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Kidney injury biomarkers after cardiac angiography in children with congenital heart disease

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Abstract

Objective: This study aims to investigate the changes in renal function and levels of urinary biomarkers before and after cardiac angiography in children with congenital heart disease (CHD).

Setting: Children with CHD are at a risk for kidney injury during contrast exposure in cardiac angiography.

Outcome Measures: We measured urinary protein, albumin, N-acetyl-β-D-glucosaminidase (NAG), β2-microglobulin (BMG), and liver-type fatty acid-binding protein (L-FABP) levels, as well as serum creatinine and cystatin C levels, before and after cardiac angiography in 33 children with CHD.

Results: No significant decrease was noted in either the creatinine-based or cystatin C-based estimated glomerular filtration rate at 24 hours after angiography compared with that before angiography. Urinary protein, NAG, BMG, and L-FABP levels were significantly increased at 24 hours after angiography, all of which returned to baseline levels at more than 7 days after angiography. An increase in urinary level of protein, albumin, NAG, or BMG was mostly associated with increased urinary L-FABP level. An increase in both urinary BMG and L-FABP, but not that in urinary L-FABP alone, was associated with increased levels of urinary protein and NAG, as well as the greater dose of contrast media.

Conclusions: Transient increases of kidney injury biomarkers following cardiac angiography are not necessarily associated with the impairment of renal function in a short time period; however, the increase in urinary protein, albumin, NAG, or BMG level may indicate greater stresses to the kidneys than the increase in urinary L-FABP alone in children with CHD.

KEYWORDS

acute kidney injury, cardiac catheterization, contrast nephropathy, liver-type fatty acid-binding protein, β2-microglobulin

1 | INTRODUCTION

Kidney injury is often a serious problem in children with congenital heart disease (CHD). Open-heart surgery with cardiopulmonary bypass in these patients is a well-known risk for postoperative acute kidney injury (AKI). Additionally, cardiac angiography, usually performed prior to heart surgery, is associated with contrast-induced kidney injury and increases the risk of postoperative AKI.[1,2] The presence of cyanotic nephropathy is also an additional risk for kidney injury.[3] Thus, children with CHD should consistently be monitored for renal functional impairment.

In adults, acute nephropathy is a well-known complication following contrast exposure and is associated with increased mortality.[4] In pediatric CHD patients, however, previous reports showed that cardiac angiography using nonionic low-osmolar contrast media, used not immediately prior to the cardiopulmonary bypass operation, does not lead to AKI defined by the conventional serum creatinine increase.[5,6] Nevertheless, recent studies have indicated that tubular injury, which is not accompanied by glomerular function loss, is also associated with adverse renal and overall outcomes, and this condition has been termed subclinical AKI.[7,8] Therefore, kidney injury biomarkers other than serum creatinine, which can detect tubular damage, are thought to be critically important for evaluating the influence of contrast exposure on the kidneys in CHD patients.[9] We have previously reported that urinary β2-microglobulin (BMG) was significantly increased after cardiac angiography in CHD patients and returned to baseline levels within two weeks after angiography without serum creatinine increase.[5] Moreover, several recent reports indicated that urinary liver-type fatty acid-binding protein (L-FABP), an intracellular protein expressed predominantly in proximal tubular cells of the human kidneys, is a useful biomarker for the detection of tubular damage.[10,11] However, the significance of these biomarkers for assessing kidney injury after cardiac angiography has not yet been fully studied. In this study, we evaluated renal function and measured urinary L-FABP and BMG levels as well as urinary N-acetyl-β-D-glucosaminidase (NAG), protein, and albumin excretions before and after cardiac angiography in pediatric CHD patients to study the significance of these biomarkers for assessing kidney injury.

2 | PATIENTS AND METHODS

This study was approved by the Medical Ethics Committee of Kyoto Prefectural University of Medicine. We collected serum and urine samples from 33 CHD patients undergoing cardiac angiography at our hospital. Serum and urine samples were obtained before and 24 hours after cardiac angiography, and urine samples were additionally obtained at more than 7 days (range; 8-204 days, mean; 53 days) after cardiac angiography (Table 1). Parental and/or patient informed consent was obtained from all individual participants. Among 33 CHD patients, 26 patients had cyanotic heart diseases and 27 patients, including 26 cyanotic CHD patients, had a history of open-heart surgery with cardiopulmonary bypass. At the time of sampling, 22 patients were taking medications, which included 9 patients with angiotensin-converting enzyme inhibitors (ACEIs), 8 patients with diuretics, 8 patients with pulmonary vasodilators, 9 patients with anticoagulants, and 10 patients with antiplatelet drugs. None of the patients studied had congenital anomalies of the kidneys or urinary tract. For cardiac angiography, iopamidol, a nonionic low-osmolar contrast media, was used in all patients and routine prehydration was performed.

Urine samples obtained from the patients were immediately stored at −80°C until use for the measurement of urinary protein, albumin, BMG, NAG, L-FABP, and creatinine levels. The urinary L-FABP concentration was measured with an ELISA kit (RENAPRO L-FABP Test TMB; CMIC Holdings, Tokyo, Japan) according to the manufacturer's instructions. Urinary BMG and L-FABP levels were expressed as micrograms per gram creatinine, and urinary protein, albumin, and NAG levels were expressed as grams per gram creatinine, milligrams per gram creatinine, and units per gram creatinine, respectively. The serum samples were immediately used for the measurement of serum creatinine levels and also stored at −80°C until use for the measurement of cystatin C level. Serum and urinary creatinine, serum cystatin C, and urinary protein, albumin, BMG, and NAG levels were measured according to routine methods. Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine levels (creatinine-based eGFR: Cr-eGFR) and also from serum cystatin C levels (cystatin C-based eGFR: CysC-eGFR) using the formula for Japanese children reported by Uemura et al.[12,13]

Statistical analysis for the differences among groups was performed using Steel-Dwass multiple comparison test, and that between two paired groups was performed using the Wilcoxon signed-ranks test. Associations among variables were assessed by Spearman rank-order correlation analysis. The statistical significance was defined as $P < .05$. Statistical analysis was performed using Statcel 3 software (OMS Publishing Inc., Saitama, Japan).

3 | RESULTS

Age at sampling, gestational age, and birth weight, as well as the percentage of patients with cyanotic heart disease, a history of AKI, ACEI use, or diuretics use, and the doses of contrast media are presented in Table 1. AKI was defined as an increase of serum creatinine greater than 50% over the baseline level within 7 days after angiography.[14] Cr-eGFR and CysC-eGFR levels before angiography and those at 24 hours after angiography, as well as urinary protein, albumin, NAG, BMG, and L-FABP levels before angiography, those at 24 hours, and those at more than 7 days after angiography are presented in Table 1 and Figure 1. The correlations between each pair of urinary L-FABP, BMG, NAG, proteins, and albumin levels at 24 hours after angiography are presented in Figure 2. The range of the reference values is shown as the dotted lines in each figure in Figures 1 and 2.

The number of patients with Cr-eGFR and CysC-eGFR levels lower than 90 mL/min/1.73 m^2 was 5 and 2 before angiography and 11 and 5 at 24 hours after angiography, respectively; however, for both Cr-eGFR and CysC-eGFR levels, there was no significant difference between before and at 24 hours after angiography, and no patient presented clinical AKI at 24 hours after angiography (Figure 1A,B).[14] Urinary protein, NAG, BMG, and L-FABP levels were significantly increased at 24 hours after angiography compared with those before angiography, all of which returned to levels comparable to those before angiography at more than 7 days after angiography (Figure 1C,E-G). No significant difference was observed in the

TABLE 1 Clinical data before and after cardiac angiography in patients with congenital heart disease

Group	Total	A	B	C	D
n	33	15	10	1	7
Males/females	18/15	9-6	4-6	1/0	4-3
AGE, years	6-20 (10.0)	6-14 (9.4)	6-13 (9.3)	6	7-20 (13.0)
gestational age, weeks	35-41 (38.4)	35-41 (38.7)	36-41 (38.4)	37	35-40 (38.0)
Birth weight, grams	1858-3400 (2811)	2150-3400 (2930)	2434-3314 (2811)	2692	1858-3244 (2573)
Cyanotic heart disease (%)	26/33 (78.8)	14/15 (93.3)	7/10 (70.0)	1/1 (100.0)	4/7 (57.1)
History of AKI (%)	11/33 (33.3)	9/15 (60.0)	0/10 (0)	0/1 (0)	2/7 (28.6)
Use of ACEI (%)	9/33 (27.3)	8/15 (53.3)	1/10 (10.0)	0/1 (0)	0/7 (0)
Use of diuretics (%)	8/33 (24.2)	6/15 (40.0)	0/10 (0)	1/1 (100)	1/7 (14.3)
Contrast media, mL/kg	1.33-5.66 (3.33)	2.58-5.66 (3.97)*	1.33-3.70 (2.89)	3.48	1.62-5.38 (2.59)
Cr-eGFR, before angiography, mL/min/1.73 m^2	72.2-157.1 (110.9)	72.2-147.8 (102.9)	97.9-157.1 (126.9)	108.2	85.1-118.2 (105.4)
Cr-eGFR, 24 h after angiography, mL/min/1.73 m^2	65.1-166.9 (107.5)	65.1-147.8 (101.9)	87.6-166.9 (122.1)	105.1	85.1-126.8 (99.3)
CysC-eGFR, before angiography, mL/min/1.73 m^2	78.2-145.3 (109.9)	78.2-132.9 (106.4)	97.3-145.3 (119.3)	107.9	66.4-117.6 (105.5)
CysC-eGFR, 24 h after angiography, mL/min/1.73 m^2	67.6-160.1 (108.7)	82.7-140.9 (108.0)	89.5-160.1 (116.3)	100.6	67.6-116.1 (100.4)
u-protein, before angiography, g/gCr	0.03-0.19 (0.08)	0.04-0.19 (0.10)*	0.03-0.14 (0.07)	0.07	0.03-0.07 (0.04)
u-protein, 24 h after angiography, g/gCr	0.03-0.70 (0.12)††	0.05-0.70 (0.18)**,†	0.05-0.11 (0.07)	0.11	0.03-0.08 (0.05)
u-protein, >7 days after angiography, g/gCr	0.02-0.53 (0.10)	0.04-0.53 (0.13) (*n* = 13)	0.02-0.08 (0.05) (*n* = 8)	0.25	0.032-0.06 (0.04) (*n* = 3)
u-albumin, before angiography, mg/gCr	1.9-94.2 (20.3)	4.9-94.2 (28.9)	1.9-45.6 (16.1)	10.9	2.6-23.1 (9.5)
u-albumin, 24 h after angiography, mg/gCr	2.8-399.0 (32.4)	5.3-399.0 (59.4)	2.8-17.2 (11.0)	7	4.2-20.8 (8.7)
u-albumin, >7 days after angiography, mg/gCr	1.9-232.0 (28.4)	5.1-232.0 (43.4) (*n* = 13)	4.9-30.7 (12.7) (*n* = 8)	23.2	1.9-16.1 (7.1) (*n* = 3)
u-NAG, before angiography, U/gCr	1.2-21.1 (5.0)	1.2-21.1 (6.3)	1.9-10.0 (4.4)	4.9	1.6-5.2 (3.2)
u-NAG, 24 h after angiography, U/gCr	1.8-8.0 (12.2) ††	1.8-68.0 (18.8)*,††	2.6-18.6 (8.6)†	6.1	2.3-9.2 (4.2)
u-NAG, >7 days after angiography, U/gCr	1.3-18.3 (5.5)	1.9-18.3 (6.9) (*n* = 13)	1.3-8.2 (4.4) (*n* = 8)	5.1	2.3-2.6 (2.4) (*n* = 3)
u-BMG, before angiography, μg/gCr	7-488 (150)	7-488 (180)	19-328 (152)	149	33-143 (82)
u-BMG, 24 h after angiography, μg/gCr	17-2559 (356)†	219-2559 (600)**,††	17-204 (112)	990	45-167 (91)
u-BMG, >7 days after angiography, μg/gCr	24-309 (122)	24-309 (143) (*n* = 13)	25-239 (103) (*n* = 8)	127	54-105 (82) (*n* = 3)
uL-FABP, before angiography, μg/gCr	1.1-12.0 (3.2)	1.4-12.0 (4.1)	1.1-3.5 (2.2)	2.9	1.5-6.4 (2.7)
uL-FABP, 24 h after angiography, μg/gCr	3.0-110.1 (22.9)††	9.8-110.1 (36.7)**,††	9.7-27.4 (15.8)**,††	7.5	3.0-7.7 (5.7)†
uL-FABP, >7 days after angiography, μg/gCr	0.5-7.7 (3.4)	0.5-5.2 (3.2) (*n* = 13)	1.3-7.7 (3.4) (*n* = 8)	7.4	2.4-3.0 (2.7) (*n* = 2)

Notes: Data are expressed as range (mean).

Group A: Patients in whom uL-FABP level and u-BMG level at 24 h after angiography were both above reference levels.

Group B: Patients in whom uL-FABP level, but not u-BMG level, at 24 h after angiography was above the reference level.

Group C: Patients in whom u-BMG level, but not uL-FABP level, at 24 h after angiography was above the reference level.

Group D: Patients in whom uL-FABP level and u-BMG level at 24 h after angiography were both within reference levels.

Abbreviations: AKI, acute kidney injury; ACEI, angiotensin-converting enzyme inhibitor; angio, angiography; Cr-eGFR, creatinine-based estimated glomerular filtration rate; CysC-eGFR, cystatin C-based estimated glomerular filtration rate; u-protein, urinary protein; u-albumin, urinary albumin; u-NAG, urinary N-acetyl-β-D-glucosaminidase; u-BMG, urinary β2-microglobulin; uL-FABP, urinary liver-type fatty acid-binding protein; 24 h after angiography, 24 hours after angiography; >7 days after angiography, more than 7 days after angiography.

**$P < .01$.

*$P < .05$ compared with that in group D.

††$P < .01$.

†$P < .05$ compared with that of "before angiography" in the same group.

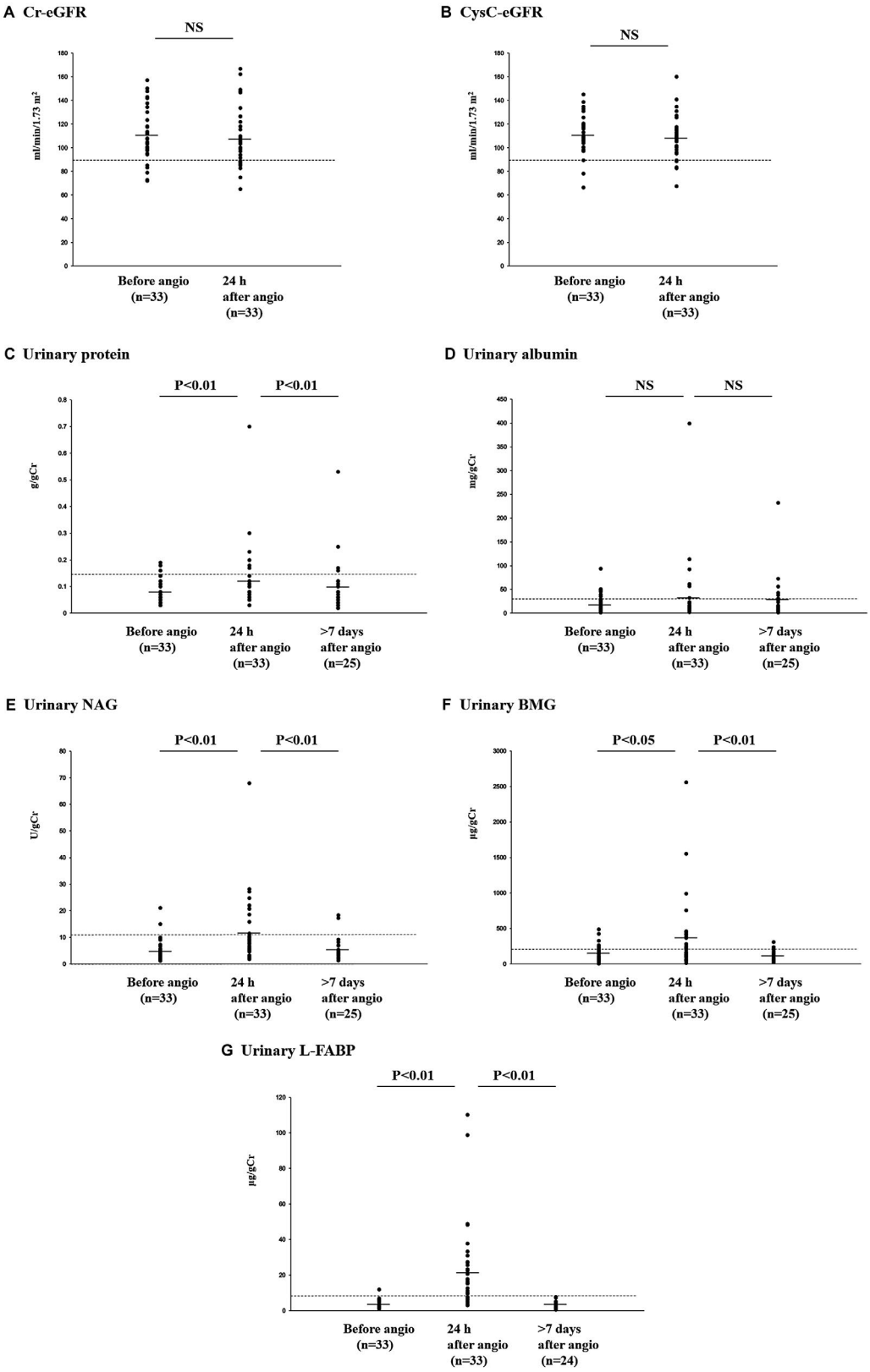

FIGURE 1 Serum creatinine-based estimated glomerular filtration rate (Cr-eGFR) (A) and serum cystatin C-based estimated glomerular filtration rate (CysC-eGFR) (B) before and at 24 hours after angiography; urinary protein (C), urinary albumin (D), urinary N-acetyl-β-D-glucosaminidase (NAG) (E), urinary β2-microglobulin (BMG) (F), and urinary liver-type fatty acid-binding protein (L-FABP) (G) levels before, at 24 hours after, and at more than 7 days after angiography. The range of the reference values are shown as the dotted lines in each figure, which corresponds to 90 mL/min/1.73 m^2 for Cr-eGFR (A) and CysC-eGFR (B) levels, 0.15 g/gCr for the urinary protein level (C), 30 mg/gCr for the urinary albumin level (D), 10.8 U/gCr for the urinary NAG level (E), 206 μg/gCr for the urinary BMG level (F), and 8.4 μg/gCr for the urinary L-FABP level (G)

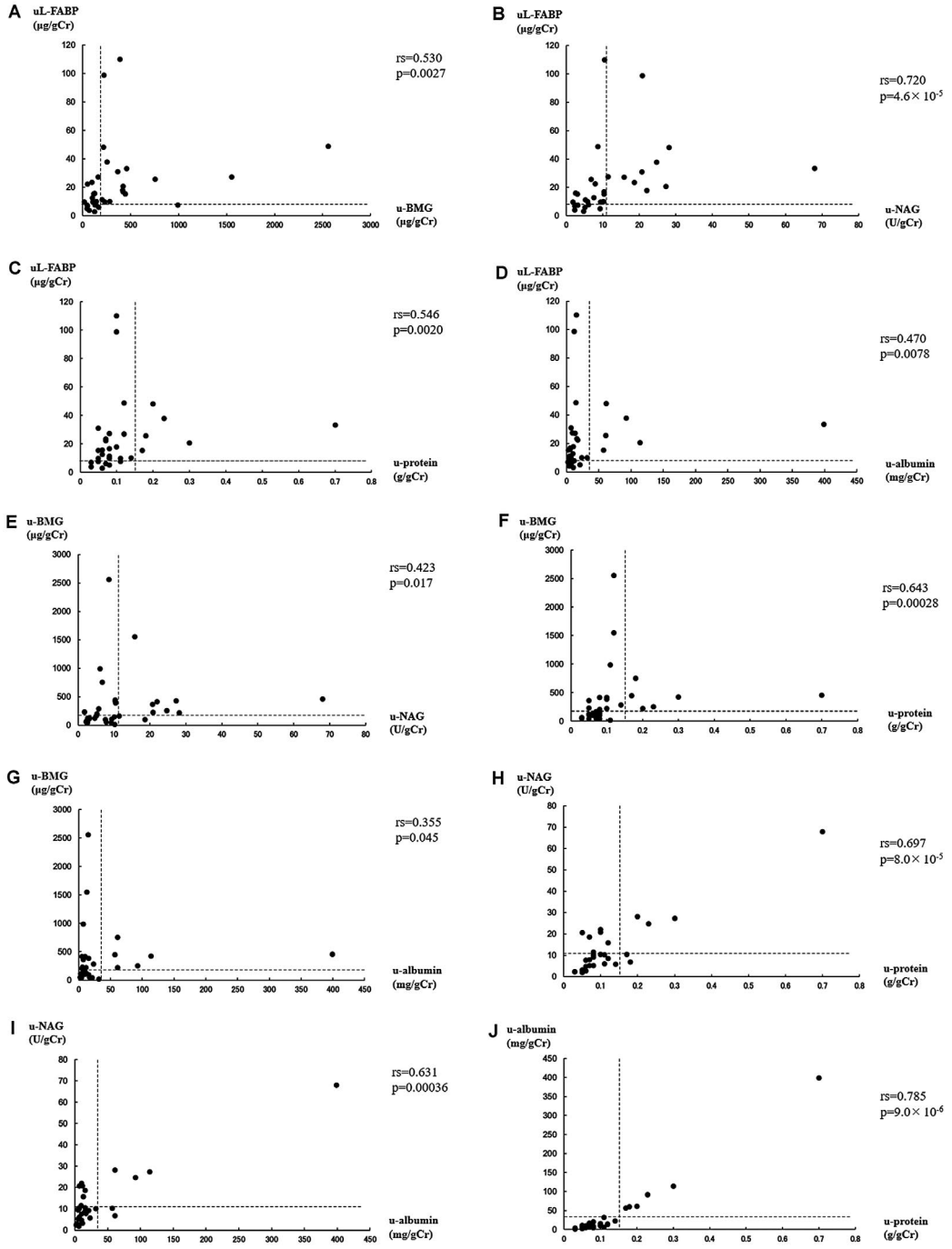

FIGURE 2 Correlation analyses between the urinary L-FABP level (uL-FABP) vs the urinary BMG level (u-BMG) (A), uL-FABP vs the urinary NAG level (u-NAG) (B), uL-FABP vs the urinary protein level (u-protein) (C), uL-FABP vs the urinary albumin level (u-albumin) (D), u-BMG vs u-NAG (E), u-BMG vs u-protein (F), u-BMG vs u-albumin (G), u-NAG vs u-protein (H), u-NAG vs u-albumin (I), and u-albumin vs u-protein (J) at 24 hours after angiography. The ranges of the reference values are shown as the dotted lines in each figure, as in Figure 1

urinary albumin level at 24 hours after angiography compared with that before angiography, or with that at more than 7 days after angiography (Figure 1D).

Regarding the correlations between each pair in Figure 2, all except one patient who showed an increased urinary BMG level over the reference value, and all patients who showed increased urinary levels of protein, albumin or NAG over the reference value, had urinary levels of L-FABP greater than the reference (Figure 2A-D). All patients who showed increased urinary levels of protein or albumin over the reference value had a urinary level of BMG greater than the reference (Figure 2F,G). Significant correlations were observed between all pairs in Figure 2; however, particularly strong correlations were observed between urinary L-FABP and NAG levels, urinary NAG and protein levels, and urinary albumin and protein levels (r's > 0.69) (Figure 2B,H,J).

In Table 1, patients were also divided into four groups based on their urinary L-FABP and BMG levels at 24 hours after angiography. In patients whose urinary L-FABP and BMG levels were both above reference levels (group A), the dose of contrast media, urinary protein levels before angiography and at 24 hours after angiography, and the urinary NAG level at 24 hours after angiography were significantly greater than those in the control (group D). The percentage of patients with cyanotic heart disease, with a history of AKI, the use of ACEI, and the use of diuretics also tended to be high in this group. However, in patients whose urinary L-FABP level, but not urinary BMG level, was above reference levels (group B), no significant differences were observed in all the parameters examined compared with the control, except for the urinary L-FABP level.

4 | DISCUSSION

In our present study, no significant deterioration in kidney function assessed by Cr-eGFR and CysC-eGFR was observed at 24 hours after angiography with the total dose of contrast media under 5.66 mL/kg. These results are consistent with previous studies examining the effects of cardiac angiography on kidney function using nonionic low-osmolar contrast media in children with CHD.[5,6] Thus, it is suggested that cardiac angiography using nonionic low-osmolar contrast media under a total dose of around 5 mL/kg seldom causes apparent clinical AKI in children with CHD.

Unlike serum creatinine and cystatin C, urinary protein, NAG, BMG, and L-FABP levels showed transient increases at 24 hours after angiography. In this regard, although the increases in urinary protein and NAG may be the result of increased filtration of these components from the glomeruli, the increases in urinary BMG and L-FABP are thought to reflect the influence of contrast media on the tubules. Thus, this indicates that even the use of nonionic low-osmolar contrast media may cause significant stresses to the kidneys, including alterations in tubular function. Although the mechanisms underlying contrast-induced nephrotoxicity are thought to be complex and have not been fully elucidated, hemodynamic effects of the contrast, such as increased tubular interstitial pressure and decreased medullary circulation, caused by increased viscosity, may lead to hypoxia and reactive oxygen species (ROS) production, resulting in increased L-FABP excretion from the proximal tubule.[15,16]

Additionally, in our study, most patients who had increased urinary levels of protein, albumin, NAG, or BMG showed an increased urinary L-FABP level as well. Furthermore, the increase in both urinary BMG and L-FABP levels, but not that in urinary L-FABP alone, was associated with increased urinary protein and NAG levels, a greater dose of contrast media, and other risk factors for kidney injury. These results suggest that the increase in either urinary protein, albumin, NAG, or BMG indicates stresses to the kidneys that is even greater than those indicated by the increase in urinary L-FABP alone.

Recent studies have suggested a higher frequency of the progression to chronic kidney disease (CKD) in CHD patients than the general population, and the need to follow these patients from an early age for the development of CKD.[17] In this study, as we did not perform long-term follow-up of kidney function or related events, the precise roles of each of the biomarkers studied in long-term adverse outcomes are still unclear. In light of the recent findings that tubular damage without apparent serum creatinine increase in a short-time period following insults to the kidneys may also be associated with adverse outcomes in the long-term, further studies regarding kidney injury biomarkers to assess contrast-induced nephrotoxicity are considered necessary. Nevertheless, our present study showed that, although transient increases of kidney injury biomarkers following cardiac angiography are not necessarily associated with the impairment of renal function in a short-time period, the increase in urinary protein, albumin, NAG, or BMG level may indicate greater stresses to the kidneys than the increase in urinary L-FABP alone in children with CHD.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Designed the study: M.N.

Contributed to the preparation and measurement of samples: S.K., Y.M., and K.N.

Performed the statistical analysis and drafted the manuscript: M.N.

Reviewed the manuscript and supervised the study process: K.I, T.I, and H.H.

All authors read and approved the final manuscript.

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