of patients who presented at the hospital within 180 days before onset of severe hypoglycemia. Nutrition-related risk prevalence observed before the onset of severe hypoglycemia was compared with that observed on the day of severe hypoglycemia occurrence. Although data on serum albumin levels were available for the previous visits, and height and weight data were rarely available. Consequently, height values were considered to have remained unchanged or to have significantly decreased. The predictive value of nutritional status for severe hypoglycemia occurrence was

 $GNRI = 14.89 \times serum albumin (g/dl) + 41.7 \times current body weight (kg) / ideal body weight (kg) = 14.89 \times serum albumin (g/dl) + 41.7 \times BMI/22$

If the current weight was greater than the ideal weight, the ratio of the current weight to the ideal weight was set to 1.

Severe hypoglycemia was defined as hypoglycemia with impaired consciousness with a Japan Coma Scale (JCS) of 1 digit or higher, requiring assistance from others for consultation and treatment, and a 50% glucose injection. Data for the administration of the 50% glucose injections were extracted from a data warehouse connected to the electronic medical record.

Severe CKD was defined as an eGFR of <30 ml/min/1.73 m². We used the Japanese eGFR estimation formula shown below

examined. The reason for assuming severe weight loss was to eliminate the concern that if severe hypoglycemia developed because of rapid weight loss between the previous visit and on the day of severe hypoglycemia onset, the nutrition-related risk on the previous visit would not be able to predict severe hypoglycemia. In the case of weight loss, patients' weight at the time of the previous visit was back-calculated at a rate of 2% change in 1 week, 5% change in 1 month, 7.5% change in 3 months, and 10% change in 6 months, based on the existing criteria for severe weight loss.¹² Based on the timing of hypoglycemia onset, patients were classified into the following groups: 1 week, 1, 3, and 6 months.

eGFR $(ml/min/1.73m^2) = 194 \times Cr^{-1.094} \times Age (years)^{-0.287}$ (Female: $\times 0.739$)

													Clin	ical Cas	e Re	por	Open Access	-WI
Sepsis (Y/N)	Z	Z	Z	Z	N	Z	Z	z	N	Z	Z	Z	Z	z	Z	Z	Z	
Dementia (Y/N)	Z	Z	Z	Υ	Z	Z	Y	Z	N	Y	Υ	Y	Z	Z	Z	Z	Y	
Liver failure (Y/N)	N	Ν	Ν	Ν	Y	N	Ν	Z	Υ	Ν	Ν	Ν	Ν	z	N	Ν	N	
Severe CKD (Y/N) (eGFR of <30 ml/min/1.73 m ²)	Υ	Υ	Ν	Ν	Υ	Ν	Υ	Z	Υ	Υ	Υ	Ν	Ν	Z	Ν	Ν	Z	
Nutrition-related risk class	Major	Major	Major	Major	Major	Major	Moderate	Moderate	Low	Low	Low	Low	Low	None	None	None	None	
GNRI	57	67	67	68	72	80	91	91	92	92	94	95	95	100	101	103	104	
HbA1c (%)	5.1	5.1	N/A	6.2	N/A	6.1	5.1	6.9	N/A	5.3	5.1	7.5	6.5	7.0	5.6	7.7	7.3 s.	
DM Type	None	None	None	None	None	Type 1	None	Type 1 (slowly progressive)	None	Type 2	Type 2	Type 2	Type 2	Type 1 (slowly progressive)	None	Type 1	Type 2 :e; DM, diabetes mellitus	
Sex	Μ	ц	Μ	Μ	Μ	Ц	Μ	М	Μ	Μ	Μ	Μ	Μ	ц	Μ	Μ	M ney diseas	
Age (years)	82	83	72	97	85	94	80	77	79	84	79	84	72	66	78	72	80 CKD, chronic kidr	
ase No	1	2	3	4	5	9	7	∞	6	10	11	12	13	14	15	16	17 bbreviations:	

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2.3 | Statistical analysis

Continuous variables were reported as medians (interquartile range), and categorical variables were reported as counts and percentages. The Mann–Whitney *U*-test was used to compare the GNRI values between patients with and without diabetes mellitus. Statistical analysis was performed using EZR version 1.51,¹³ an extended version of R Commander. *p* values of < 0.05 were considered statistically significant.

3 | RESULTS

A total of 75 outpatients presented with hypoglycemia that required 50% glucose injection between September 1, 2018, and June 15, 2021. Among them, 58 patients experienced impaired consciousness. Overall, 17 patients had data on serum albumin levels, height, and weight values that were required for the GNRI calculation; these patients were included in further analysis. The variance between the date of measurement of height and weight and the date of onset of hypoglycemia used for the calculation of GNRI was in the interquartile range of -323.0-0.0 days for height and 1.0-9.0 days for weight. The median age was 80.0 (77.0-84.0) years. Fourteen (82.4%) patients were male. The sample included 4 (23.5%), 5 (29.4%), and 8 (47.1%) patients with type 1 and type 2 diabetes, and without diabetes, respectively. Severe hypoglycemia occurred even in patients who were not receiving treatment for lower blood glucose levels. The patients' characteristics are presented in Table 1. According to the GNRI, 6 (35.3%), 2 (11.8%), 5 (29.4%), and 4 (23.5%) patients were at major, moderate, low, and no risk, respectively. Overall, 13 of 17 (76.5%) patients had nutrition-related risk.

Patient's medications and causes of severe hypoglycemia are shown in Table 2. The causes of hypoglycemia, as evaluated by the attending physician, were decreased food intake, use of hypoglycemic medicines, alcohol intake, sick day, use of hypoglycemia-inducing medicines for conditions other than diabetes, and insulin autoimmune syndrome. Four of 5 patients at major risk were attributed to decreased food intake, and one was attributed

TABLE 2 Clinical findings and medications prescribed for patients experiencing severe hypoglycemia

				Insulin (Y/N))			
Case No	DM Туре	GNRI	Nutrition-related risk class	Long-acting	Short-acting	Premixed	Sulfonylurea (Y/N)	Glinides (Y/N)
1	None	57	Major	Ν	Ν	Ν	Ν	Ν
2	None	67	Major	Ν	Ν	Ν	Ν	Ν
3	None	67	Major	Ν	Ν	Ν	Ν	Ν
4	None	68	Major	Ν	Ν	Ν	Ν	Ν
5	None	72	Major	Ν	Ν	Ν	Ν	Ν
6	Type 1	80	Major	Y	Υ	Ν	Ν	Ν
7	None	91	Moderate	Ν	Ν	Ν	Ν	Ν
8	Type 1 (slowly progressive)	91	Moderate	Y	Ν	Ν	Ν	Y
9	None	92	Low	Ν	Ν	Ν	Ν	Ν
10	Type 2	92	Low	Ν	Y	Y	Ν	Ν
11	Type 2	94	Low	Ν	Ν	Ν	Ν	Y
12	Type 2	95	Low	Y	Ν	Ν	Ν	Ν
13	Type 2	95	Low	Y	Y	Ν	Ν	Ν
14	Type 1 (slowly progressive)	100	None	Y	Y	Ν	Ν	Ν
15	None	101	None	Ν	Ν	Ν	Ν	Ν
16	Type 1	103	None	Y	Y	Ν	Ν	Ν
17	Type 2	104	None	Ν	Ν	Y	Ν	Ν

Abbreviations: DM, diabetes mellitus; GNRI, geriatric nutritional risk index; JCS, Japan coma scale.

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to insulin. In contrast, 3 of 4 patients at no risk were using insulin, and 1 patient had insulin autoimmune syndrome. When divided by with and without diabetes, 1 of 9 patients with diabetes had a decreased food intake, and 5 of 8 patients without diabetes had a decreased food intake. All patients at major risk experienced severe hypoglycemia due to decreased food intake.

Recurrent hypoglycemia after hospitalization occurred in 3 (17.6%) patients at major and 1 (5.9%) patient at low nutrition-related risk. The patients who died within 90 days of the onset of severe hypoglycemia were 3(17.6%)patients at major, 1 (5.9%) patient at moderate, and 1 (5.9%) patient at low nutrition-related risk. Both patients were at nutrition-related risk (Table 3).

3.1 | GNRI, severe hypoglycemia, and diabetes mellitus

Among 8 patients without diabetes, 1 patient had insulin autoimmune syndrome, which may cause spontaneous hypoglycemia; consequently, this patient was excluded from further analysis. Among patients without and with diabetes, the median GNRI was 68 (67.0–81.5) and 95 (92.0–100.0), respectively (Figure 1).

3.2 | Predictive value of past nutritional status for severe hypoglycemia

A total of 13 patients had data on serum albumin levels obtained on the day of their previous visit, recorded within 180 days of severe hypoglycemia onset. Prevalence rates of nutrition-related risk on the day of severe hypoglycemia onset and at the time of the previous visit were 76.9% (10/13) and 69.2% (9/13), respectively, given unchanged weight and weight loss. Given unchanged weight, 3 (23.1%) patients were classified in a milder risk category than the category recorded on the day of hypoglycemia onset; meanwhile, 10 (76.9%) patients remained in the same category. Given weight loss, 4 (30.8%) patients were classified as at milder risk than that observed at the time of hypoglycemia onset; meanwhile, 9 (69.2%) patients remained in the same risk group (Table 4).

Other diabetes medicines (Medicine Name/N)	Drug-induced hypoglycemia in non-diabetes medicine (Medicine Name/N)	JCS (digit-code)	Blood glucose level before glucose administration (mg/dl)	Cause of hypoglycemia (physician evaluated records)
Ν	Tramadol	2	37	Decreased food intake
Ν	Trimethoprim-sulfamethoxazole	2	68	Decreased food intake
Ν	Ν	2	24	Decreased food intake
Ν	Ν	1	52	Decreased food intake
Ν	Bisoprolol	1	47	Decreased food intake
Ν	Carvedilol	1	62	Effects of hypoglycemic medicines
Ν	Tramadol, Pregabalin	1	67	Effects of drug-induced hypoglycemia in non-diabetes medicine
Ν	Ν	2	19	Effects of hypoglycemic medicines
Ν	Ν	1	29	unknown
Linagliptin	Ν	3	15	Effects of hypoglycemic medicines
Linagliptin	Ν	3	Low	Effects of hypoglycemic medicines
Duraglutide	Carvedilol	1	32	Effects of hypoglycemic medicines
Empagliflozin, Linagliptin	Carvedilol	2	57	Decreased food intake, Alcohol intake
Empagliflozin, Metformin	Imidapril	3	34	Effects of hypoglycemic medicines
Ν	Tramadol	1	19	Insulin autoimmune syndrome
Ν	Ν	2	54	Effects of hypoglycemic medicines
Ν	Imidapril	1	31	Sick day

TABLE 3 Pa	atient outcomes, includin£	g 90-day mortali	ty rates, following severe hype	oglycemia diagnosis		
Case No	DM Type	GNRI	Nutrition-related risk class	Length of stay (days)	Number of recurrent hypoglycemia events during hospitalization (times)	Death within 90 days after severe hypoglycemia (Y/N)
1	None	57	Major	7	5	Y
2	None	67	Major	28	0	Y
3	None	67	Major	32	18	Ν
4	None	68	Major	5	0	Y
5	None	72	Major	7	0	Ν
6	Type1	80	Major	6	1	Ν
7	None	91	Moderate	4	0	Ν
œ	Type 1 (slowly progressive)	91	Moderate	17	0	Y
6	None	92	Low	2	0	Y
10	Type 2	92	Low	13	0	Ν
11	Type 2	94	Low	8	1	Ν
12	Type 2	95	Low	26	0	Ν
13	Type 2	95	Low	4	0	Ν
14	Type 1 (slowly progressive)	100	None	6	0	N
15	None	101	None	17	0	Ν
16	Type 1	103	None	1	0	Ν
17	Type 2	104	None	12	0	Ν
Abbreviations: DN	1, diabetes mellitus; GNRI, ge	riatric nutritional	risk index.			

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TABLE 4 Nutrition-related risk class at baseline and at the time of severe hypoglycemia diagnosis

		Date of previous visit				
	Date of severe hypoglycemia	Weight unchanged	Weight loss			
Case No	Nutrition-related risk class	Nutrition-related risk class	Nutrition-related risk class			
1	Major	Major	Major			
2	Major	Major	Major			
3	Major	Major	Major			
5	Major	Major	Moderate			
6	Major	Moderate	Moderate			
7	Moderate	Low	Low			
9	Low	Low	Low			
11	Low	Low	Low			
12	Low	Low	Low			
13	Low	None	None			
14	None	None	None			
16	None	None	None			
17	None	None	None			

4 | DISCUSSION

This study examined the association between severe hypoglycemia and nutrition-related risk, assessed by the GNRI, in outpatients aged ≥ 65 years. The results showed that patients who developed severe hypoglycemia often had nutrition-related risk on the day of onset. In addition, patients without diabetes had a lower GNRI than patients with diabetes. Finally, the differences in nutrition-related risk scores between the day of hypoglycemia onset and the previous hospital visit were small, suggesting that nutrition-related risk may predict severe hypoglycemia.

Among patients with severe hypoglycemia, 13 of 17 (76.5%) had nutrition-related risk. Five of 6 patients with

major risk had hypoglycemia due to decreased food intake, and one was due to insulin. In contrast, in the no risk patients, it was not due to decreased food intake. Furthermore, in our previous study,⁷ the rate of nutritionrelated risk at admission was 49.3% (864/1754) in hospitalized patients with type 2 diabetes. Meanwhile, the rate of nutrition-related risk at admission in patients who experienced hypoglycemia during hospitalization was 84.0% (68/81), similar to the rate in this study. These findings suggest that nutritional status as assessed by GNRI may be associated with the occurrence of severe hypoglycemia in outpatients.

Patients without diabetes had lower GNRI values. In fact, medical records of most patients without diabetes suggested malnutrition, including decreased food intake,

as the cause of severe hypoglycemia. Leibovitz et al.⁶ have previously shown an association between malnutrition assessed using the NRS-2002 and the incidence of hypoglycemia during hospitalization, reporting an odds ratio of approximately 2. This association was stronger in patients without than in those with diabetes, which may be due to the use of hypoglycemic medication, masking the association between hypoglycemia and malnutrition in patients with diabetes. In the present study, most diabetes patients received hypoglycemic medicines such as insulin, which were the cause of severe hypoglycemia. Simultaneously, 6 of 9 diabetes patients had nutritionrelated risk, although their risk class was milder than that of non-diabetes patients in most cases. These findings suggest that malnutrition and medications are independent risk factors for hypoglycemia, and that they may act synergistically. Therefore, patients at nutritionrelated risk as assessed by GNRI may benefit from attention to the occurrence of severe hypoglycemia, with or without diabetes.

The difference in nutrition-related risk prevalence between the preceding and hypoglycemia onset visit was approximately 8%, regardless of weight change assumptions. Although the risk class varied in a few patients, past nutrition-related risk may be predictive of severe hypoglycemia. This association warrants further research.

The cause of hypoglycemia in malnourished individuals remains unclear; however, it may be associated with the depletion of glycogen stores.^{14,15} In glycogen storage disease, glycogen accumulates in tissues such as the liver and muscles due to congenital abnormalities in the enzymes required for glycogen degradation. As a result, glycogen is not broken down into glucose, and hypoglycemia may occur. People with malnutrition may develop hypoglycemia due to the lack of glucose, resulting from glycogen depletion.

The GNRI is easy to use and allows the assessment of nutritional status with an objective formula, which is not the case with other similar tools. Using the GNRI to identify nutrition-related risk factors may help screen patients and deliver suitable interventions, including changing the type and dose of prescribed drugs, and to educate patients on the early symptoms of hypoglycemia and an optimum response. More recently, oral nutritional supplements have been shown to potentially reduce the risk of hypoglycemia.¹⁶ These approaches may support medical staff across specialties.

The results of this study are the first to examine the association between nutrition-related risk and the occurrence of severe hypoglycemia in outpatients using the GNRI. However, it is limited by the number of patients included in the study. The risk ratio and predictive power of nutrition-related risk and the occurrence of severe hypoglycemia need to be proven in further clinical trials.

5 | CONCLUSION

In this study, we conducted a detailed investigation of older adult outpatients who developed severe hypoglycemia, and found that they had problems with their nutritional status as assessed by GNRI, regardless of whether they had diabetes or not. To prevent the occurrence of hypoglycemia in the future, we would like to identify high-risk patients, including their nutritional status, and examine whether interventions to improve their nutritional status can reduce the risk of occurrence of hypoglycemia.

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CONFLICT OF INTEREST None declared.

None declared.

AUTHOR CONTRIBUTIONS

YK collected the data, drafted the manuscript, and revised the manuscript. MA reviewed and revised the manuscript and served as a corresponding author. NK coordinated and supervised the data collection and critiqued the manuscript. All authors approved the final version of the manuscript.

ETHICAL APPROVAL

All procedures were performed in accordance with the 1964 Declaration of Helsinki and subsequent versions. The study protocol was approved by the ethics committees of Soka Municipal Hospital (approval number: Reiwa-3-No.8, date of approval: July 5, 2021) and Meiji Pharmaceutical University (approval number: 202121, date of approval: September 3, 2021).

CONSENT

The patients signed the informed consent, which explained the use of the information from the clinical history and laboratory data, for medical research purposes and publication in scientific media. Also, all patients were given the option to opt-out of this study on the institution's website, and no patients opted out.

DATA AVAILABILITY STATEMENT

All data used to support the results of this study are included in the manuscript. Due to the nature of the study, the corresponding author may provide additional information upon request to the extent that it does not compromise the confidentiality of the individuals who participated.

ORCID

Yoshinobu Kimura Dhttps://orcid. org/0000-0002-3809-0430 Manabu Akazawa Dhttps://orcid. org/0000-0002-4112-6035

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