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Original Article

Relationship between basal liver function test levels and contrast-induced nephropathy in patients undergoing coronary angiography

Koroner anjiyografi yapılan hastalarda bazal karaciğer fonksiyon test düzeyleri ile kontrasta bağlı nefropati gelişimi arasındaki ilişki

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Abstract

Background: The purpose of this study was to evaluate the relationship between initial levels of convantional liver function tests (ALT:Alanine aminotransferase; AST:Aspartate aminotransferase; GGT: gama glutamil transferase; ALP: alkaline phosphatase) and contrast induced nephropathy (CIN). **Material and methods:** We conducted a retrospective study of 373 subjects with acute coronary syndrome who underwent coronary angiography (CAG). According to the development of CIN, the patients were divided into two groups as those who did not develop contrast nephropathy (Group 1) and those who did (Group 2). Both groups were compared in terms of age, gender, diabetes mellitus, hypertension, estimated glomerular filtration rate (eGFR), laboratory parameters and conventional liver enzymes (ALT, AST, GGT, ALP). The patients were given isotonic solution at a rate of 1 mL/kg/hour as a standard before and after the procedure. CIN is defined as a ≥ 0.5 mg/dL rise in serum creatinine or a 25% increase, assessed within 48-72 hours after administration of contrast medium (CM). **Results:** Overall, CIN developed in 104 patients (group 2 [27.8%]). Age, ALT and AST levels were significantly higher in patients who developed CIN than those without CIN (p=0.025, p<0.001, p<0.001; respectively). In correlation analysis, creatinine increase rate was positively correlated with ALT and AST levels (r = 0.161, p = 0.002; r=0.318, p=<0.001; respectively). Multivariate logistic regression analysis demonstrated that AST level was an independent predictor of CIN (OR 1.006, 95% CI 1.003–1.009, p<0.001). **Conclusions:** According to study; high AST levels may predict CIN in patients who undergoing CAG.

Keywords: Liver function tests, contrast induced nephropathy, coronary angiography

Öz

Amaç: Bu çalışmanın amacı, konvansiyonel karaciğer fonksiyon testlerinin (ALT- Alanin aminotransferaz; AST- Aspartat aminotransferaz; GGT- gama glutamil transferaz; ALP- alkalin fosfataz) başlangıç düzeylerinin kontrast kaynaklı nefropati (KKN) ile arasındaki ilişkiyi değerlendirmektir. **Gereç ve Yöntem:**Koroner anjiyografi (KAG) uygulanan akut koroner sendromlu 373 hastayla retrospektif bir çalışma yürüttük. Hastalar KKN gelişimine göre; kontrast nefropati gelişmeyenler (Grup 1) ve gelişenler (Grup 2) olarak iki gruba ayrıldı. Her iki grup yaş, cinsiyet, diabetes mellitus, hipertansiyon, başlangıç tahmini glomerüler filtrasyon hızı (eGFH), laboratuvar parametreleri ve konvansiyonel karaciğer enzimleri (ALT, AST, GGT, ALP) açısından karşılaştırıldı. Hastalara işlem öncesi ve sonrası standart olarak 1 mL/kg/saat hızında izotonik solüsyon verildi. KKN, kontrast maddenin (KM) uygulanmasından sonraki 48-72 saat içinde değerlendirilen, serum kreatinin düzeyinde ≥ 0,5 mg/dL'lik bir artış veya %25'lik bir artış olarak tanımlanır. İncelenen parametreler ile KKN oluşumu arasındaki ilişkiyi analiz ettik. **Bulgular:**Toplam olarak 104 hastada kontrast nefropati gelişti (grup 2 [%27.8]). KKN gelişen hastalarda , KKN gelişmeyenlere göre yaş, ALT, AST düzeyleri anlamlı olarak daha yüksekti (p=0.025, p<0.001, p<0.001 ;sırasıyla). Korelasyon analizinde kreatini artış oranı, ALT ve AST seviyeleri ile pozitif korelasyon gösterdi (sırasıyla r = 0.161, p = 0.002; r=0.318, p=<0.001). Çok değişkenli lojistik regresyon analizi, AST seviyesinin KKN'yi bağımsız bir şekilde öngördüğü tespit edildi (OR 1.006, %95 CI 1.003–1.009, p<0.001). **Sonuç:** Çalışmamıza göre; yüksek bazal AST seviyeleri, KAG yapılan hastalarda KKN gelişimini öngörebilir.

Anahtar Kelimeler: Karaciğer fonksiyon testleri, kontrast kaynaklı nefropati, koroner anjiyografi

Introduction

Contrast-induced nephropathy (CIN), which is also called contrast-induced acute kidney injury (CI-AKI), is an iatrogenic disease occurring after the intravascular injection of iodinated radiographic contrast media (1). It accounts for 11–12% of all cases of in-hospital AKI and is also associated with an overall in-hospital mortality rate of 6% (2). CIN can result from intravenous or intraarterial injections of iodine-based contrast medium (CM) during advanced x-ray and computed tomography (CT) imaging studies or coronary artery interventions (3). Of all procedures using CM for diagnostic or therapeutic purposes, coronary angiography and percutaneous coronary intervention (PCI) are associated with the highest rates of CIN (4). More than half of cases are diagnosed after cardiac catheterization; these cases constitute 10-15% of hospitalizations for acute renal failure (5). Although various pathways have been proposed, including contrast-induced tubular toxicity, inadequate renal perfusion, reperfusion injury, inflammation, and apoptosis, the specific mechanisms of CIN are unclear (6). The incidence of CIN may be much higher in patients undergoing coronary angiography if there are underlying conditions such as chronic kidney disease (CKD), diabetes, heart failure or advanced age (7,8). CIN is also associated with longer hospital stay, increased morbidity and mortality, and additional cost (9).

Although many risk factors affecting the development of CIN after coronary angiography have been defined, the relationship between them has not been fully elucidated. There is insufficient data in the literature between routinely measured liver function tests and the development of CIN. The relationship between chronic liver disease and contrast nephropathy has been demonstrated in previous studies (10,11). However, the relationship between liver function tests, which is one of the indicators of acute liver injury, and CIN is not clear. Determining the predictive parameters and risk factors for CIN that may develop in patients undergoing coronary angiography is important in terms of prognosis. In this study, we aimed to elucidate the relationship between routine parameters showing liver function (ALT, AST, GGT, ALP) at the time of admission and CIN in patients who underwent coronary angiography with the diagnosis of acute coronary syndrome.

Materials and Methods

Study population

This study was a retrospective observational study performed at a single center, in which we performed a retrospective review of 373 consecutive cardiac catheterizations because of acute coronary syndrome from June 2021 to December 2021. In terms of population homogeneity, only patients presenting with non-ST-elevation myocardial infarction (NSTEMI) were included in the study. Diagnosis and treatment of acute coronary syndrome was performed according to current guidelines. The exclusion criteria, were as follows: chronic liver disease, active hepatitis, acute and chronic biliary system disease, active infection, chronic inflammatory disease involving the skeletal system, chronic renal disease (GFR < 15 mL/min or haemodialysis treatment), right heart failure and advanced pulmonary hypertension, history of cancer and cases given more than 4 ml/kg of contrast agent. Patients were hydrated with 0.9% saline at 1 mL/kg/hr for 24 hours after admission to the intensive care unit and coronary catheterization. In patients with acute coronary syndrome and decompensated heart failure, the hydration rate was reduced to 0.5 mL/kg/h. A non-ionic, low osmolality, iodinated contrast agent (Iohexol-Omnipaque®) was used for catheterization. Maximal contrast agent usage was limited to 4 mL/kg. Although the amount of opaque administered to each patient varied, less opaque material was tried to be used in patients with chronic renal failure. Informed consent was obtained from all patients. This study was approved by the ethics committee of our hospital.

Study protocols and definitions

Patients conforming to the standards stated above were included and then divided into two groups (CIN developing group [group 2] and non-CIN developing group [group 1]). Clinical characteristics and in-hospital outcomes were extracted from patients' medical records. Serum ALT , AST, GGT, ALP levels and other biochemical parameters were measured before cardiac catheterization by the enzymatic colorimetric test at 37°C . This analysis was done

with the Roche/Hitachi analyzer (Mannheim,Germany). CRP, levels of total cholesterol, triglyceride, Ldl , Hdl and glucose levels were measured using standard enzymatic methods within 24 hours. Serum creatinine concentrations were measured before and within 48–72 hours of contrast agent administration in every patient. Patient demographics, clinical and baseline laboratory data were assessed. Renal function was assessed by the eGFR using the Modification of Diet in Renal Disease Study (MDRD). The MDRD formula is (186 × serum creatinine – 1.154 × age – 0.203) [× 0.742 if female]. CIN is defined as a ≥ 0.5 mg/dL rise in serum creatinine or a 25% increase, assessed within 48-72 hours after administration of contrast medium (CM)[1].

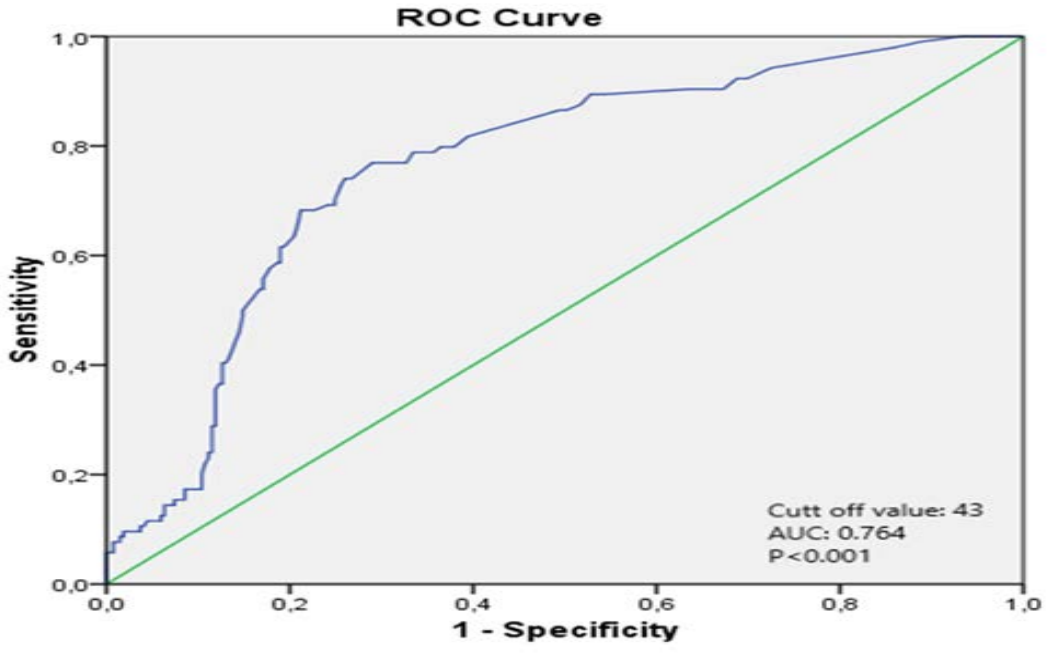
Statistical analysis

Statistical analyses were performed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). Mean ± standard deviation, median and [maximum–minimum] were used for continuous variables, while percentages were used for categorical variables. The Kolmogorov-Smirnov test was used to test the normal distribution of the data. Continuous variables were expressed as mean ± SD or median (interquartile range) and compared with Student's t or Mann-Whitney U tests according to distribution. Categorical variables were expressed as percentages and numbers and compared with the Chi-square test. Sperman correlation analysis was performed to determine the correlation of creatinine increase rate with other continuous variables. In addition, Univariate and multivariate regression analyses were performed to determine the independent predictors of CIN. The baseline variables for which evident significance ($p < 0.10$) was found by univariate analysis were included in the multivariate logistic regression analysis. Receiver operating characteristic (ROC) analysis was performed to determine the optimum cut-off value of the AST level for predicting CIN. The results of the model were reported as a 95% confidence interval (CI) and p-values. All p-values were two-sided in the tests and p-values less than 0.05 were considered to be statistically significant.

Results

373 patients who were diagnosed as acute coronary syndrome were included in our study. The baseline demographics and clinical characteristics of the patients are set out according to the development of contrast-induced nephropathy in Table 1. 227 (60%) of the patients were male and 146 (40%) were female. There was no statistically significant difference between the groups in terms of gender, diabetes mellitus (DM), hypertension, hyperlipidemia and smoking. CIN was observed in 27% of patients. Advanced age, low initial creatinine, low albumin and low Hdl as well as high ALT, AST levels were correlated with the development of CIN (Table 1).

Figure 1. Receiver operating characteristic curve analysis of aspartate aminotransferase and contrast-induced nephropathy



Positive correlation was detected between CIN and advanced age, ALT, AST levels in the correlation analysis and negative correlation was detected between eGFR, initial creatinine and albumin levels (Table 2). Advanced age and high ALT, AST levels were found to be predictors of CIN development in univariate regression analysis and advanced age and a high AST level was found to be predictors of CIN development in multivariate binary logistic regression analysis [OR 1.006, 95% CI 1.003–1.009, p<0.001] (Table 3). The best cut-off value of AST in predicting the development of CIN was determined by ROC analysis (Figure 1). Accordingly, the sensitivity of an AST level ≥43 in predicting the development of CIN was 77%, and the specificity was 71% (area under the curve [AUC]: 0.764, 95% confidence interval [CI]: 0.712-0.817, p<0.001)

Table 1. Distribution of clinical and dem characteristics of the patients according to the development of contrast-induced nephropathy

Variables	Group 1 (CIN-) n=269	Group 2 (CIN+) n=104	P
Age*	59.5 ± 11.3	62.6 ± 13.2	0.025
Gender ,male (%)	169 (%62)	58 (%55)	0.388
Diabetes mellitus, (%)	81 (%30)	37 (%35)	0.309
Hypertension ,(%)	163 (%60)	66 (%63)	0.610
Hyperlipidemia ,(%)	214 (%79)	87 (%83)	0.368
Smoking, (%)	148 (%55)	54 (%51)	0.591
Initial glucose,(mg/dL)**	122 (99-75)	125 (99-169)	0.653
Initial creatinine ,(mg/dL)**	0.8 (0.70-1.00)	0.7 (0.66-0.90)	0.001
Postprocedural creatinine, (mg/dL)**	0.9 (0.73-1.0)	1.0 (0.90-1.29)	<0.001
Uric acid , (mg/dL)**	5.2 (4.3-6.1)	5.0 (3.9-6.1)	0.579
Albumin, (mg/dL)**	4.2 (4.0-4.5)	4.0 (3.7-4.4)	0.001
Triglycerides , (mg/dL)**	150 (100-209)	135 (102-197)	0.664
Total cholesterol, (mg/dL)*	177±41	182±48	0.457
High-density lipoprotein , (mg/dL)**	35 (30-41)	34 (26-39)	0.033
Low-density lipoprotein, (mg/dL)*	108 ± 35	109 ± 39	0.699
C-Reactive protein, (mg/dL)**	0.54 (0.16-1.32)	0.66 (0.20-1.52)	0.335
e-GFR, (mL/min)**	92 (74-101)	90 (75-102)	0.956
White blood cell, (x1000/mm3)**	9.0 (7.4-11.3)	9.6 (7.1-12.6)	0.477
Hemoglobin, (mg/dL)*	14 (13-15)	13 (12-15)	0.110
Hematocrit, (%) **	143 (39-47)	41 (38-46)	0.380
Platelet count (x1000/mm3)**	256 (214-302)	265 (223-315)	0.308
Alanine aminotransferase 0-34 U/L) **	26 (18-40)	40 (21-75)	<0.001
Aspartate aminotransferase(0-35 U/L)**	29 (20-51)	76 (45-97)	<0.001
Gama glutamil transferase (U/L) **	25 (18-40)	27 (18-45)	0.302
Alkaline phosphatase (mg/dL)**	83 (68-103)	86 (70-110)	0.141

Abbreviations: CIN: contrast-induced nephropathy;e-GFR: estimated glomerular filtration rate; * sign ; shows the Student's t test applied for the normal distribution. ** sign ; points to the Mann-Whitney U test applied for variables that do not fit the normal distribution.

Table 2. Correlation analysis between creatinine increase rate and laboratory parameters

Variables	r	P
Age	0.127	0.014
Alanine aminotransferase (0-34 U/L)	0.161	0.002
Aspartate aminotransferase (0-35 U/L)	0.318	<0.001
Estimated glomerular filtration rate, (mL/min)	0.218	0.014
High-density lipoprotein, (mg/dL)	-0.034	0.507
Albumin,(mg/dL)	0.164	0.002
Initial creatinine,(mg/dL)	-0.298	<0.001
C-Reactive protein, (mg/dL)	0.004	0.936

Table 3. Univariate and multivariate logistic regression analysis of CIN

Variables	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Age	1.022 (1.003-1.043)	0.026	1.022 (1.002-1.043)	0.034
Aspartate aminotransferase	1.006 (1.003-1.009)	<0.001	1.006 (1.003-1.009)	<0.001
Alanine aminotransferase	1.015 (1.008-1.040)	<0.001	1.004 (1.001-1.008)	0.10
Diabetes mellitus	1.282 (0.794-2.068)	0.309		
Hypertension	1.129 (0.707-1.804)	0.610		
Albumin	1.034 (0.933-1.146)	0.519		
C-Reactive protein	1.015 (1.008-1.023)	0.460		
White blood cell	1.007 (0.976-1.040)	0.651		

DISCUSSION

In this study, we aimed to investigate the relationship between basal liver function test levels and contrast-induced nephropathy. The main finding of our study was: Basal AST levels was significantly higher in patients who developed CIN and was an independent predictor for the development of CIN.

The liver is the body's largest single discrete organ. It has four major functions: metabolism and synthesis; excretion; storage; and the detoxification of potential poisons. These diverse functions mean that a single test does not give enough information to assess fully how the liver is functioning (12). These tests consist of markers of hepatocellular injury (ALT,AST and ALPs); tests of liver metabolism (total bilirubin); and tests of liver synthetic function (serum albumin and prothrombin time) (13). The routine use of such tests has led to the increased detection of liver diseases in otherwise asymptomatic patients, often providing the first clue of the presence of liver pathology. Aminotransferases are markers of hepatocyte injury and do not reflect liver synthetic function (13). Therefore, in this study, we aimed to reveal the relationship between routine liver function tests and CIN, which are only associated with hepatocellular damage.

The liver contains a large number of enzymes in high concentration, some of which are found in very low concentrations in serum. Processes leading to necrosis of hepatocytes or damage to the hepatocyte cell membrane with increased permeability result in release of AST and ALT into the blood within a few hours of liver injury. Serum enzyme tests can be divided into two groups: Elevated serum aminotransferases suggest injury of hepatocytes; and elevations in ALP, GGT suggest injury to any part of the biliary tree (14). The distinction between these 2 main models of liver injury provides clues for further testing. However, in practice, patients present with a mixed pattern of liver damage (15).

ALT and AST are normally intracellular enzymes with mitochondrial and cytoplasmic forms (16). Their names reflect specifically their role in catalyzing chemical reactions during gluconeogenesis, in which the amino groups of alanine and aspartic acid are transferred to the alpha-keto group of ketoglutaric acid. ALT and AST are commonly found in cells throughout the body and are found in the liver, skeletal muscle, brain, kidney, heart, and pancreas. ALT is cytoplasmic only and is mainly found in the liver and kidney, with very minor amounts in the heart and skeletal muscle(16). Therefore, ALT is more specific to the liver.

In addition to liver damage, aminotransferase may be affected by many factors such as hyperthyroidism, alcohol consumption, exercise, high BMI, celiac sprue, anorexia nervosa, Addison disease, muscle injury (17-19). Evaluating the pattern and extent of elevation in liver enzymes can help elucidate the cause of liver injury and guide subsequent diagnostic testing and management. Any liver cell injury can cause moderate elevations in serum aminotransferase levels. Levels up to 300 IU/L are non-specific and can be seen in any liver disorder (20). Aminotransferase levels greater than 1000 IU/L suggest ischemic hepatitis, viral hepatitis, and toxic hepatitis.

Serum ALP is a membrane-anchored ectoenzyme that catalyses the hydrolysis of organic pyrophosphate, which has been shown to be a protective factor for vascular integrity (21).Elevation in serum ALP occurs when the hepatocyte canalicular membrane is disrupted, causing translocation from the canalicular membrane to the basolateral (ie, sinusoidal) surface of the hepatocyte and leakage into serum (13). Hepatic GGT is a microsomal enzyme found on the surface of hepatocytes and biliary epithelia. Clinically, its main utility is suggesting a hepatic source for an elevated AP (22). Both ALP and GGT are markers of cholestasis and their levels increase in hepatobiliary diseases (14,20).

Contrast-induced nephropathy is a common cause of renal failure and is associated with significant morbidity and mortality (23,24). Multiple studies in the medical literature have estimated a risk of 2% in low-risk patients, rising to 50% in those with risk factors such as DM, pre-existing renal disease, congestive heart failure, advanced age, anemia, and dehydration (6,25,27). There are some markers, including creatinine, GFR, cystatin C, and neutrophil-gelatinase-associated lipocalin (NGAL), that are administered by clinicians to assess the individual risk for the development of CIN following coronary angiography. However, there is still debate about predisposing factors for CIN (28,29). The exact mechanism of CIN is still unclear. In addition to the direct toxic effects of the contrast medium, renal blood flow disturbances, vasoconstriction of renal vessels, oxidative stress, free radical damage and endothelial dysfunction are thought to be major mechanisms in the development of CIN (30,32).

We found a statistically significant relationship between the development of CIN and high ALT,AST levels in our study. We did not find a significant relationship between development of CIN and GGT , ALP levels. We postulated that excessive symphatic activity and cardiac depression during acute coronary syndrome creates hepatic ischemia by increasing hepatic and splanchnic oxygen requirements. The higher incidence of CIN in patients with anterior myocardial infarction and left anterior descending artery stent implantation patients may support this view (31).

Hypoxic liver injury is defined as a massive, but transient, increase in serum transaminase levels due to an imbalance between hepatic oxygen supply and demand in the absence of other acute causes of liver damage. It typically occurs in elderly individuals with right-sided congestive heart failure and low cardiac output (34). An imbalance between oxygen demand and supply as liver also plays a role in radiocontrast-induced outer medullary hypoxic damage (35). Cardiorenal and hepatorenal syndrome, which has been well defined before, is important in terms of showing the interrelationship of all 3 vital organs (heart, kidney, liver) (36,37). Renal and hepatic hypoperfusion due to hypotension and/or decreased flow rate developing during acute coronary syndrome causes increased sympathetic activity, increased secretion of renin angiotensin aldosterone and arginine vasopressin, and ultimately water-salt retention, peripheral vasoconstriction, organ congestion, which predisposes both the liver and kidney to ischemic injury (37,38). Since the common mechanisms in hepatorenal syndrome and cardiorenal syndrome and the development mechanisms in contrast mediated acute renal failure are similar, it can be said that all three organs are closely related to each other in terms of acute damage. Although cardiorenal syndrome and hepatorenal syndrome

develop on the basis of more advanced and chronic diseases, the same developmental mechanisms are also present in case of acute damage to 3 vital organs (37,38). Therefore, the increase in hepatic damage enzymes (ALT, AST), which may indicate that acute cardiac damage is more advanced, may predict that the kidney may be more vulnerable for the development of CIN. The lack of a significant increase in cholestasis enzymes (ALP, GGT) compared to damage enzymes (ALT, AST) supports this hypothesis. The fact that AST increase is statistically more significant than ALT can be attributed to the presence of AST in all 3 vital organs (heart, kidney and liver) (13). Thus, in cardiac and hepatic damage, the increase in AST will be greater than that of ALT, which is more specific to the liver.

In our study, the risk of contrast nephropathy was higher in those with low albumin levels. Although iodinated contrast agents have a plasma protein binding rate of less than 2% (39), less CIN observed in patients with higher albumin levels may be attributed to the attenuation of the nephrotoxic effects of the contrast agent by binding to plasma proteins. Less CIN seen in those with higher Hdl values can be attributed to the vasculoprotective and antioxidant properties of Hdl (40).

Interestingly, contrast nephropathy development was higher in patients with low baseline creatinine, unlike the literature. This may be due to the fact that very small increases in low basal creatinine values immediately reach the 25% increase limit proportionally, even though they remain within the normal range. For example: a patient with a baseline creatinine of 0.4 mg/dl will have a 0.1 mg/dl increase in postprocedural creatinine values, which meets the 25% increase limit, but a patient with a baseline creatinine of 0.5 mg/dl, 0.1 mg/dl increase in creatinine values after the procedure does not meet the 25% increase limit. Therefore, in our opinion, the definition of classical contrast nephropathy cannot adequately cover the patient group with very low baseline creatinine.

Limitation of the study

This study has the following limitations. First, this was a single center study with a relatively small sample size. Second, the duration of the procedure, and whether there was percutaneous intervention which played roles in the development of CIN, were not evaluated. Therefore, multicenter studies with larger sample sizes are needed to further clarify the correlation between CIN and liver function test levels.

CONCLUSIONS

Our results suggest a possible relationship between the role of ALT and AST levels in the development of CIN. A high ALT and especially AST level may predict the development of CIN.

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