The value of De Ritis ratio in patients undergoing percutaneous coronary intervention for prediction of contrast-associated acute kidney injury

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Abstract

Background: The most serious side effect of percutaneous coronary intervention (PCI) is contrast-associated acute kidney damage (CA-AKI), an injury to the kidneys caused by the body's reaction to the contrast chemicals that were injected into the bloodstream.

Objectives: The purpose of this trial was to assess the correlation among the De-Ritis ratio & CA-AKI in PCI.

Patients and methods: Five hundred people with ischemic heart disease (IHD) who had PCI were included in this study. Complete medical histories and physical examinations were performed on all individuals. Upon admittance, or the following morning, blood routine testing, aspartate aminotransferase, fasting lipid profile, samples from blood were taken for alanine aminotransferase, international normalized ratio, bilirubin, fasting blood glucose, evaluation of Uric Acid in the Blood. The aspartate aminotransferase-to-alanine aminotransferase ratio was determined by aspartate aminotransferase (AST) activity (U/L)/ALT alanine aminotransferase (U/L).

Results: A total number of 500 cases undergoing elective PCI was enrolled. Mean of Model for End Stage Lived Disease (MELD) score was 7.25 & ranged from 7 to 9 and Mean of Model for End Stage Lived Disease excluding INR (MELD-XI) score was 9.97 and ranged from 9 to 11. A total of 35 (7%) patients developed AKI. AST/ALT ratio can detect AKI at cutoff 1.1 with sensitivity, specificity was 100%, and 58.1% respectively ($p< 0.001$) and AUC was 0.761 as illustrated in table (3) and figure (1). ALT can detect AKI at cutoff 19 with sensitivity, specificity was 100%, and 81.7% respectively ($p< 0.001$) and AUC was 0.896. Model for End-Stage Liver Disease score can detect AKI at cutoff 7 with sensitivity, specificity was 42.9%, and 77.4% respectively ($p< 0.001$) and AUC was 0.608. MELD excluding international normalized ratio score can detect AKI at cutoff 9 with sensitivity, specificity was 42.9%, and 82.8% respectively ($p< 0.001$) and AUC (Area under the curve) was 0.677. ALT had the best AUC followed by aspartate aminotransferase to alanine aminotransferase ratio then Model for End-Stage Liver Disease -XI scores and MELD score.

Conclusion: Long-term unfavorable clinical results are related with a high De Ritis ratio among individuals receiving elective PCI, as well a cut off value of over 1.1 makes the De Ritis ratio a good predictor for CA-AKI.

Keywords: Aspartate aminotransferase; Percutaneous coronary intervention; De Ritis ratio; Alanine aminotransferase; AKI.

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Introduction

The most common & serious complication that can arise following percutaneous cardiac intervention is known as CA-AKI. This injury is caused by the intravascular infusion of contrast chemicals. As a 3rd major contributor to AKI **(Fähling et al., 2017)**, contrast-associated acute kidney damage is an important cause of extended dialysis hospital stay, persistent renal injury & elevated risk of **death (Wi et al., 2011; Cheng et al., 2020; McCullough et al., 2006)**. Preoperative identification of those at high risk as well as successful preventive treatments are of utmost importance due to the deleterious & preventable nature of contrast-associated acute kidney damage.

The degree of liver failure is inversely proportional to the AST to ALT ratio, suggesting a significant connection among the two **(Giannini et al., 1999)**. Recent research has linked a raised De-Ritis ratio to worse cardiovascular results. **(Steininger et al., 2018; Liu et al., 2021; Su et al., 2022; Maeda et al., 2021)**.

Hepatocytes are home to ALT, making it a useful marker of liver health. In addition to the liver, the heart & kidneys are important sources of AST secretion **(Woreta et al., 2014)**. Because of this, the ratio of AST to ALT can indicate disease in organs and tissues other than the liver. Systemic hypoperfusion, triggered by the reduced cardiac output of AMI, causes systemic aseptic inflammation, which is indicated by the De Ritis ratio **(Ndrepepa et al., 2023; Güvendi Şengör et al. 2023)**. Moreover, oxidative stress injury & tubular degradation are both exacerbated by the renal hypoperfusion brought on by contrast agents **(Liu, Schmerbach et al., 2014)**. Due to their various subcellular localizations, the De Ritis ratio & oxidative stress due to mitochondrial malfunction are likely to be closely linked **(Su et al., 2022; Botezelli et al., 2012)**.

The correlation among the AST/ALT ratio & contrast-associated acute kidney damage, however, has not been established. Therefore, the goal of this trial was to measure the correlation among the De-Ritis ratio & CA- acute kidney injury in percutaneous coronary intervention individuals.

Patients and methods

This retrospective observational trial enrolled 500 IHD patients who underwent PCI at Cardiology Department, Faculty of Medicine, Sohag University, from May 2021 to May 2022.

Hemodynamic instability prior to PCI, immediate or urgent coronary artery bypass grafting during an emergency PCI procedure, severe renal disfunction (including dialysis), dangerously contagious diseases, use of contrast agents or nephrotoxic drugs within the previous two weeks, allergy to iodine as well as iodinated contrast media, along with loss of monitoring were the criteria for exclusion.

Each person underwent a comprehensive history review as well as a clinical examination. Admittance day or the following morning, blood samples were obtained in order to measure international normalized ratio, bilirubin, alanine aminotransferase, serum uric acid, & aspartate aminotransferase. Fasting lipid profile, bilirubin, fasting blood sugar along with international normalized ratio were also measured. The measures of serum creatinine were taken at 3 distinct periods in time: upon admission, followed by again two days in a row after the procedure. All of the procedures were carried out by skilled interventional cardiologists who made use of a nonionic, low-osmolality contrast medium (either 370

mgI/mL of Ultravist or Iopamiron). Saline solution was infused intravenously at 1 ml/kg/h for a duration of 12 hours throughout the perioperative phase (0.5 ml/kg/h for heart failure participants).

The De Ritis ratio was obtained by AST activity (U/L)/ALT activity (U/L). The eGFR was measured as $186.3 \times (SCr)^{-1.154} \times (age)^{-0.203} \times 0.742$ (if the cases were female) **(National Kidney Foundation 2002)**, accordance to the improved dietary changes for renal disease. The following equation was used to determine the standard Model for End-Stage Liver Disease (MELD) score: 3 3.78 × ln (total bilirubin, mg/dl) + 11.2 × ln (international normalized ratio) + 9.57 × ln (SCr, mg/dl) + 6.43 **(Fan et al., 2020)**. The Model for End-Stage Liver Disease excluding international normalized ratio (MELD-XI) score used the following equation to determine: 5.11 × ln (total bilirubin, mg/dl) + 11.76 × ln (SCr, mg/dl) + 9.44 **(Kim et al., 2013)**. For the purpose of avoiding negative scores, the minimum value for all parameters was fixed at 1.0, while the extreme value for creatinine was determined to be 4.0 mg/dl. We classified anemia as having a hematocrit below 0.39 in males & under 0.36 in females.

Within the initial 2 days after being exposed to the contrast agent, CA-AKI was defined as a rise in the level of serum creatinine of over 0.3 mg/dl or fifty percent compared with the value at baseline. This definition did not take into account any other causes that could cause renal impairment.

Statistical analysis

Once the data were entered, analysis was performed out using IBM SPSS version 20.0 (IBM Corp. Released 2017). Armonk, New York: IBM Corporation, 2005. IBM SPSS Statistics for Windows, Version 25.0. The mean & standard deviation (±SD) of the quantitative data, as well as the frequency also distribution of the qualitative data, were both included in the calculations for the descriptive statistics pertaining to the information. After determining that the groups were not normal using the Shapiro–Wilk test of normality, the significance of the variations among them was analysed using either the Chi-square test, the Student t-test, or the Mann Whitney test. This was done as part of the statistical comparison that was carried out among the various groups. For the purpose of determining the Sensitivity and Specificity of quantitative Diagnostic measures, the ROC Curve (also known as the receiver operating characteristic) was utilized. Logistic Regression to determine the De Ritis ratio-independent variable association. A P value below 0.05 directed statistical significance in all analyses.

Results

A total number of 500 individuals undergoing elective PCI was enrolled. The age of studied cases fluctuated among 59–68 years, mean ± standard deviation age was 63.02± 2.81 years and median were 64 years. There were 280 (56%) males & 220 (44 percent) women with man to female ratio was 1.27:1. The most common comorbidity included in our study was hypertension (35%) cases followed by D.M in 170 (34%) cases then MI in 95 (19%) cases and hyperuricemia in 60 (12%) cases. Twenty (45) cases reported EF <40%. Acute kidney injury developed in 35 (7%) cases (**Table.1**). Mean of MELD score was 7.25 and ranged from 7 to 9 and MELD -XI score was 9.97 & ranged from 9 to 11. Laboratory data were illustrated in in (**Table.2**).

Table 1. Patients' characteristics of the examined cases

Variables		Studied cases (N= 500)	
		N	%
Age (years)	**Mean± SD**	63.02± 2.81	
	Median (range)	64.0 (59.0- 68.0)	
Sex	**Male**	280	56.0%
	Female	220	44.0%
Comorbidities	**HTN**	175	35.0%
	D.M	170	34.0%
	MI	95	19.0%
	Hyperuricemia	60	12.0%
Procedure	**LAD**	115	23.0%
	RCA	115	23.0%
	LCX	115	23.0%
	LM	40	8.0%
	Multivessels	115	23.0%
EF <40%		20	4.0%
AKI		35	7.0%

Table 2. laboratory data & MELD score among the studied cases

Variables	Mean	± SD	Median	IQR		Range	
Hb	12.80	.64	12.70	12.2	13.5	12.20	13.50
WBCs	7.20	.26	7.25	6.9	7.4	6.90	7.40
Platelets	224.77	20.65	223.00	215.0	241.0	215.00	241.00
AST	26.23	4.88	26.00	24.0	29.0	24.00	29.00
ALT	23.56	5.84	22.00	21.0	27.0	21.00	27.00
AST:ALT Ratio	1.18	.40	1.10	.8	1.6	.80	1.60
Creatinine	.81	0.16	0.80	.7	.9	.70	.90
eGFR	86.62	11.69	86.00	79.0	91.0	79.00	91.00
Total bilirubin	0.68	0.23	0.67	.5	.8	.47	.82
INR	1.02	.01	1.02	1.0	1.0	1.01	1.03
Triglyceride,	143.94	6.18	145.00	139.0	147.0	139.00	147.00
Cholesterol	164.43	3.81	164.00	162.0	165.0	162.00	165.00
HDL	40.43	1.24	41.00	40.0	41.0	40.00	41.00
LDL	107.21	2.51	107.00	105.0	110.0	105.00	110.00
MELD score	7.25	.81	7.00	7.0	8.0	7.00	9.00
MELD-XI score	9.97	.59	10.00	9.0	10.0	9.00	11.00

In all, 35 (seven percent) participants got AKI. The effectiveness of Model for End-Stage Liver Disease score, Model excluding international normalized ratio score, & AST/ALT ratio in addition to its components to expect AKI was equated using receiver operating characteristic (ROC) analysis. AST/ALT ratio can detect AKI at cutoff 1.1 with sensitivity, specificity was 100%, and 58.1% respectively (p below 0.001) & AUC was 0.761 as illustrated in (**Table .3**) and (**Fig.1**). ALT can detect AKI at cutoff 19 with sensitivity, specificity was 100%, and 81.7% respectively (p< 0.001) and AUC was 0.896. Model for End-Stage Liver Disease score can detect AKI at cutoff 7 with sensitivity, specificity was 42.9%, and 77.4% respectively (p< 0.001) and AUC was 0.608. MELD-XI score can detect AKI at cutoff 9 with sensitivity, specificity was 42.9%, and 82.8% respectively (p< 0.001) and AUC was 0.677. The area under the curve was highest for ALT, then the AST/ALT ratio, the international normalized ratio score, & finally the MELD, (**Table .3**).

Table (3): Validity of AST/ALT ratio to detect AKI Patients group.

Parameter	Best cutoff value	AUC	Sensitivity	Specificity	PPV	NPV	P value
AST/ALT ratio	>1.1	0.761	100%	58.1%	70.5%	100%	<0.001
AST	25	0.530	100%	46.2%	65%	100%	0.197
ALT	19	0.896	100%	81.7%	84.5%	100%	<0.001
MELD score	7	0.608	42.9%	77.4%	65.5%	57.5%	0.002
MELD-XI score	9	0.677	42.9%	82.8%	71.4%	59.2%	<0.001

PPV= Positive Predictive Value, NPV= Negative Predictive Value,

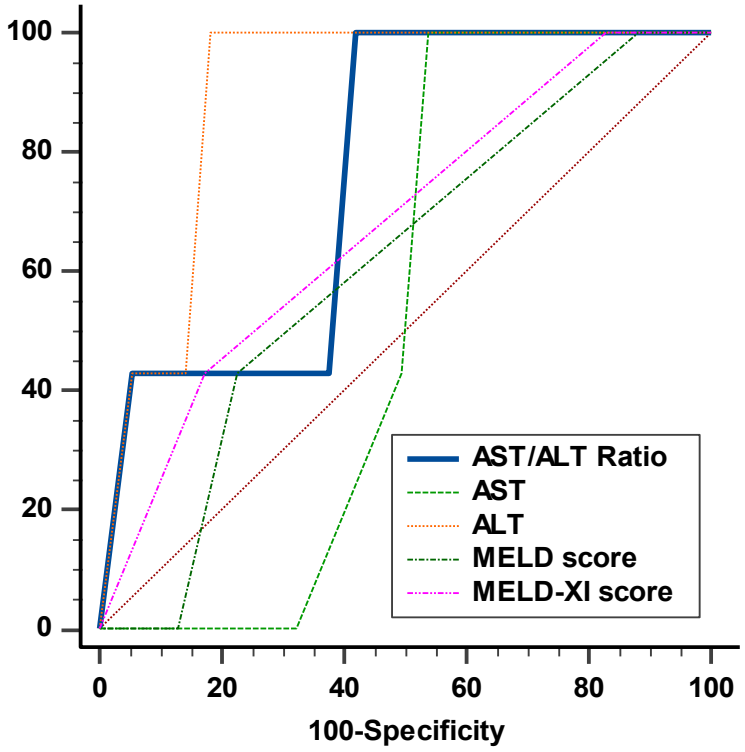

Fig. 1. ROC curves analysis of AST/ALT ratio, AST, ALT, MELD score and; MELD-XI, in prediction of AKI

Individuals with high aspartate aminotransferase-to-alanine aminotransferase ratio ratios were older and more likely male. The high AST/ALT ratio group had more DM and less myocardial infarction, hypertension, & hyperuricemia than the low group. Furthermore, the high AST/ALT ratio group had higher white blood cell, Hb, total bilirubin, aspartate aminotransferase, cholesterol, INR, Model for End-Stage Liver Disease score, & MELD-XI score than the low group. The high AST/ALT ratio group had less alanine aminotransferase, hemoglobin, in addition eGFR than the low group (**Table.4**).

Table 4. Characteristics of individuals at the start of the trial, broken down into groups based on where the aspartate aminotransferase-to-alanine aminotransferase ratio cut off.

Variables		AST/ALT ratio ≤1.1 (n= 270)		AST/ALT ratio >1.1 (n= 230)		p- value#
		Mean	± SD	Mean	± SD	
Age		62.59	±3.08	63.39	±2.51	**<0.001**
Hb		12.95	±0.68	12.68	±0.58	**<0.001**
WBCs		7.15	±0.24	7.26	±0.27	**<0.001**
Platelets		221.04	±24.47	229.15	±13.77	0.167
AST		22.98	±3.46	30.04	±3.28	**<0.001**
ALT		27.31	±5.19	19.15	±2.57	**<0.001**
Creatinine		0.80	±0.13	0.83	±0.18	0.142
Egfr		90.61	±12.62	81.93	±8.34	**<0.001**
Total bilirubin		0.64	±0.23	0.73	±0.22	**<0.001**
INR		1.02	±0.01	1.02	±0.01	**<0.001**
Triglyceride,		143.61	±6.50	144.33	±5.76	**0.313**
Cholesterol		163.26	±2.24	165.80	±4.72	**<0.001**
HDL		40.35	±1.37	40.52	±1.06	0.496
LDL		107.11	±2.90	107.33	±1.95	0.184
MELD score		7.09	±0.70	7.43	±0.88	**<0.001**
MELD-XI score		9.93	±0.61	10.02	±0.57	**0.049**
		N	**%**	**N**	**%**	**p- value***
Sex	**Male**	130	48.1%	150	65.2%	**<0.001**
	Female	140	51.9%	80	34.8%	
Medical history	**D.M**	40	14.8%	130	56.5%	**<0.001**
	HTN	135	50.0%	40	17.4%	**<0.001**
	Hyperuricemia	40	14.8%	20	8.7%	**0.050**
	MI	55	20.4%	40	17.4%	**0.014**
Procedure Performed	**LAD**	40	14.8%	75	32.6%	**<0.001**
	RCA	115	42.6%	0	0.0%	**<0.001**
	LCX	40	14.8%	75	32.6%	**<0.001**
	LM	20	7.4%	20	8.7%	1.00
	Multivessel	55	20.4%	60	26.1%	0.159

EF	**>40%**	250	92.6%	230	100.0%	**<0.001**
	<40%	20	7.4%	0	0.0%	
AKI	**No**	270	100.0%	195	84.8%	**<0.001**
	Yes	0	0.0%	35	15.2%	

p≤0.05 is statistically significant, p≤0.01 is high statistically significant, # Mann-Whitney U Test * Chi-Square Test

A multivariate logistic regression analysis to obtain was performed for identifying the independent effect that the AST/ALT ratio has on CA-AKI, as well as multiple multivariate models were developed as a result of this investigation. After taking into account factors such as gender & age, the aspartate aminotransferase-to-alanine aminotransferase ratio exhibited a significant association with acute kidney injury in model 1 [OR=49.62, 95% CI: 7.63–322.57, p under 0.001]. In model 2, the connotation amongst the AST/ALT ratio also acute kidney injury remained significant (OR=22.44, 95% CI: 2.8– 179.66, p=0.003). After making adjustments for the factors that were considered for model 3, a similar finding was discovered (OR=9.7, 95% CI: 6.9- 23.72, p = 0.002). In addition, the multivariate logistic analysis revealed that the AST/ALT ratio was independently related with acute kidney injury. This was the case even after taking into account the score assigned by the Model for End-Stage Liver Disease (Model 4: OR=8.9, 95% CI: 6.05–28.71, p = 0.002) or MELD excluding international normalized ratio score (Model 5: OR=1.27, 95% CI: 1.01–3.12, p = 0.001) (**Table.5**).

Additional subgroup analyses were carried out on the relations amongst the ASR/ALT ratio & acute kidney injury, as well as the results demonstrated that There were insignificant cross-group interaction effects (**Fig.2**).

Table 5. Connotation amongst the AST/ALT ratio & AKI in diverse multivariate logistic regression models.

Parameters	P-value	Odds ratio (OR)	95%CI	
			Lower limit	Upper limit
Unadjusted	**<0.001**	28.17	7.46	106.32
Model 1	**<0.001**	49.62	7.63	322.57
Model 2	**0.003**	22.44	2.80	179.66
Model 3	**0.002**	9.7	6.05	23.72
Model 4	**0.002**	8.9	6.19	28.71
Model 5	**0.001**	1.27	1.01	3.12

OR: odds ratio**,** CI: Confidence interval

Model 1: accounted for gender & age.

Model 2: adjusted for parameters incorporated in Model 1 plus medical history, ejection fraction <40%, and multi-vessel disease.

Model 3: adjusted for variables incorporated in Model 2 + white blood cell counts.

Model 4: adjusted for parameters incorporated in Model 3 in addition MELD score.

Model 5: adjusted for variables incorporated in Model 3 along with MELD-XI score.

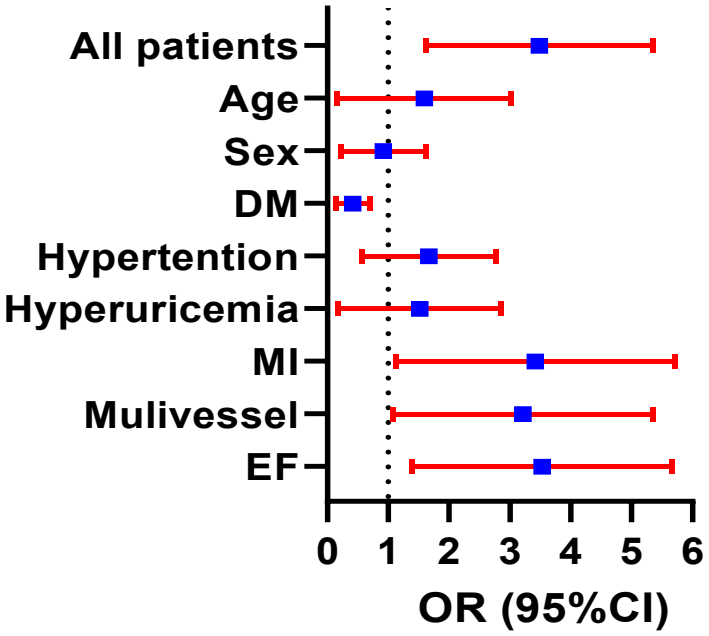

Fig. 2. Forest plot of the subgroup analyses for connotation amongst the AST/ALT ratio also AKI.

Discussion

It has been proven that preoperative liver dysfunction is a condition that is associated with a poor prognosis after major operation. Recent studies have found that an enlarged De-Ritis ratio, which stands for aspartate aminotransferase-to-alanine aminotransferase ratio, is indicative of liver disease & is linked to unfavorable outcomes in the cardiovascular & renal systems (**Ndrepepa, 2021; Ndrepepa et al., 2022**). However, the De-Ritis ratio's predictive importance on contrast-associated acute renal damage for individuals undergoing elective percutaneous coronary intervention remains unclear. In this study, our objective was to determine whether or not the De-Ritis ratio can accurately predict CA-AKI in individuals who were scheduled to undergo elective PCI.

Persons with a high De-Ritis ratio were found to be more likely to develop CA-AKI. The Model for End-Stage Liver Disease score as well as the MELD without international normalized ratio score had no effect on this correlation. No statistically interaction effects among both of the groups were observed. In fact, Malinchoc et al. suggested the Model for End-Stage Liver Disease score in 2000; it was initially used to measure the short-term prognosis in persons with cirrhosis they were getting a shunt placed between their liver & their digestive system (**Chen et al., 2021**). The MELD score also its variants are now widely used & have been linked to poor outcome following percutaneous coronary intervention (**Kırıs et al., 2018; He et al., 2021**). High scores on the Model for End-Stage Liver Disease and its variants were also substantially linked to AKI. The risk of acute kidney injury was shown to be higher in cases with cirrhosis who had a high Model for End-Stage Liver Disease score, according to a meta-analysis of thirty research studies involving a total of 18,474 individuals (Tariq R et al., 2020).

In accordance with the findings of a retrospective trial done by Ding et al. (**Ding**

et al., 2021) on 283 individuals suffering from postcardiotomy cardiogenic shock who required venoarterial extracorporeal membrane oxygenation, the Model for End-Stage Liver Disease with no an International Normalized Ratio score was related with Acute Kidney Injury. Our research determined that the AUC of the Model for End-Stage Liver Disease score was 0.608 & the AUC of the MELD-XI score was 0.677 for predicting CA-AKI, with a p value of 0.002 and under 0.001, respectively. However, oral anticoagulant medication significantly alters the reliability of the Model for End-Stage Liver Disease score as well as its modified versions in evaluating liver function. The MELD score & its variants also have a convoluted calculation formula and lack a standard criterion for selection. Therefore, there is an immediate requirement for a straightforward, quick, and reliable method of evaluating liver function before to PCI. Based on the findings of our research, a greater De-Ritis ratio predicted an increased risk of CA-AKI after PCI better than alanine and aspartate aminotransferases alone. Additionally, the Model for End-Stage Liver Disease as well as its exclusion of the international normalized ratio score were surpassed by the prognostic value of the De-Ritis ratio, which was greater. The simple, fast, & effective De-Ritis ratio can predict contrast-associated acute kidney damage following percutaneous coronary intervention as an alternate pre-procedure liver function testing technique. It's very important to identify and manage liver insufficiency in patients with high De-Ritis ratios. Hydration and diligent monitoring during periprocedure can also lesser CA-AKI risk.

The method via which De-Ritis ratio increases CA-AKI is unknown. As indicated previously, high De-Ritis ratios damage liver function **(Steininger et al., 2018)**. Furthermore, liver dysfunction generates a disparity amongst vasodilatory as well as vasoconstrictive molecules, leading to impaired renal function via splanchnic in addition to systemic vasodilation & renal vasoconstriction **(Simonetto et al., 2020; Zhang et al., 2020)**. In addition, the De-Ritis ratio's association with inflammation has been documented **(Zoppini et al., 2016)**. Also, aspartate aminotransferase detected in hepatocyte cytoplasm along with mitochondria, while alanine aminotransferase is found solely in the cytoplasm. Therefore, it was speculated that mitochondrial malfunction due to oxidative stress could be associated with an increased De-Ritis ratio **(Lu et al., 2020)**. It is well established that oxidative stress as well as inflammation are linked to CA-AKI **(Zhang et al., 2020)**.

The current trial came to the conclusion that a De Ritis ratio cut-off point of over 1.1 was the most accurate in predicting CA-AKI following PCI. Important research investigated the impact that the De Ritis ratio has on acute kidney injury after a variety of surgical procedures. Following radical retropubic prostatectomy, Gultekin et al. discovered that a postoperative De Ritis ratio of 1.2 was considered to be a cut-off value for predicting acute kidney injury **(Park, et al., 2021)**. Gultekin Y et al. **(Gultekin et al., 2021)** demonstrated that a De Ritis ratio of at least 1.22 was able to accurately predict acute kidney injury after coronary artery bypass grafting operation. Further, He et al. **(He et al., 2022)** demonstrated that the De Ritis ratio contained a certain prediction potential for CA-AKI among individuals who were undergoing PCI, along with a cutoff value of 1.3 served as the optimal threshold for this capacity. The diverse study populations may have explained the small De Ritis ratio cut-off value.

Limitations exist in this trial. First, limited samples, one facility, & short-term follow-up may affect results reliability. Second, only both ALT & AST were tested on admission and cannot indicate De Ritis ratio dynamics. No comparisons were made with oxidative stress, inflammation, or kidney damage biomarkers.

Conclusion

An elevated De Ritis proportion is related with long-term unfavorable clinical results in percutaneous coronary intervention persons & is a robust predictor of contrast-associated acute kidney damage with a cut off value of above 1.1. These associations need more study.

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