Received: 5 April 2023 | Revised: 1 July 2023 | Accepted: 18 July 2023

DOI: 10.1002/hsr2.1467

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Hypouricemia in the emergency department: A retrospective, single-center study

Ryuichiro Makinouchi | Teppei Koyama | Shinji Machida | Naohiko Imai

Department of Internal Medicine, Division of Nephrology and Hypertension, St. Marianna University Yokohama Seibu Hospital, Yokohama, Japan

Correspondence
Naohiko Imai, Department of Internal Medicine, Division of Nephrology and Hypertension, St. Marianna University Yokohama Seibu Hospital, 1197-1 Yasashi-cho, Asahi-ku, Yokohama, Kanagawa, Japan.
Email: naohiko.imai@gmail.com

Abstract

Backgrounds: Few studies have reported the prevalence and characteristics of hypouricemia in the emergency department (ED). We investigated the prevalence and characteristics of hypouricemia in the ED of a university-affiliated hospital in Japan.

Methods: This is a retrospective cross-sectional single-center study. All adult patients (18 years old or older) who had their serum uric acid (SUA) measured at the ED between 2011 and 2021 were included. Information collected included age, sex, SUA, and serum creatinine. Hypouricemia was defined as an SUA level ≦2.0 mg/dL.

Results: A total of 10,551 patients were included in the study. Fifty-one percent were male. The median SUA levels were significantly higher in men than in women (6.0 [4.8–7.4] vs. 4.7 [3.7–6.1], $p < 0.001$). The prevalence of hypouricemia was higher in women than in men (2.0% vs. 0.9%, $p < 0.001$). A possible cause of hypouricemia was identified in 88 patients. Malignancy and diabetes were the major possible cause of hypouricemia ($p < 0.001$).

Conclusion: The distribution of SUA levels and prevalence of hypouricemia differed significantly by sex and age in the ED. Malignancy was the leading cause of hypouricemia in the ED.

KEYWORDS

adolescent health, emergency medicine

1 | INTRODUCTION

Hypouricemia is defined as a serum uric acid (SUA) concentration of ≦2.0 mg/dL.[1,2] Seventy percent to eighty percent of the daily urate excretion is excreted by the kidneys, with the remainder being excreted by secretion from the intestines.[3] Hypouricemia may result from decreased uric acid production, decreased renal tubular reabsorption due to hereditary or acquired disease, or uric acid oxidation due to treatment with uricase.[4] Hypouricemia has received more attention in recent years as the role of urate transporters has become better understood. Apical urate transporter 1 (URAT1) and basolateral glucose transport like protein 9 (GLUT9) are two representative renal urate transporters.[5,6] URAT1 functions as the primary urate/anion exchanger responsible for luminal urate reabsorption. On the other hand, GLUT9 functions as the major mechanism for basolateral reabsorption into the blood.[7] Renal hypouricemia is classified as type 1 when caused by abnormalities in the URAT1 gene and type 2 when caused by abnormalities in the GLUT9 gene.[8]

Several studies have reported the prevalence and characteristics of hypouricemia in outpatient and inpatient settings. Most of these

studies are small, and only a few studies have reported the prevalence of hypouricemia in more than 10,000 patients. The prevalence of hypouricemia is so small that studies with large sample sizes are needed to examine it thoroughly. The prevalence of hypouricemia from major studies varies from 0.19% to 4.14%, and the prevalence of hypouricemia is higher in hospitalized patients than in outpatients.

Hypouricemia has been reported mostly in outpatient, inpatient, and health checkup settings, and to the best of our knowledge, few studies have reported the prevalence of hypouricemia in the emergency department (ED). Therefore, in this study, we aimed to investigate the prevalence and characteristics of hypouricemia in the ED in Japan.

2 | MATERIALS AND METHODS

All adult patients (18 years old or older) who had their SUA measured on arrival to our ED between 2011 and 2021 were included in this study (Figure 1). For patients who visited the ED more than once and had SUA levels measured more than once, the value from the first visit was used. Hypouricemia was defined as an SUA level ≦2.0 mg/dL as in previous studies. Information collected included age, sex, SUA, and serum creatinine. Diseases and conditions that may cause hypouricemia were extracted from the electronic medical records. The estimated glomerular filtration rate (eGFR) of each participant was calculated using the following formula: eGFR (mL/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age $^{-0.287}$ × 0.739 (if female).[9]

2.1 | Statistical analyses

Continuous variables were expressed as median (first quartile to third quartile), and categorical variables were expressed as percentages. Continuous variables were analyzed using the Mann–Whitney *U* test. Categorical variables were analyzed using the χ^2 test. A *p*-value of <0.05 was considered statistically significant. Data analysis was performed using SPSS, Version 21.0 (IBM Corp.).

3 | RESULTS

3.1 | Characteristics

From 2011 to 2021, a total of 10,551 adult patients had their SUA measured at our ED. The key characteristics of the patients are summarized (Table 1). The median age of all patients was 71 (52–80) years, 51% were male, and the median SUA level was 5.4 (4.2–6.9) mg/dL. The median SUA levels were significantly higher in men than in women (6.0 [4.8–7.4] vs. 4.7 [3.7–6.1], $p < 0.001$). The median age was 73 (50–81) years for hypouricemic patients and 71 (52–80) years for non-hypouricemic patients ($p = 0.79$). The median eGFR was 91 (65–125) mL/min/1.73 m^2 for hypouricemic patients and 66 (44–87) mL/min/1.73 m^2 for non-hypouricemic patients ($p < 0.001$). The median SUA was 1.7 (1.3–1.9) mg/dL for hypouricemic patients and 5.4 (4.2–6.9) mg/dL for non-hypouricemic patients ($p < 0.001$). The distribution of patients by SUA level is shown (Figure 2).

3.2 | Prevalence and distribution of patients with hypouricemia

The prevalence (number) of hypouricemia among all patients was 1.4% (152).

The prevalence of hypouricemia in men was 0.9% (50) and that in women was 2.0% (102) ($p < 0.001$). The distribution of hypouricemic patients by SUA levels and age in men and women are shown (Figure 3A–D).

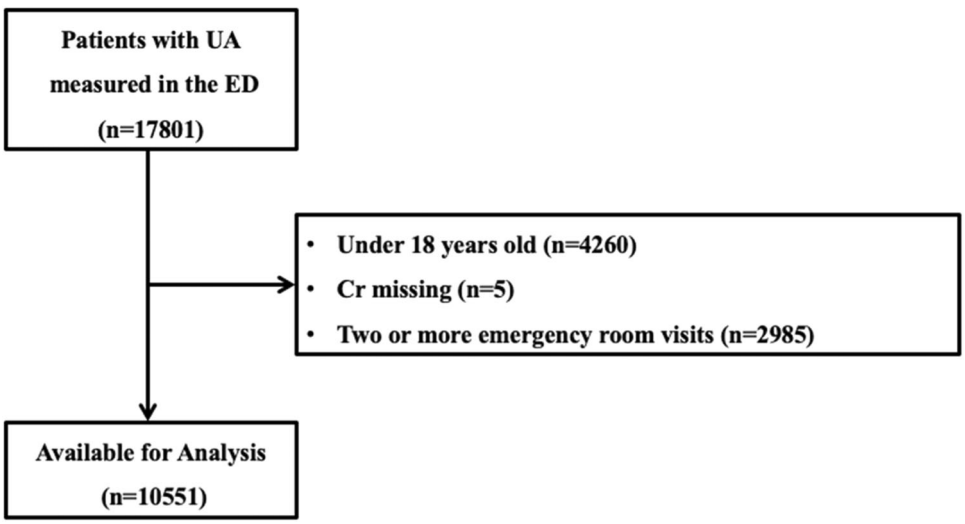

FIGURE 1 Flow chart of the selection of patients. EA, emergency department; UA, uric acid.

TABLE 1 Characteristics of patients.

	All	Hypouricemic	Non-hypouricemic	*p*
N	10,551	152	10,399	
Age (years)	71 (52–80)	73 (50–81)	71 (52–80)	0.79
Male (%)	51	33	52	<0.001
Serum creatinine (mg/dL)	0.8 (0.6–1.2)	0.6 (0.4–0.8)	0.8 (0.6–1.2)	<0.001
eGFR (mL/min/1.73 m^2)	66 (44–87)	91 (65–125)	66 (44–87)	<0.001
Serum uric acid (mg/dL)	5.4 (4.2–6.9)	1.7 (1.3–1.9)	5.4 (4.2–6.9)	<0.001

Abbreviation: eGFR, estimated glomerular filtration rate.

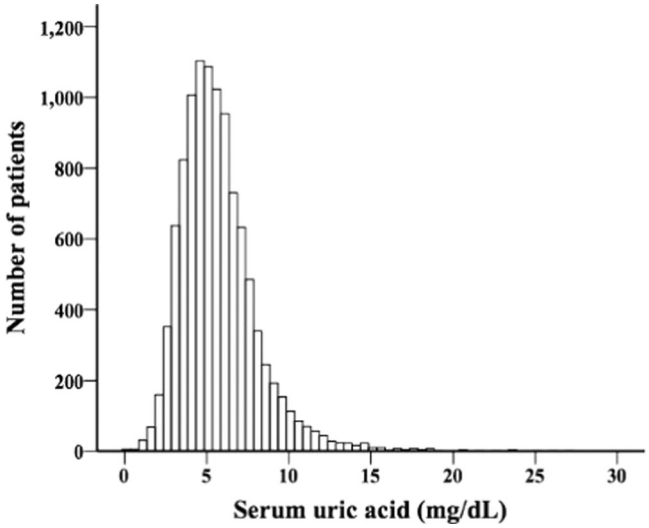

FIGURE 2 Distribution of patients by SUA level. SUA, serum uric acid.

3.3 | Characteristics of patients with hypouricemia

Among the 152 subjects with hypouricemia, 50 (33%) were male (Table 2). The median age was 76 (63–82) years for men and 71 (40–80) years for women, respectively ($p = 0.13$). The median eGFR was 86 (20–119) for men and 95 (72–128) for women ($p = 0.03$).

3.4 | Possible causes of hypouricemia

Possible causes of hypouricemia were identified in 88 patients (Table 3). Malignancy ($n = 29$), diabetes ($n = 26$), intracranial disease ($n = 15$), drug ($n = 14$), and pregnancy ($n = 14$) were the major possible cause of hypouricemia. The most common malignancies were colorectal cancer ($n = 3$), breast cancer ($n = 3$), multiple myeloma ($n = 3$), cholangiocarcinoma ($n = 3$), pancreatic cancer ($n = 2$), and renal cancer ($n = 2$). Two of the diabetic patients had type 1 diabetes and the rest had type 2 diabetes. The most frequent intracranial diseases were cerebral infarction ($n = 5$), subarachnoid hemorrhage ($n = 4$), and subdural hematoma ($n = 4$). The most frequent drugs were febuxostat ($n = 8$), allopurinol ($n = 3$), losartan ($n = 2$), and irbesartan ($n = 1$). Eight of the pregnant patients had an imminent preterm delivery.

4 | DISCUSSION

The prevalence of hypouricemia has been reported in a variety of settings, including inpatient, outpatient, and health checkups, but to the best of our knowledge, few studies have reported the prevalence and characteristics of hypouricemia in the ED. The prevalence of hypouricemia in major studies varies from 0.19% to 4.14%[10] (Table 4). The prevalence of hypouricemia was 1.4% in our study.

The subjects of this study were patients who visited the ED. The prevalence of hypouricemia is higher in hospitalized patients than in outpatients.[10] This is likely because the number of medications or diseases that might trigger hypouricemia is greater in the inpatient.[11] The prevalence of hypouricemia in the ED can be somewhere between outpatient and inpatient.

In contrast to hyperuricemia, which is more common in men, hypouricemia is known to be more common in women. In our study, the prevalence of hypouricemia was about twice as high in women, which is similar to that reported previously. The prevalence of hypouricemia differs between areas in Japan.[2] The proposed possibilities include regional differences in the prevalence of the G774A mutation of the SLC22A12 gene responsible for hypouricemic Japanese and different ratios of men to women in the studied population.[2,12] Further study is needed to clarify whether there is also a regional difference in hypouricemia in the ED.

In this study, the median SUA was 5.4 mg/dL. This result is higher compared to the previous studies. This might be related to the older age of the patients in our study. Also, as our subjects are patients who visited the ED, this might be associated with the acute disease that could raise the SUA levels. Furthermore, our study was exclusively Japanese, and our result likely differs from the reported mean SUA level of 6.0 mg/dL in Black men, 5.8 mg/dL in White men, 4.9 mg/dL in Black women, and 4.4 mg/dL in White women.[13]

In our study, the prevalence of hypouricemia was highest among men and women in their 70s, respectively. In women, there was also a peak prevalence of hypouricemia in their 30s. The biphasic peak in prevalence in women, which is similar to our results, has been

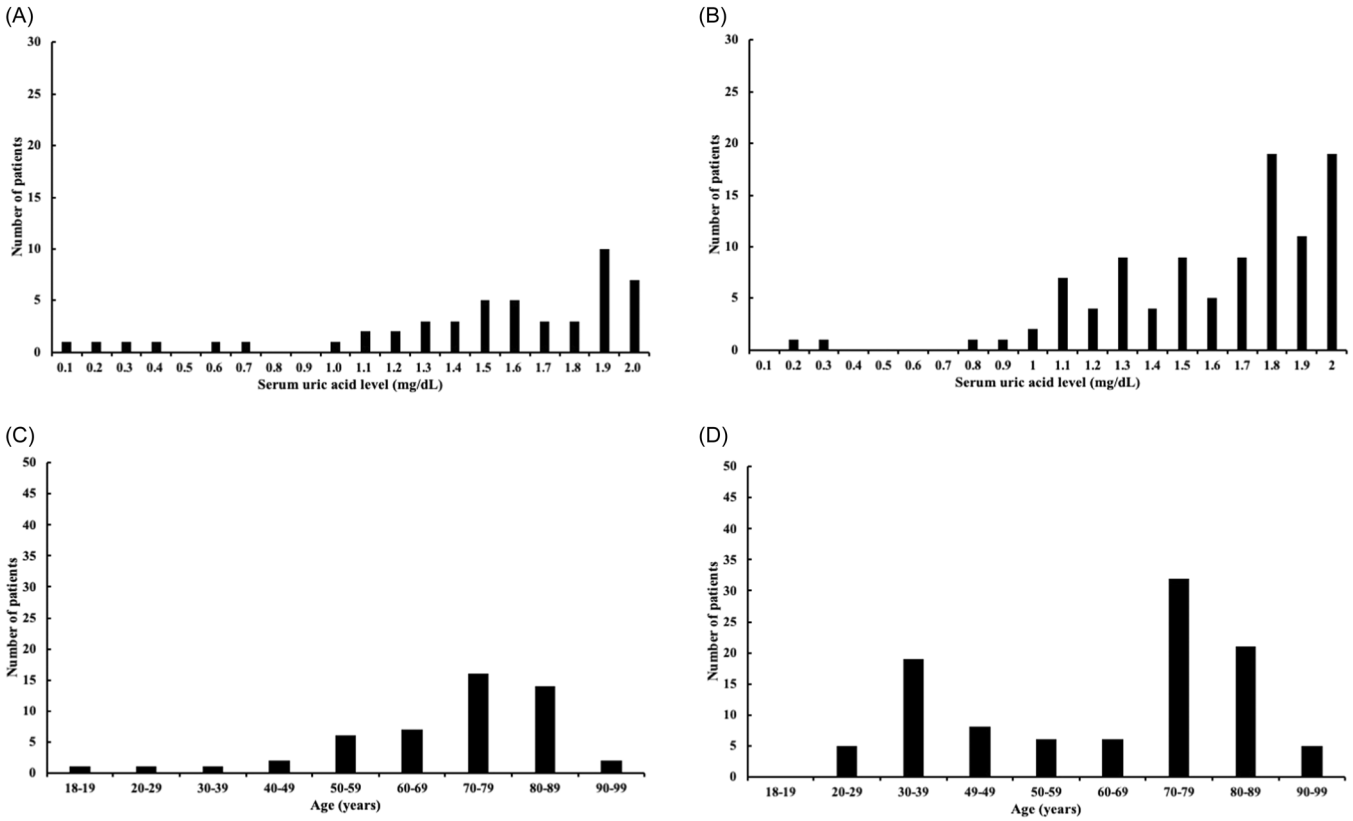

FIGURE 3 (A) Distribution of SUA levels in men. (B) Distribution of SUA levels in women. (C) Distribution of age in men. (D) Distribution of age in women. SUA, serum uric acid.

TABLE 2 Characteristics of patients with hypouricemia.

	All	Male	Female	*p*
N	152	50 (33%)	102 (67%)	<0.001
Age (years)	73 (50–81)	76 (63–82)	71 (40–80)	0.13
Serum creatinine (mg/dL)	0.6 (0.4–0.8)	0.7 (0.6–2.5)	0.5 (0.4–0.7)	<0.001
eGFR (mL/min/1.73 m^2)	91 (65–125)	86 (20–119)	95 (72–128)	0.03
Serum uric acid (mg/dL)	1.7 (1.3–1.9)	1.6 (1.3–1.9)	1.7 (1.3–1.9)	0.40

Abbreviation: eGFR, estimated glomerular filtration rate.

reported.[14] The peak frequency of hypouricemia seen in women in their 30s was due to pregnancy. SUA levels are known to decrease during pregnancy.[15]

There was a peak in the number of patients with hypouricemia at 1.9 mg/dL in men and at 1.8 mg/dL in women. This is similar to previous studies reporting peaks at 1.6 and 2.0 mg/dL, respectively.[2] On the other hand, prior studies have reported that hypouricemia also peaks around 0.6–0.8 mg/dL, but we did not observe this finding in our study.[2,16] The number of patients with hypouricemia was smaller than in previous studies, which may explain why the peak was not observed at SUA levels below 1.0 mg/dL.

Uric acid excretion due to medical diseases or drugs can result in hypouricemia. In this study, malignancy was the leading etiology of hypouricemia, followed by diabetes mellitus, which was similar to previous studies.[10] It is well known that malignancy, diabetes mellitus, and drugs can cause hypouricemia.[17,18] Among the 152 subjects with hypouricemia in our study, 64 cases were of an unknown cause.

Malignancy, diabetes, pregnancy, intracranial disease, and SIADH have been reported to cause hypouricemia by increasing uric acid excretion.[18–23] Drugs such as febuxostat and allopurinol cause hypouricemia by decreasing uric acid production, while losartan and irbesartan cause hypouricemia by increasing uric acid excretion.[24]

Many reports on the association between uric acid and renal function have focused on the association between hyperuricemia and renal function. Many studies have reported that hyperuricemia is an independent risk factor for the development and progression of CKD.[25–27] On the other hand, only a few studies have reported an

association between hypouricemia and CKD.[1,28] Uric acid is the major antioxidant in human plasma and is associated with oxidative stress.[29] Further studies are needed to clarify the effect of severe hypouricemia on renal function in the ED.

TABLE 3 Possible cause of hypouricemia.

	N = 88
Malignancy[a]	29 (33%)
Colorectal cancer	3
Breast cancer	3
Multiple myeloma	3
Cholangiocarcinoma	3
Pancreatic cancer	2
Renal cancer	2
Diabetes[a]	26 (30%)
Type 1 diabetes	2
Type 2 diabetes	24
Intracranial disease	15 (17%)
Cerebral infarction	5
Subarachnoid hemorrhage	4
Subdural hematoma	4
Drug	14 (16%)
Febuxostat	8
Allopurinol	3
Losartan	2
Irbesartan	1
Pregnancy	14 (16%)
Imminent preterm delivery	8
SIADH	5 (5%)

Note: Some patients had more than one cause.

Abbreviation: SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

[a]$p < 0.001$.

This study is not without its limitations. First, this is a single-center study, and the patients enrolled are subject to possible selection bias. Second, SUA levels were assessed only once, and it was not possible to verify whether hypouricemia was transient or persistent. Third, urinary excretion of uric acid was not measured. It is not known whether hypouricemia is caused by a decrease in uric acid production or an increase in urinary excretion. Fourth, it was not possible to assess the association between the patient's general condition or disease severity and SUA levels. Fifth, the information in the medical record at the time of the emergency room visit is not always complete, and omissions in the medical history can be expected. Therefore, it is not possible to rule out all diseases causing hypouricemia.

In conclusion, the distribution of SUA levels and prevalence of hypouricemia differed significantly by sex and age in the ED. The prevalence of hypouricemia was approximately two times higher in women than in men. Malignancy was the leading etiology of hypouricemia in the ED.

AUTHOR CONTRIBUTIONS

Ryuichiro Makinouchi: Conceptualization; data curation; formal analysis; investigation; methodology; validation; writing—original draft; writing—review and editing. **Teppei Koyama**: Conceptualization; writing—review and editing. **Shinji Machida**: Conceptualization; writing—review and editing. **Naohiko Imai**: Conceptualization; data curation; formal analysis; investigation; methodology; validation; writing—original draft; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

TRANSPARENCY STATEMENT

The lead author Naohiko Imai affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA AVAILABILITY STATEMENT

The data sets used and analyzed during the current study are available from the corresponding author upon reasonable request.

TABLE 4 The prevalence of hypouricemia in major studies.

Study	*N*	Prevalence (%)	Subject type	Country
Casas, 1990	27,987	0.61	Inpatients	Spain
Bugadayci, 2008	18,330	0.51	Outpatients	Turkey
Wakasugi, 2015	227,645	0.32	Health checkups	Japan
Son, 2019	23,534	0.53	Outpatients	Korea
Son, 2019	7223	4.14	Inpatients	Korea
Kuwabara, 2019	90,143	0.19	Health checkups	Japan
Kawasoe, 2019	246,923	0.46	Health checkups	Japan
This study, 2022	10,551	1.44	Emergency department	Japan

ETHICS STATEMENT

Ethical approval for this study was obtained from the ethical committee of St. Marianna University. The institutional review board at our facility approved this retrospective study and waived the need for written consent. All the data were anonymized.

ORCID

Naohiko Imai http://orcid.org/0000-0001-9984-2889

REFERENCES

1. Wakasugi M, Kazama JJ, Narita I, et al. Association between hypouricemia and reduced kidney function: a cross-sectional population-based study in Japan. *Am J Nephrol*. 2015;41:138-146.
2. Kuwabara M, Niwa K, Ohtahara A, et al. Prevalence and complications of hypouricemia in a general population: a large-scale cross-sectional study in Japan. *PLoS One*. 2017;12:e0176055.
3. So A, Thorens B. Uric acid transport and disease. *J Clin Invest*. 2010;120:1791-1799.
4. Maesaka J, Fishbane S. Regulation of renal urate excretion: a critical review. *Am J Kidney Dis*. 1998;32:917-933.
5. Ichida K, Hosoyamada M, Hisatome I, et al. Clinical and molecular analysis of patients with renal hypouricemia in Japan-influence of URAT1 gene on urinary urate excretion. *JASN*. 2004;15:164-173.
6. Dinour D, Gray NK, Campbell S, et al. Homozygous SLC2A9 mutations cause severe renal hypouricemia. *JASN*. 2010;21:64-72.
7. Estiverne C, Mandal AK, Mount DB. Molecular pathophysiology of uric acid homeostasis. *Sem Nephrol*. 2020;40:535-549.
8. Otani N, Ouchi M, Misawa K, Hisatome I, Anzai N. Hypouricemia and urate transporters. *Biomedicines*. 2022;10:652.
9. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*. 2009;53:982-992.
10. Son C-N, Kim J-M, Kim S-H, et al. Prevalence and possible causes of hypouricemia at a tertiary care hospital. *Korean J Intern Med*. 2016;31:971-976.
11. Bairaktari ET, Kakafika AI, Pritsivelis N, et al. Hypouricemia in individuals admitted to an inpatient hospital-based facility. *Am J Kidney Dis*. 2003;41:1225-1232.
12. Sugihara S, Hisatome I, Kuwabara M, et al. Depletion of uric acid due to SLC22A12 (URAT1) loss-of-function mutation causes endothelial dysfunction in hypouricemia. *Circ J*. 2015;79:1125-1132.
13. Maynard JW, McAdams-DeMarco MA, Law A, et al. Racial differences in gout incidence in a population-based cohort: atherosclerosis risk in communities study. *Am J Epidemiol*. 2014;179:576-583.
14. Koo BS, Jeong H-J, Son C-N, et al. Distribution of serum uric acid levels and prevalence of hyper- and hypouricemia in a Korean general population of 172,970. *Korean J Intern Med*. 2021;36:S264-S272.
15. Lind T, Godfrey KA, Otun H, Philips PR. Changes in serum uric acid concentrations during normal pregnancy. *Obstet Gynecol Surv*. 1984;39:565-566.
16. Kawasoe S, Ide K, Usui T, et al. Distribution and characteristics of hypouricemia within the Japanese general population: a cross-sectional study. *Medicina (Kaunas)*. 2019;55(3):61. doi:10.3390/medicina55030061
17. Lesmes A, Díaz-Curiel M, Castrillo JM. Tumoural hypouricemia. *Adv Exp Med Biol*. 1980;122A:145-148.
18. Shichiri M. Diabetic renal hypouricemia. *Arch Intern Med*. 1987;147:225.
19. Beck LH. Hypouricemia in the syndrome of inappropriate secretion of antidiuretic hormone. *N Engl J Med*. 1979;301:528-530.
20. Maesaka JK, Venkatesan J, Piccione JM, Decker R, Dreisbach AW, Wetherington JD. Abnormal urate transport in patients with intracranial disease. *Am J Kidney Dis*. 1992;19:10-15.
21. Lind T, Godfrey KA, Otun H, Philips PR. Changes in serum uric acid concentrations during normal pregnancy. *BJOG: Int J Obstetrics Gynaecol*. 1984;91:128-132.
22. Magoula I, Tsapas G, Kountouras I, Paletas K. Cholangiocarcinoma and severe renal hypouricemia: a study of the renal mechanisms. *Am J Kidney Dis*. 1991;18:514-519.
23. Magoula I, Tsapas G, Paletas K, Mavromatidis K. Insulin-dependent diabetes and renal hypouricemia. *Nephron*. 1991;59:21-26.
24. Hamada T, Ichida K, Hosoyamada M, et al. Uricosuric action of losartan via the inhibition of urate transporter 1 (URAT 1) in hypertensive patients. *Am J Hypertens*. 2008;21:1157-1162.
25. Iseki K, Ikemiya Y, Inoue T, Iseki C, Kinjo K, Takishita S. Significance of hyperuricemia as a risk factor for developing ESRD in a screened cohort. *Am J Kidney Dis*. 2004;44:642-650.
26. Hsu C, Iribarren C, McCulloch CE, Darbinian J, Go AS. Risk factors for end-stage renal disease: 25-year follow-up. *Arch Intern Med*. 2009;169:342-350.
27. Sonoda H, Takase H, Dohi Y, Kimura G. Uric acid levels predict future development of chronic kidney disease. *Am J Nephrol*. 2011;33:352-357.
28. Kanda E, Muneyuki T, Kanno Y, Suwa K, Nakajima K. Uric acid level has a U-shaped association with loss of kidney function in healthy people: a prospective cohort study. *PLoS One*. 2015;10:e0118031.
29. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. *Proc Natl Acad Sci*. 1981;78:6858-6862.

How to cite this article: Makinouchi R, Koyama T, Machida S, Imai N. Hypouricemia in the emergency department: a retrospective, single-center study. *Health Sci Rep*. 2023;6:e1467. doi:10.1002/hsr2.1467