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The detection of hyaline casts in patients without renal dysfunction suggests increased plasma BNP

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ABSTRACT

Background and aim

Casts in urinary sediments are useful in the identification of kidney diseases. Among them, hyaline casts have not previously been considered as pathognomonic. However, hyaline casts can occasionally be found in patients undergoing cardiovascular treatment without renal dysfunction. We evaluated the background of these patients and also investigated their levels of plasma brain natriuretic peptide (BNP).

Materials and methods

Samples from patients who visited the Division of Cardiovascular Disease at Nihon University Hospital (2014-2018) were examined. We set extract conditions from the laboratory information system database, setting the threshold over 60 mL/min/1.73 m^2 for the estimated glomerular filtration rate (eGFR), and proteinuria as absent (-) or trace (±). One hundred

forty-seven of 3137 (4.7%) samples showed hyaline casts (M:F=102:45, mean age 69.5±11.2 years). Samples with hyaline casts were divided into three rank groups. We compared BNP levels among each cast group and age-matched controls using Kruskal-Wallis analysis.

Results

The median BNP levels of the controls and the three casts groups were 23.3 pg/mL in the controls, 31.1 pg/mL in group (1+), 35.5 pg/mL in group (2+), and 45.8 pg/mL in group (≥3+). The median BNP levels differed significantly between two casts groups (group (2+) and group (≥3+)) and the control group ($P<0.05$ and $P<0.01$, respectively).

Conclusion

Hyaline casts could be detected in patients with normal renal function. When hyaline casts are more than 2+, the physician should consider checking plasma BNP levels of the patient.

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INTRODUCTION

Examination of the urinary sediment, especially in conjunction with assessment of proteinuria, is useful in the detection of chronic kidney disease. Casts are components of the urinary sediments, and most of them are useful in the identification of the type of kidney disease, such as erythrocyte casts in glomerulonephritis[1]. Among these casts, hyaline casts have previously not been considered to be pathognomonic, but are commonly detected in all kidney diseases[2]. They may also be seen in normal subjects who perform strenuous exercise and in non-renal disorders such as fever or dehydration[3].

However, hyaline casts occasionally can be found in patients undergoing treatment for cardiovascular disease. We have found a relationship between the number of urinary hyaline casts and the levels of plasma brain natriuretic peptide (BNP) from laboratory data on patients without proteinuria[4]. In that study, the number of hyaline casts and BNP levels were positively correlated, but we used only laboratory data from urine and blood without patient background data. Therefore, it was possible that the data included subjects with a history of kidney disease and heart failure. In the present study, we also reviewed medical histories to assess renal function and patient background. The aim of this study was to investigate whether hyaline casts in urine can be detected in patients with normal renal function, and to examine the relationship between their levels of plasma BNP and the number of hyaline casts.

SUBJECTS AND METHODS

Subjects

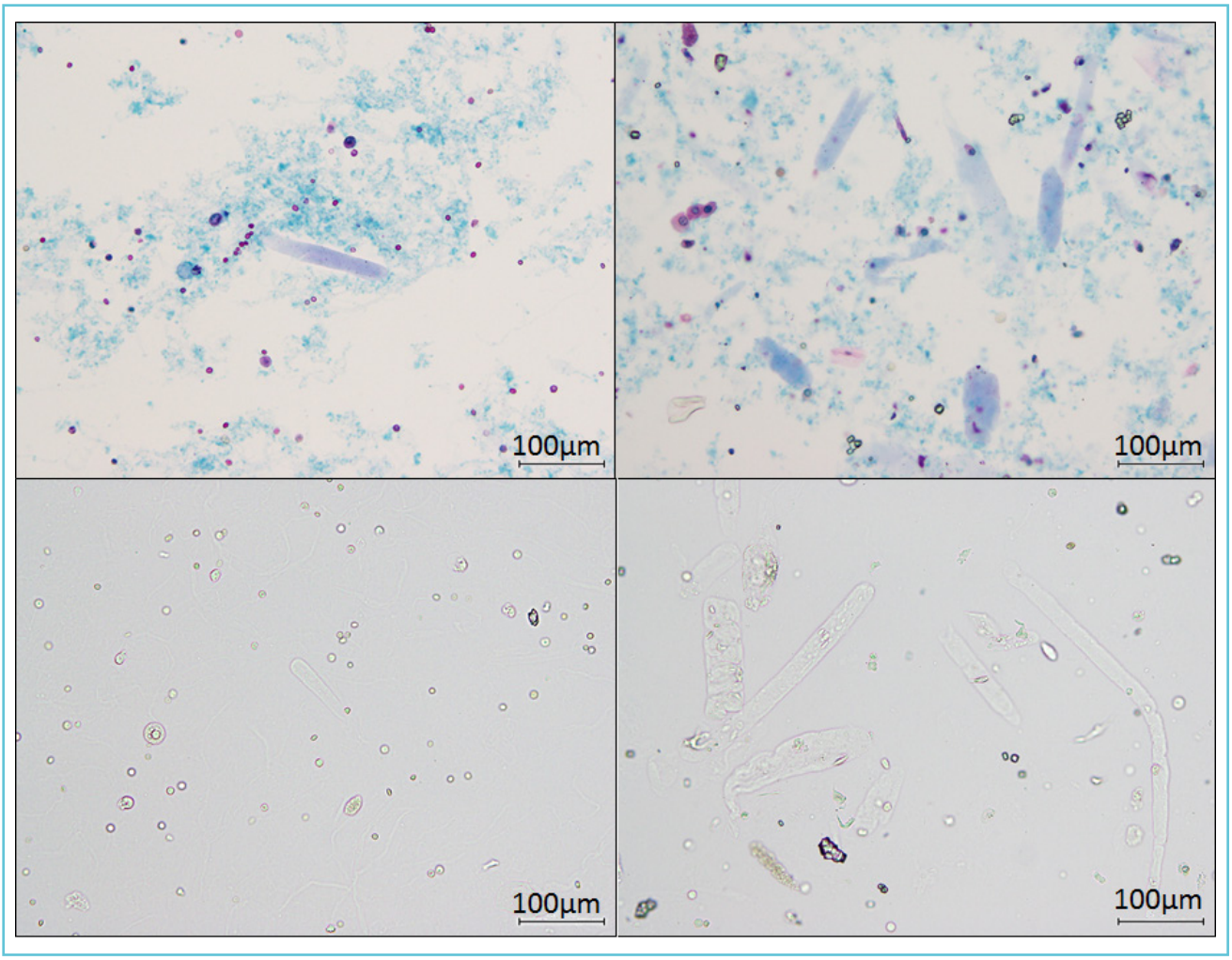
Samples from patients who visited and were tested in the Department of Laboratory Medicine at Nihon University Hospital from October 1, 2014 to December 31, 2018 were examined. We set extract conditions from the laboratory information system database of blood examination and urinalysis as follows. 1) Blood examination and urinalysis including urinary sediment examination were performed on the same day. 2) The threshold was set to over 1.8 mmol/L and under 7.5 mmol/L for blood urea nitrogen (BUN) and over 60 mL/min/1.73 m^2 for the estimated glomerular filtration rate (eGFR), and proteinuria was absent (-) or at a trace level (±). To exclude renal disease and renal dysfunction, the information of all patients' medical records was reviewed for five years. The medical records included demographic data, history of comorbid conditions, and use of cardiac medication. Exclusion criteria were as follows: a known history of renal dysfunction, defined as an eGFR of <60 mL/min/1.73 m^2; proteinuria; detection

of urine casts other than hyaline casts; or a history of acute infectious disease, cardiovascular surgery, myocardial infarction, or cerebral infarction. Because patients with chronic arterial fibrillation and chronic heart failure show increased BNP levels even in a medically stable condition[5,6], they were also excluded from the study.

Measurements

Urine samples were collected and examined using the method proposed by the Japanese Committee for Clinical Laboratory Standards (JCCLS)[7]. Proteinuria was assessed by a dipstick (Uriace, Eiken, Tokyo, Japan). Urine sediment was assessed by two trained laboratory technicians within four hours after collection. In preparing the urine sediment for examination, 10 mL of urine was centrifuged at 500 *g* (1,730 rpm; radius, 15 cm) for 5 min. Urinary casts were counted in whole fields at low power field (100×). Results from microscopic examination are described as approximate counts in the whole field (WF). Examples of hyaline casts under a microscope at low power field are presented in Figure 1.

Figure 1 Examples of hyaline casts under low power field (100×)



The upper two are after Sternheimer staining, and the lower two are without staining. The left panels are examples of group (1+) (1-9/WF) and/or group (2+) (10-29/WF). The right panels are examples of group (≥3+) (≥30/WF).

Serum creatinine (Hitachi Chemical Diagnostics Systems, Tokyo, Japan) and BUN (Serotec, Sapporo, Japan) were measured by enzymatic methods using fully automated analysis (LABOSPECT 008, Hitachi High-Technologies Co., Tokyo, Japan). We used eGFR equations devised by the Japanese Society of Nephrology (JSN) in the main analysis. The equations are: eGFRcreat [mL/min/1.73 m^2] = 194 × (s-Cr /88.4)[μmol/L] (-1.094) × age [years](-0.287) for males; and eGFRcreat [mL/min/1.73 m^2] = 194 ×(s-Cr /88.4) [μmol/L](-1.094) × age [years](-0.287) × 0.739 for females.

Plasma BNP levels (concentrations) were measured by fully automated enzyme immunoassay analysis using AIA-2000ST (TOSOH Bioscience, Tokyo Japan).

Transthoracic echocardiography was performed to assess left ventricular function (Vivid S6, GE Healthcare; Vivid E9, GE Healthcare; EPIQ 7, Philips; CX50, Philips). We measured the ejection fraction (EF) and left atrial diameter (LAD).

Data on medical history, use of antihypertensive medication, blood pressure in the right arm of the seated patient on the same day of blood and urine sample collection, and body weight and height were reviewed in each patient. Body weight and height were measured while the patient was wearing light clothing without shoes. Blood pressure was measured using an electronic sphygmomanometer (H55, TERUMO, Tokyo, Japan). Two consecutive measurements in the right arm of each seated patient were taken, and the second measurement was used for analysis. Hypertension, diabetes mellitus, hyperlipidemia, and angina pectoris were defined according to documentation of the diagnosis or the use of medications.

Statistical analysis

Samples with hyaline casts were divided into three rank groups according to JCCLS. They were defined by the number of the casts (1-9/WF as (1+), 10-29/WF as (2+), and ≥30/WF as (≥3+/WF)).

We compared BNP levels among each hyaline rank group and controls using Kruskal-Wallis analysis. A one-way analysis of variance (ANOVA) for repeated measures was used to compare the intragroup values of age, body mass index (BMI), eGFR, heart rate, and blood pressure. A Bonferroni correction and Tukey's honestly significant difference test were used for *post hoc* analysis. The *t* test was used to assess differences in EF and LAD in echocardiograms between the hyaline cast groups and controls. $P<0.05$ was considered statistically significant. Statistical analysis was performed using commercially available software (IBM SPSS Statistics for Windows, version 22.0.0.0, Armonk, NY). The statistical analysis was conducted at a 95% confidence level.

Ethical principles

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki in line with the Ethical Guidelines for Epidemiological Research by the Japanese government. This study was approved by the Ethics Committee of Nihon University Hospital (No. 20191001).

RESULTS

Initially, 4302 samples (M:F=2925:1377, mean age 65.6±12.2 years, range 18 to 95 years) were extracted from the laboratory information system database. According to the exclusion criteria mentioned above, we excluded 1165 samples out of 4302 (1165/4302, 27%). The remaining 3137 (M:F=2104:1033, mean age 67.9±9.14 years) were examined. One hundred forty-seven (M:F=102:45) out of 3137 (147/3137, 4.7%) samples showed hyaline casts (M:F=102:45, mean age 69.5±11.2 years, range

45 to 92 years). The clinical characteristics of all samples are presented in Table 1.

We used samples from patients without hyaline casts and who had transthoracic echocardiograms within three months as controls. We excluded those under 50 years of age, leaving for the control analysis (N=302, M:F=193:109, mean age 69±9.0 years, range 51 to 88 years) a population with matched age. The characteristics of the control and each hyaline group according JCCLS rank are presented in Table 2. The ratio of hypertension in controls was lower than in the total hyaline cast groups (65% and 80% respectively). The ratios of diabetes mellitus and dyslipidemia in the controls were also lower than in the total hyaline cast groups, but in each group the ratio of diabetes mellitus was around 30%. The ratio of angina pectoris in the controls was higher than in the total hyaline cast groups.

The prescribed antihypertensive drugs are presented in Table 3. Angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) were prescribed in 65% of the control group and in 49% of the cast groups. The most prescribed antihypertensive medications were ACEI/ARB in the control group (65%) and calcium channel blockers in the cast groups (60%). Diuretics were prescribed more frequently in the cast groups (13%) than in controls (2%).

Table 4 shows a comparison among four groups. The median BNP levels of the control and three casts groups were 23.3 pg/mL in the control, 31.1 pg/mL in group (1+), 35.5 pg/mL in group (2+), and 45.8 pg/mL in group (≥3+). These were significantly different in the two cast groups (group (2+) and group (≥3+)) compared to the control group ($P<0.05$ and $P<0.01$, respectively). There was a significant increase in BNP levels as the cast rank increased.

Table 1 Background clinical characteristic of the samples

	All samples (n=3137)
Age (years), mean (SD)	67.9 (9.14)
Sex (M/F)	2104/1033
Weight (kg), mean (SD)	64.23 (11.81)
BMI (kg/m^2), mean (SD)	24.3(3.7)
Medical history diagnosis	**n (%)**
Hypertension	69%
Diabetes mellitus	35%
Dyslipidemia	58%
Angina pectoris	22%

BMI: body mass index.

Table 2 Background clinical characteristic of controls and samples with hyaline casts

	Control (n=302)	Total samples with hyaline casts (n=147)	Hyaline cast rank		
			(1+) (n=70)	(2+) (n=37)	(≥ 3+) (n=40)
Age (years), mean (SD)	69.0 (9.0)	69.5 (11.2)	67.8 (10.5)	69.9 (11)	71.7 (11.8)
Sex (M/F)	193/109	102/45	46/24	23/14	33/7
Medical history diagnosis, n (%)					
Hypertension	197/302 65%	118/147 80%	54/70 77%	28/37 77%	36/40 90%
Diabetes mellitus	83/302 27%	43/147 29%	24/70 34%	10/37 27%	9/40 23%
Dyslipidemia	150/302 50%	94/147 64%	43/70 61%	24/37 65%	29/40 73%
Angina pectoris	59/302 20%	20/147 13%	10/70 14%	8/37 22%	2/40 5%

Table 3 Types and ratios of prescribed antihypertensive agents in control and hyaline cast groups

		Control (n=302)	Total samples with hyaline casts (n=147)	Hyaline cast level		
				(1+) (n=70)	(2+) (n=37)	(≥ 3+) (n=40)
Hypertension		197/302 65%	118/147 80%	54/70 77%	28/37 77%	36/40 90%
Types of antihypertensive medication	ACEI/ARB	132/302 65%	72/147 49%	36/70 51%	15/38 39%	21/40 53%
	Ca-blocker	138/302 44%	88/147 60%	37/70 53%	24/38 63%	27/40 68%
	β-blocker	48/302 46%	65/147 44%	28/70 40%	15/38 39%	22/40 55%
	Diuretic	7/302 2%	19/147 13%	4/70 6%	5/38 13%	10/40 25%

ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin II receptor blockers.

Table 4 Comparison between control and hyaline cast ranks

	Control (n=302)	Hyaline cast level		
		(1+) (n=70)	(2+) (n=37)	(≥ 3+) (n=40)
BNP, pg/mL, median	23.3	31.1	35.5*	45.8**
eGFR, mL/min/1.73 m², mean (SD)	73.8 (9.2)	73.9 (8.6)	75.1 (11)	71.3 (8.7)
BMI, kg/m², mean (SD)	24.2 (4.0)	23.7 (3.9)	24.1 (5)	24.1 (4.5)
Heart rate, beats/min mean (SD)	67.5 (11.3)	63.5 (14)	63.5 (16)	64.2 (15.1)
BP, mmHg, systolic, mean (SD)	131.8 (18)	130 (14.8)	126 (13)	129 (14)
diastolic, mean (SD)	78.1* (11.2)	72 (10.3)	70.2 (11)	70.9 (10.2)

*BNP: B-type natriuretic peptide, eGFR: estimated glomerular filtration rate, BMI: body mass index, BP: blood pressure. *P<0.05, **P<0.01.*

No significant differences were observed in age, BMI, and eGFR among the groups. There were no significant differences in heart rate or systolic blood pressure, but diastolic blood pressure was significantly higher in the control group (P<0.05).

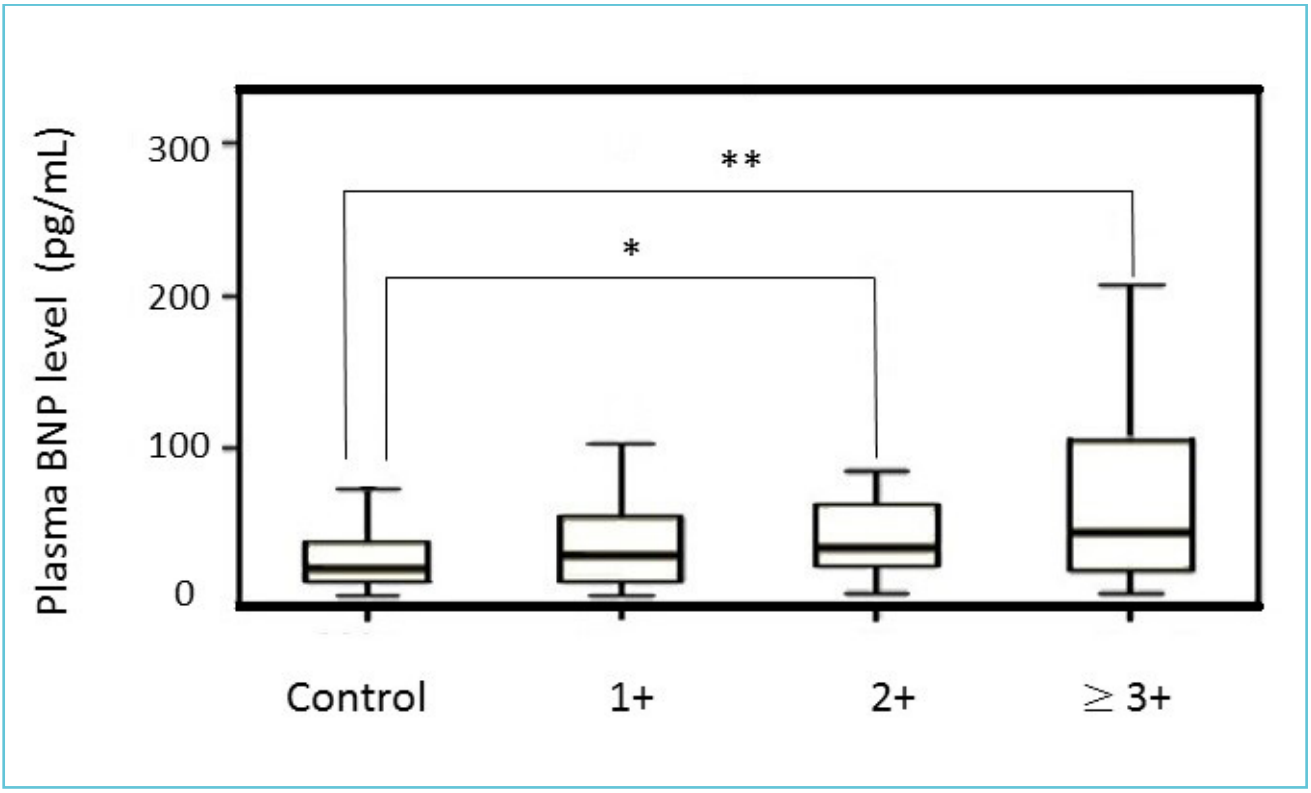
Box plots showing median levels of BNP were compared among the control and three hyaline cast groups (Figure 2). These differed significantly in the two casts groups (group (2+) and group (≥3+)) compared to the control group (*P<0.05 and ** P<0.01, respectively).

Table 5, on the following page, shows a comparison of echocardiography measurements between the control and cast groups. There were no significant differences in EF and LAD from echocardiography measurements between the cast and control groups according to *t* tests.

DISCUSSION

The significance of hyaline casts that appear in patients with normal renal function has rarely been investigated. We previously showed a relationship between the number of urine hyaline casts and plasma BNP levels using only laboratory data[4]. Therefore, patients with a history of kidney disease[8,9] might have been included in that data. Furthermore, diseases that show increased BNP such as congestive heart failure[10], acute infection with fever, and atrial fibrillation[5,6] were not excluded. In the present study, we excluded 27% of samples according to former evaluation criteria. However, the relationship between the number of urine hyaline casts and plasma BNP levels was still significant, showing an increase in BNP levels with an increasing number of hyaline casts. We also found no significant differences in eGFR among groups.

Figure 2 Box plots comparing control and hyaline cast ranks



*Box plots showing median levels of BNP were compared among the control and three hyaline cast groups. Median BNP levels were significantly different between two cast groups (group (2+) and group (≥3+)) and the control group. *P<0.05, **P<0.01.*

Table 5 Comparison of echocardiography measurements between control and cast groups.

	Control (n=302)	Samples with hyaline casts (n=34)
Age (years), mean (SD)	69.0 (9.0)	68.3 (12.2)
Sex (M/F)	193/109	21/13
Echocardiography measurements		
EF (%), mean (SD)	68.8 (7.5)	65.6 (11.1)
LAD (mm), mean (SD)	36.7 (5.8)	37.8 (6.8)

EF: ejection fraction; LAD: left atrial dimension.

These results confirmed that hyaline casts could be detected in urine from patients with normal renal function and that they suggest possibly elevated plasma BNP.

Normally, very few casts are seen in urine examinations without renal dysfunction. Hyaline casts are the most frequently observed, and zero to two casts per low-power field is considered normal. Increased urine concentration, such as from dehydration, and elevated albumin concentration also affect the emergence of hyaline urine casts[11]. In this study, subjects with proteinuria and/or high BUN were excluded. Hyaline casts may also be seen when the decline in renal perfusion leads to sluggish urinary flow[12].

Consistently low urine flow was excluded from the causes of cast formation by our exclusion criteria. Furthermore, there was no significant difference in EF and LAD from echocardiography measurements between the cast and control groups. Imhof et al.[13] reported that loop diuretics, not thiazide diuretics, cause the production of hyaline casts without any proteinuria. In this study, 80% of cast group subjects suffered hypertension, whereas 65% of control group subjects did. Diuretic therapy may contribute to the production of hyaline casts in some patients. However, diuretic use was only at 13% in the cast groups, less than the use of ACEI/ARB and Ca-blocker agents. Therefore, drug use cannot sufficiently explain the emergence of hyaline casts in this study.

BNP is a neurohormone secreted by the cardiac ventricles in response to ventricular volume overload[14]. Both BNP and N-terminal proBNP (which is generated from the same molecule of BNP) are used as reliable diagnostic markers for heart failure and preclude the need for echocardiography in cardiovascular patients[15]. Plasma BNP levels are also related with heart failure severity and are increased in more advanced New York Heart Association (NYHA) functional classes[14]. Furthermore, in asymptomatic cohorts, plasma natriuretic peptide levels predict the risk of cardiovascular mortality, a first cardiovascular event, heart failure, and stroke or transient ischemic attack[16]. NT-proBNP is also an independent predictor of mortality and cardiovascular risk in hypertensive patients[17].

The Japanese Heart Failure Society recommends echocardiography in patients with a BNP level over 100 pg/mL. In cases with many risk factors and with a BNP level of 40–100 pg/mL, chest X-ray, electrocardiogram, and echocardiogram are recommended[18,19]. However, for asymptomatic patients, a physician should check plasma BNP by clinical signs and/or baseline characteristics. There is no definitive recommendation of when physicians should check plasma BNP, and the high cost might make it an impractical screening tool. However, if urinalysis can be used for screening before checking plasma BNP, nearly three-quarters of the cost can be saved. The Japanese Heart Failure Society also states that patients with a BNP level of 40–100 pg/mL may have mild heart failure. In this study, the median BNP level in the (≥3+) group was 45.8 pg/mL. This is within the range that mild heart failure, which is equivalent to NYHA I, may be present.

The mechanism of the interaction between hyaline casts and plasma BNP is unknown. Hyaline casts may appear to be related to blood pressure that is high enough to need an antihypertensive agent including a diuretic, because 80% of patients with casts showed hypertension whereas only 65% of control patients did. However, there were no significant differences in systemic blood pressure, indicating that blood pressure was under control in the cast groups. Temporary high blood pressure therefore does not explain this phenomenon. An arteriosclerosis-related change in some kind of emulgent may affect the emergence of hyaline casts, which could also be related to the increase in plasma BNP.

In conclusion, even though the mechanism is unclear, our findings indicate that physicians should consider measuring plasma BNP levels in subjects presenting hyaline casts in urine, even if they show normal renal function. Especially for samples with ≥2+ number of casts, increased plasma BNP can be expected.

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