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The predictive value of AGEF score for contrast-induced nephropathy in patients with lower extremity peripheral artery disease

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Abstract

Background Lower extremity peripheral artery disease (LEAD) is a disease that impairs quality of life, causes amputation and is associated with mortality. Percutaneous interventions are performed for therapeutic purposes in patients with LEAD. Contrast-induced nephropathy (CIN) may emerge due to the contrast media used during these interventions. This study aimed to investigate the predictive value of six scoring systems, including AGEF, ACEF, Zhi-Feng Yao, $CR_4EATME_3AD_3$, Mehran, and Tziakas, for CIN.

Methods This retrospective study included 690 patients with LEAD. The study population was divided into two groups according to the presence of CIN.

Results In our study, the AGEF, ACEF, Tziakas, Zhi-Feng Yao, $CR_4EATME_3AD_3$, and Mehran scoring systems demonstrated robust predictive capabilities for the development of CIN following percutaneous intervention in patients with LEAD. Moreover, the AGEF, Zhi-Feng Yao, $CR_4EATME_3AD_3$, and Mehran scores were identified as independent predictors of CIN development in patients with LEAD revascularized via endovascular interventions.

Conclusion The findings of this study revealed that various scoring systems performed well in predicting CIN in LEAD patients. In addition, among these scoring systems, AGEF has been shown to be the best in terms of predictive power.

Keywords LEAD, CIN, Peripheral artery disease, AGEF, Contrast media, Kidney failure

Introduction

Lower extremity peripheral artery disease (LEAD) is a vascular condition characterized by arterial narrowing or occlusion due to atherosclerotic plaque buildup. This leads to reduced blood flow, causing symptoms such as claudication, pain, and limb weakness. LEAD is not only a major cause of impaired mobility and diminished quality of life but also a marker of systemic atherosclerosis, significantly increasing the risk of cardiovascular events, limb ischemia, amputation, and mortality [1, 2].

Endovascular procedures are instrumental in both diagnosing and treating the LEAD. These procedures

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employ contrast dye to improve the visibility of blood vessels during imaging and interventions. However, the use of contrast agents incurs the risk of contrast-induced nephropathy (CIN), resulting in acute kidney injury (AKI). This complication can lead to adverse outcomes, including the necessity for dialysis, prolonged hospitalization, an elevated risk of chronic kidney disease (CKD), cardiovascular complications, and increased mortality, significantly impacting both kidney function and overall health [3, 4].

Various scoring systems and risk prediction models are used to assess the likelihood of developing CIN following contrast-enhanced procedures. These scoring systems, including AGEF [5], ACEF [6], $CR_4EATME_3AD_3$ [7], New CIN Score by Yao et al. [8], New CIN Score by Mehran et al. [9], and New CIN Score by Tziakas et al. [10], have demonstrated associations with CIN development across diverse patient groups. All these scores have been studied in coronary artery patients undergoing PCI, and their predictive power has been validated and widely cited in the literature. However, to our knowledge, these scores have not been investigated in patients with lower extremity arterial disease.

This study aims to systematically compare the predictive performance of these six scoring systems in patients with LEAD. By addressing this gap, we seek to determine the most effective tool for identifying high-risk patients and optimizing preventative strategies to mitigate CIN-related complications.

Material and method

Population and sample

The population of this retrospective study comprised patients who underwent peripheral angiography at the Kafkas University Cardiology Clinic between January 2017 and November 2023. Inclusion criteria were (1) patients with age of over 18 years, (2) patients diagnosed as LEAD with conventional angiography. Exclusion criteria were as follows; (1) history of contrast allergy or intolerance, (2) patients with missing data, (3) end-stage renal disease (defined as patients on hemodialysis or peritoneal dialysis), (4) pregnancy or other conditions that would interfere with contrast use or follow-up. A graphical abstract (Fig. 1) was created showing the design of the study.

Patients were considered for endovascular intervention based on current guidelines including symptomatic LEAD, intermittent claudication limiting daily activities or critical limb ischemia. Anatomical suitability for endovascular treatment, including lesion location, length, and degree of occlusion, was evaluated. In addition, patients' overall clinical status and comorbidities were assessed to ensure procedural safety and optimize outcomes. All endovascular procedures were performed using a non-ionic, low-osmolality contrast agent (Iohexol).

Due to the retrospective nature of the study, all available medical records were reviewed. Twelve patients were excluded because they lacked essential clinical or laboratory follow-up data required to define contrast-induced

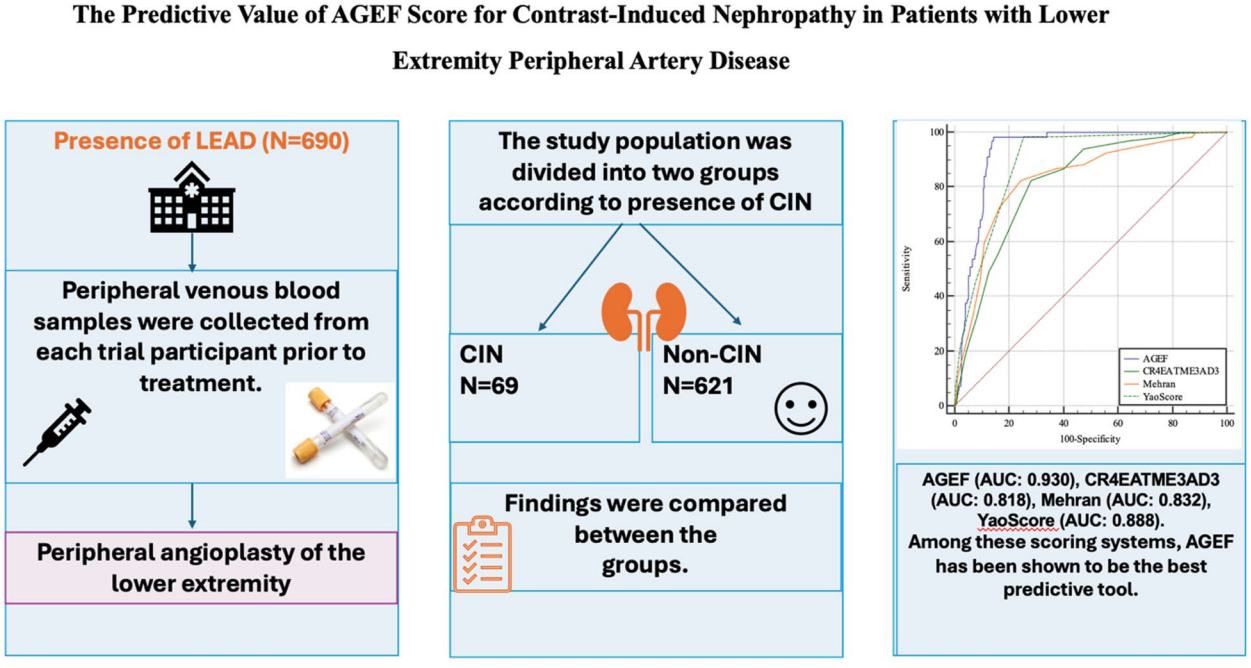


Fig. 1 A graphical abstract was created showing the design of the study. Abbreviations: LEAD: Lower extremity peripheral artery disease, CIN: Contrast-induced nephropathy

nephropathy (CIN), primarily missing baseline or 48–72 h post-procedure creatinine measurements, or because they were missing key variables necessary for the calculation of the scoring systems evaluated in this study. For the remaining patients, all relevant variables were complete, and no imputation was performed. The study protocol was approved by the Kafkas University Medicine Faculty Local Ethics Committee prior to the conduct of the study. The study was carried out in accordance with the ethical principles set forth in the Declaration of Helsinki and the ethical standards set by the authorized ethics committee on human experimentation.

Definition of CIN

All the patients with CKD were hydrated according to the recent literature data [11–13]. In general, hydration was performed with 0.5 to 1 mL/kg/h of normal (0.9%) saline for 12 to 24 h before intervention and continued for 12 to 24 h after the procedure. The rate and duration were adjusted according to baseline renal function and clinical status. Additionally, after initial imaging, the interventional procedure was postponed until the patient's clinical condition allowed adequate hydration, and revascularization was performed thereafter.

CIN is commonly defined as a ≥ 25% increase in serum creatinine from the baseline value or an absolute increase of at least 0.5 mg/dL within 48–72 h after the administration of radiographic contrast media (CM) [14, 15]. In this base, we prioritized the criterion that was first met, whether it was the 0.5 mg/dL increase or the 25% increase within 48–72 h following the operation.

Data collection

The patients' medical histories, including comorbidities and echocardiographic data, were collected retrospectively from their charts. Patients who had been taking medication for diabetes mellitus (DM), with plasma glucose concentration of ≥ 200 mg/dL, or with a fasting plasma glucose concentration of ≥ 126 mg/dL were deemed to have DM. Oral antidiabetic medications of patients with DM were discontinued 24 h before the procedure. Patients who had been taking antihypertensive medication, had a systolic blood pressure of ≥ 140 mmHg or a diastolic blood pressure of ≥ 90 mmHg were deemed to have hypertension (HT). Patients with an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m^2 for at least three months were deemed to have CKD. Patients who had been taking medications for chronic obstructive pulmonary disease (COPD) or showing the corresponding respiratory symptoms and tested positive for COPD via spirometry were deemed to have COPD.

Blood samples were collected from all patients at the time of their admission to the outpatient clinic for hemogram testing and measurements of biochemical markers. An automated hematology and biochemical analyzer (Roche Diagnostics Cobas 8000 c502, Indianapolis, USA) was used to perform the hemogram test and measure the biochemical markers. The eGFR was calculated based on the formula provided in the Modification of the Diet in Renal Disease study [16]. The calculation of the risk scores using the risk scoring systems (i.e., AGEF [5], ACEF [6], Tziakas et al. [10], $CR_4EATME_3AD_3$ [7], Yao et al. [8], and Mehran et al. [9] was performed as described in the literature. Other potential scoring systems were considered but excluded due to limited clinical adoption or lack of essential variables in our dataset. In our study, acute leg ischemia was considered an emergency condition in the $CR_4EATME_3AD_3$ score.

Statistical analysis

The descriptive statistics derived from the collected data were presented as mean and standard deviation (SD) values for continuous variables conforming to a normal distribution, as median and interquartile ranges for continuous variables not conforming to a normal distribution, and as percentage values for categorical variables. The normal distribution characteristics of the continuous variables were assessed using the Kolmogorov–Smirnov test. To analyze differences between groups in terms of continuous variables, the two-sample Student's t-test or Mann–Whitney U-test was employed.

Two separate models using Logistic regression analysis was created to identify variables significantly correlated with CIN. The model 1 examined the predictive values of six different risk scores including Tziakas, AGEF, ACEF, Yao, $CR_4EATME_3AD_3$, and Mehran. This model consisted of variables showing a significant correlation with CIN in the univariate analysis such as HT, insulin use, infrapopliteal lesions and interventions. The model 2 assessed the prognostic value of AGEF solely by including the variables showing a significant correlation with CIN in the univariate analysis ($p < 0.05$) and parameters (age, contrast media volume, eGFR) which are known to be predictors of CIN development according to the literature. Correlations were reported using odds ratio (OR) with 95% confidence interval (CI). The regression model exclusively examined the fundamental and sub-variables. Multicollinearity between AGEF, AGEF components (Age, EF, eGFR) and the other scores were assessed by Eigen value and condition index. Linearity was tested by interacting with the logarithmic transformation of each parameter itself. Models fit were assessed by the overall $\chi 2$ test, and the goodness of fit was assessed by the Hosmer-Lemeshow statistic. The achived effect size (Cohen's d) and power value (1–β) for AGEF score, compared between patients with and without CIN, were calculated using G*Power 3.1 software. The alpha level used for this

analysis was < 0.05. The effect size and power value were 0.74 and 0.989, respectively.

The prognostic powers of the AGEF, ACEF, Tziakas et al., Yao et al., $CR_4EATME_3AD_3$, and Mehran et al. scoring systems in predicting CIN development were evaluated using the area under the curve (AUC) values obtained from the receiver operating characteristic (ROC) curve analysis. The predictive validity of each scoring system was quantified based on the area under the ROC curve (c statistics). The c statistics were compared using DeLong's test. For all statistical analyses, the SPSS 22.0 software package was used (Statistical Product and Service Solutions for Windows, Version 22.0, IBM Corp., 2013). A p value of < 0.05 was considered statistically significant.

Results

After exclusion of 12 patients with missing data, 9 undergoing peripheral artery bypass surgery, 13 receiving routine hemodialysis or peritoneal dialysis, a total of 690 patients with LEAD included in the final analysis. Among these, 621 (91%) were male and 69 (9%) were female, with a mean age of 62 ± 10 years.

The patients were stratified into two groups: those who developed CIN and those who did not; CIN was observed in 69 (10%) patients. A comparative analysis revealed that patients with CIN were older (mean, SD; 67 ± 9 vs. 62 ± 10, $p < 0.001$) and exhibited a higher prevalence of HT [n: 59 (85.5%) vs. n: 440 (70.9%), $p = 0.010$], DM [n: 53 (76.8%) vs. n: 356 (57.3%), $p = 0.002$], and CKD [n: 60 (87.0%) vs. n: 115 (18.5%), $p < 0.001$] and a higher usage of insulin [n: 26 (37.7%) vs. n: 71 (11.4%), $p < 0.001$] and metformin [n: 53 (76.8%) vs. n: 294 (47.3%), $p < 0.001$]. These patients also had higher creatinine levels (mean (SD); 3.12 ± 2.11 vs. 0.9 ± 0.21, $p < 0.001$) and C-reactive protein (CRP) [median interquartile range (IQR); 29 (5–35) vs. 18 (3.37–18.37), $p = 0.026$], along with lower levels of eGFR (mean (SD); 26 ± 15 mg/min/m^2 vs. 85 ± 18 mg/min/m^2, $p < 0.001$) compared to those who did not develop CIN. Additionally, concerning angiography findings between the two groups, the ratio of infrapopliteal lesions [n: 47 (68.11%) vs. n: 274 (44.12%), $p < 0.001$] and infrapopliteal interventions [n: 16 (23.18%) vs. n: 60 (9.66%), $p = 0.001$] was higher in patients with CIN. Moreover, Tziakas, AGEF, ACEF, Yao, $CR_4EATME_3AD_3$, and Mehran scores were higher in patients with CIN compared to the patients without CIN [median (IQR), 5 (4–6) vs. 3 (1–4), $p < 0.001$); mean (SD); 2.35 (± 0.40) vs. 1.25 (± 0.53), $p < 0.001$); mean (SD); 1.86 (± 0.63) vs. 1.14 (± 0.37), $p < 0.001$); median (IQR); 2 (2–3) vs.0 (0–2), $p < 0.001$; median (IQR); 10 (8–12) vs. 5 (4–8), $p < 0.001$; and mean (SD); 11.06 ± 3.21 vs. 6.65 ± 3.22, $p < 0.001$]. Ejection fraction (EF) was significantly lower in patients who developed CIN compared to those did not develop CIN [mean (SD); 51% (± 10) vs. 56% (± 9), $p < 0.001$]. The contrast media volume amount was similar among the two groups [median (IQR); 192 (100–220) vs. 188 (120–220), $p = 0.861$]. The baseline demographic, laboratory, and angiographic features of the patients are presented in Table 1.

Logistic regression analyses of the variables in predicting CIN

A univariate logistic regression analysis indicated that the presence of HT, infrapopliteal lesions and interventions, and scores for Tziakas, AGEF, ACEF, Yao, $CR_4EATME_3AD_3$, and Mehran were significant prognostic factors for CIN in patients with LEAD. Then, the factors that were found to be significant in the univariate analysis were included in the multivariate model 1 (Table 2). This model revealed that insulin usage (OR: 2.303, 95% CI: 1.109–4.783; $p = 0.025$), AGEF score (OR: 6.571, 95% CI: 3.188–13.542; $p < 0.001$), Yao score (OR: 1.704, 95% CI: 1.226–2.370; $p = 0.002$), $CR_4EATME_3AD_3$ score (OR: 1.191, 95% CI: 1.060–1.532; $p = 0.005$), and Mehran score (OR: 1.218, 95% CI: 1.093–1.358; $p < 0.001$) were independently correlated with CIN development in patients with LEAD revascularized via endovascular intervention (Table 2). According to the model 2, AGEF score and eGFR were the predictors of CIN development [OR: 3.316, 95% CI: 1.074–11.354; $p = 0.012$ and OR: 0.764, 95% CI: 0.695–0.840; $p < 0.001$, respectively] (Table 3).

Comparison of the prognostic powers of risk scoring systems in predicting CIN

The ROC curve analyses of the scoring systems investigated for predicting CIN development revealed AUC values between 0.818 and 0.930 [AGEF (AUC: 0.930, 95% CI 0.908–0.948, $p < 0.001$), Yao (AUC: 0.888, 95% CI 0.862–0.910, $p = 0.002$), Mehran (AUC: 0.832, 95% CI 0.802–0.860, p = < 0.001), and $CR_4EATME_3AD_3$ (AUC: 0.818, 95% CI 0.787–0.846, $p = 0.005$)]. Additionally, AGEF demonstrated a significantly higher AUC compared to ACEF ($p = 0.001$), $CR_4EATME_3AD_3$ ($p < 0.001$), New CIN Score by Yao et al. ($p < 0.0006$), New CIN Score by Mehran et al. ($p = 0.001$), and New CIN Score by Tziakas et al. ($p < 0.001$).

AGEF emerged as the most effective predictor of CIN, with a specificity of 85.7% and sensitivity of 98.6% for AGEF values > 1.82, compared to $CR_4EATME_3AD_3$ (specificity: 72%, sensitivity: 82.6% for values > 7), Mehran (specificity: 75.5%, sensitivity: 82.6% for values > 8), and Yao (specificity: 74.6%, sensitivity: 98.6% for values > 1) (Fig. 2).

Discussion

In this study, we evaluated the predictive accuracy of six CIN risk scoring systems-AGEF, ACEF, Tziakas et al., Yao et al., $CR_4EATME_3AD_3$, and Mehran et al.-in patients

Table 1 The baseline demographic, laboratory and angiographic characteristics of the study population according to the development of CIN

		Contrast Induced Nephropathy (CIN)			
Variable		**CIN (-), *n* = 621**	**CIN (+), *n* = 69**	**Total, *n* = 690**	***P* Value**
Age, years (SD)		62.0 (± 10)	67.0 (± 9)	62.0 (± 10)	**< 0.001**
Male, n (%)		567 (91.3)	61 (88.4)	628 (91)	0.425
Hypertension, n (%)		440 (70.9)	59 (85.5)	499 (72.3)	**0.010**
DM, n (%)		356 (57.3)	53 (76.8)	409 (59.3)	**0.002**
Previous Stroke n (%)		47 (7.6)	6 (8.7)	53 (7.7)	0.739
AFib, n (%)		54 (8.7)	10 (14.5)	64 (9.3)	0.116
CAD, n (%)		365 (58.8)	52 (75.4)	417 (60.4)	**0.008**
Current Smoker, n (%)		286 (46.1)	40 (58)	326 (47.2)	0.060
Systolic BP, mm/Hg (SD)		131.0 (± 34)	129.0 (± 34)	132.0 (± 33)	0.270
Diastolic BP, mm/Hg (SD)		77.0 (± 21)	77.0 (± 21)	77.0 (± 20)	0.770
Heart rate, beat/min (SD)		77.0 (± 18)	77.0 (± 16)	77.0 (± 18)	0.823
Previous PAD, n (%)		206 (33.2)	23 (33.3)	229 (33.2)	0.979
CKD, n (%)		115 (18.5)	60 (87.0)	175 (25.4)	**< 0.001**
COPD, n (%)		140 (22.5)	11 (15.9)	151 (21.9)	0.209
Insulin, n (%)		71 (11.4)	26 (37.7)	97 (14.1)	**< 0.001**
Metformin, n (%)		294 (47.3)	53 (76.8)	347 (50.3)	**< 0.001**
GLP-1R antagonist, n (%)		64 (10.3)	6 (8.7)	70 (10)	0.674
DPP-4 inhibitors, n (%)		49 (7.89)	4 (5.79)	53 (7.7)	0.536
ACEI, n (%)		85 (13.7)	11 (15.9)	96 (13.9)	0.608
ARB, n (%)		62 (10)	10 (14.5)	72 (10.4)	0.248
NSAID, n (%)		66 (10.6)	8 (11.6)	74 (10.7)	0.806
SGLT2 inhibitors, n (%)		42 (6.76)	9 (13.04)	51 (7.4)	0.059
Statin, n (%)		487 (78.42)	53 (76.81)	540 (78.3)	0.740
Cilostazol, n (%)		249 (40.09)	22 (31.88)	271 (39.3)	0.182
WBC count, 10^9/L (SD)		12.58 (± 4.05)	11.48 (± 2.80)	12.47 (± 3.96)	0.059
Neutrophil, 10^9/L (SD)		5.90 (± 2.15)	6.02 (± 2.19)	5.91 (± 2.15)	0.648
Lymphocyte, 10^9/L (SD)		2.39 (± 1.14)	2.19 (± 1.20)	2.37 (± 1.14)	0.088
Hemoglobin, gr/dL (SD)		12.21 (± 2.32)	12.41 (± 2.09)	12.23 (± 2.30)	0.437
Hematocrit, % (SD)		37.59 (± 6.77)	37.82 (± 5.73)	37.61 (± 6.67)	0.650
Platelet, 10^9/L (SD)		277.59 (± 93.89)	260.81 (± 89.39)	275.0 (± 93)	0.073
Albumin, g/L (SD)		4.04 (± 0.52)	3.98 (± 0.49)	4.04 (± 0.52)	0.213
Glucose, mg/dL (IQR)		161 (100–187)	157 (96–192)	131 (100–189)	0.664
Creatinine, mg/dL (SD)		0.9 (± 0.21)	3.12 (± 2.11)	1.12 (± 0.96)	**< 0.001**
eGFR, mL/min/1.73 m^2 (SD)		85.0 (± 18)	26.0 (± 15)	79.0 (± 25)	**< 0.001**
Triglycerides, mg/dL (IQR)		180 (103–212)	189 (96–232)	148 (103–212)	0.656
Total-Cholesterol, mg/dL (SD)		180.0 (± 52)	176.0 (± 51)	180.0 (± 52)	0.605
HDL-C, mg/dL (SD)		40.0 (± 10)	38.0 (± 12)	40.0 (± 11)	0.374
LDL-C, mg/dL (SD)		107.0 (± 44)	103.0 (± 39)	107.0 (± 43)	0.556
C-Reactive Protein, mg/dL (IQR)		18 (3.37–18.37)	29 (5–35)	9.36 (3.37–18.37)	**0.026**
Rutherford stages, n (%)	*1*	4 (0.6)	0 (0)	4 (0.6)	0.072
	2	111 (17.9)	10 (14.5)	121 (17.5)	
	3	327 (52.7)	32 (46.4)	359 (52)	
	4	96 (15.5)	11 (15.9)	107 (15.5)	
	5	50 (8.1)	13 (18.8)	63 (9.1)	
	6	33 (5.3)	3 (4.3)	36 (5.2)	
EF, % (SD)		56(± 9)	51(± 10)	56(± 9)	**< 0.001**
Acute limb ischemia, n (%)		95 (15.29)	19 (27.53)	114 (16.5)	0.009
Iliac lesion, n (%)		112 (18.03)	13 (18.84)	125 (18.11)	0.893
Iliac intervention, n (%)		60 (9.66)	6 (8.69)	66 (9.6)	0.781
Femoropopliteal Lesion, n (%)		134 (21.6)	17 (24.6)	151 (21.9)	0.584
Femoropopliteal intervention, n (%)		108 (17.4)	16 (23.2)	124 (18)	0.284

Table 1 (continued)

	Contrast Induced Nephropathy (CIN)			
Variable	**CIN (-), *n* = 621**	**CIN (+), *n* = 69**	**Total, *n* = 690**	***P* Value**
Infra-popliteal lesion, n (%)	274 (44.12)	47 (68.11)	321 (46.4)	**< 0.001**
Infra-popliteal intervention, n (%)	60 (9.66)	16 (23.18)	76 (11)	**0.001**
Contrast volume, mL (IQR)	188 (120–220)	192 (100–220)	180 (120–220)	0.861
Procedure time, minute (IQR)	55 (31–51)	63 (31–88)	48 (31–73)	0.186
Tziakas score (IQR)	3 (1–4)	5 (4–6)	3 (1–5)	**< 0.001**
AGEF score (SD)	1.25 (± 0.53)	2.35 (± 0.40)	1.36 (± 0.61)	**< 0.001**
ACEF score (SD)	1.14 (± 0.37)	1.86 (± 0.63)	1.21 (± 0.46)	**< 0.001**
Yao score (IQR)	0 (0–2)	2 (2–3)	0 (0–2)	**< 0.001**
$CR_4EATME_3AD_3$*score (IQR)*	5 (4–8)	10 (8–12)	6 (4–9)	**< 0.001**
Mehran score (SD)	6.65 (± 3.22)	11.06 (± 3.21)	7.09 (± 3.48)	**< 0.001**

SD Standard Deviation, *IQR* Interquartile Range, *DM* Diabetes Mellitus, *Afib* Atrial fibrillation, *CAD* Coronary artery disease, ***BP*** Blood pressure, *PAD* Lower extremity peripheral artery disease, *CKD* Chronic kidney disease, *COPD* Chronic obstructive pulmonary disease, *GLP-1R* The glucagon-like peptide 1 receptor, *DPP-4* Dipeptidyl-peptidase IV, *ACEI* Angiotensin-converting enzyme inhibitor, *ARB* Angiotensin receptor blocker, *NSAID* Nonsteroidal anti-inflammatory drug, *SGLT2* Sodium-glucose cotransporter-2, *WBC* White Blood Cell, *eGFR* Estimated glomerular filtration rate, *HDL-C* High-Density Lipoprotein Cholesterol, *LDL-C* Low Density Lipoprotein Cholesterol, *EF* Ejection Fraction

Table 2 Results of the multivariate analysis when six different scoring systems are included along with significant parameters known to be associated with contrast-induced nephropathy

	Univariate				Multivariate			
Variables	**OR**	**95% C.I.**		***p* value**	**OR**	**95% C.I.**		***p* value**
Hypertension	2.427	1.215	4.850	0.012	-			
Insulin	4.684	2.713	8.086	0.000	2.303	1.109	4.783	**0.025**
Infra-popliteal lesion	2.474	1.490	4.109	0.000	-			
Infra-popliteal intervention	2.797	1.506	5.197	0.001	-			
Tziakas score	1.816	1.556	2.118	0.000	1.307	0.974	1.752	0.074
AGEF score	12.634	7.686	20.766	0.000	6.571	3.188	13.542	**< 0.001**
ACEF score	10.087	6.147	16.554	0.000	-			
Yao et al.	3.305	2.588	4.221	0.000	1.704	1.226	2.370	**0.002**
$CR_4EATME_3AD_3$***score***	1.339	1.247	1.438	0.000	1.191	1.060	1.532	**0.005**
Mehran et al.	1.433	1.321	1.554	0.000	1.218	1.093	1.358	**< 0.001**

AGEF score age, left ventricular ejection fraction, and estimated glomerular filtration rate, *ACEF* score age, serum creatinine, and left ventricular ejection fraction, $CR_4EATME_3AD_3$*score* Contrast media volume, estimated glomerular filtration rate, emergency procedure, age, hypotension, myocardial infarction, left ventricular ejection fraction, anemia, and diabetes

Table 3 Results of the multivariate analysis when only AGEF Score is included along with other significant parameters known to be associated with contrast-induced nephropathy

	Univariate				Multivariate			
Variables	**OR**	**95% C.I.**		***p* value**	**OR**	**95% C.I.**		***p* value**
Hypertension	2.427	1.215	4.850	0.012	-			
Insulin	4.684	2.713	8.086	0.000				
Infra-popliteal lesion	2.474	1.490	4.109	0.000	-			
Infra-popliteal intervention	2.797	1.506	5.197	0.001	-			
Age	1.061	1.033	1.091	0.000				
eGFR	0.815	0.769	0.863	0.000	0.764	0.695	0.840	**< 0.001**
Contrast Media Volume	1.0	0.998	1.003	0.769	-			
AGEF score	12.634	7.686	20.766	0.000	3.316	1.074	11.354	**0.012**

eGFR Estimated glomerular filtration rate, *AGEF Score* Age, eGFR, Ejection Fraction.

undergoing endovascular interventions for LEAD. Our findings demonstrate that all six models effectively predict CIN, with AGEF, Yao, $CR_4EATME_3AD_3$, and Mehran scores emerging as independent predictors. Notably, AGEF exhibited the highest predictive performance, with an AUC of 0.930 in our LEAD cohort, surpassing the original study's AUC of 0.88 in ST-Segment Elevation Myocardial Infarction (STEMI) patients.

The use of contrast agents during diagnostic and therapeutic procedures in LEAD patients introduces the risk of CIN, a well-recognized cause of acute kidney injury associated with increased morbidity, prolonged

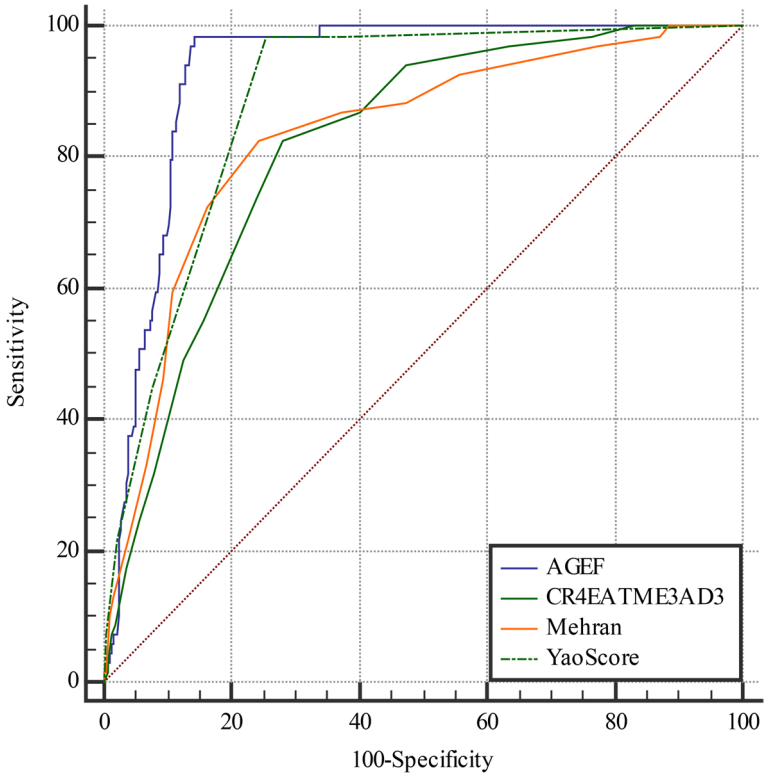


Fig. 2 Receiver operating characteristic (ROC) curve analyses of the risk scoring systems in predicting contrast-induced nephropathy (CIN). AGEF (AUC: 0.930), CR4EATME3AD3 (AUC: 0.818), Mehran (AUC: 0.832), YaoScore (AUC: 0.888)

hospitalization, and higher healthcare costs. Considering the procedure time and the amount of contrast used, predicting CIN in patients who underwent intervention due to peripheral artery disease is an important clinical situation in terms of mortality, morbidity and cost. While the pathogenesis, prevalence, and risk stratification of CIN are well-established in the coronary artery disease (CAD) cohort undergoing percutaneous coronary intervention (PCI), it has not been studied well in patients with LEAD [17–19]. We believe that the population undergoing endovascular interventions for LEAD represents a distinct group in some important ways. The vascular territories involved, the technical aspects of the interventions, and the potential duration in LEAD patients differ from CAD patients. The lower extremity vascular interventions also tend to be more protracted and may involve more contrast material compared to PCI, potentially increasing the risk for CIN. In this context, we especially investigated association between CIN and various scoring models in patients with LEAD [20–23]. Although increased contrast volume is a well-established risk factor for CIN, the mean contrast volumes in our study were similar between the CIN and non-CIN groups. The contrast volume was actually higher in the CIN group, but this difference did not reach statistical significance. This finding may reflect our institutional practice of contrast minimization, particularly in high-risk patients, and the cautious approach of operators in using lower volumes in those with baseline renal dysfunction. Moreover, several studies in the literature have demonstrated that CIN can develop independently of contrast volume, supporting the multifactorial nature of this complication [24, 25]. Furthermore, the lack of difference in contrast medium amount between the groups in our study may have led to AGEF superior to other scores that use contrast medium as a scoring variable.

Our study identified hypertension, insulin-dependent diabetes, and infrapopliteal interventions as significant risk factors for CIN. Hypertension has been consistently linked to kidney ischemia, nephron loss, and reduced glomerular filtration, contributing to CIN susceptibility [26]. Similarly, diabetes accelerates renal injury through oxidative stress, endothelial dysfunction, and impaired microcirculation, further heightening the risk of CIN [26]. In our cohort, insulin-dependent diabetes was associated with a higher CIN incidence, aligning with previous studies. Additionally, infrapopliteal interventions were more common among patients who developed CIN. Possible reasons for this phenomenon could be as follow; first, infrapopliteal disease is often associated with more advanced stages of peripheral artery disease (PAD), where there may be greater microvascular impairment and reduced renal perfusion [27]. This could lead to a higher susceptibility to renal injury when exposed to

contrast media. Furthermore, the hemodynamic changes during and after endovascular procedures in the distal arterial territories may also play a role. Infrapopliteal interventions can sometimes cause more significant fluctuations in systemic blood pressure and renal perfusion, both of which can exacerbate renal injury when contrast is used. Finally, arterial calcification, which is frequently seen in patients with severe LEAD and especially in the infrapopliteal arteries, could contribute to endothelial dysfunction and impaired vascular response to contrast, thereby increasing the risk of CIN. This aspect has been suggested by studies in PAD populations, although the precise mechanism remains an area for further research [28].

Various previous studies have explored different scoring systems for predicting CIN development in endovascular interventions [29]. In our study, we assessed the predictive capabilities of the AGEF, ACEF, Tziakas, Yao, $CR_4EATME_3AD_3$, and Mehran scoring systems for CIN. Among the scoring systems analyzed, AGEF demonstrated the highest predictive accuracy for CIN in LEAD interventions. This score, which consists of just three parameters-age, eGFR, and EF is designed based on the principle of parsimony, allowing for straightforward application in clinical practice [5]. AGEF was originally developed to predict CIN risk in STEMI patients undergoing PCI, where it showed strong prognostic performance. In our study, AGEF not only retained its predictive strength in the LEAD population but also outperformed other scoring models, yielding an even higher prediction power. This superior performance may be attributable to the relevance of its three components, which are closely tied to the pathophysiology of CIN.

Age is a well-recognized risk factor for CIN, as aging is associated with structural and functional renal deterioration, reduced nephron count, and impaired renal autoregulation. Additionally, elderly patients often have a higher burden of comorbidities, including hypertension, diabetes, and cardiovascular disease, all of which contribute to CIN risk. Mehran et al. previously identified age over 75 as an independent predictor of CIN [9], a finding supported by our results. Renal function, reflected by eGFR, plays a pivotal role in CIN susceptibility. CKD is one of the strongest predictors of contrast-induced renal injury, as impaired kidneys are less capable of handling the hemodynamic and oxidative stress imposed by contrast agents. Multiple studies have demonstrated a steep rise in CIN incidence as eGFR falls below 60 mL/min/1.73 m^2 [5, 6, 29, 30]. In our cohort, lower eGFR was strongly associated with CIN development, reinforcing the utility of AGEF in identifying high-risk patients. EF, a measure of left ventricular systolic function, is another key determinant of CIN risk. Reduced EF is linked to systemic hypoperfusion, renal hypoxia, and heightened sympathetic activation, all of which contribute to renal dysfunction and increase the susceptibility to CIN. Additionally, patients with reduced EF often experience chronic congestion, leading to increased renal venous pressure, decreased renal perfusion, and a greater likelihood of contrast-related injury [31, 32]. Similarly, lower EF was associated with the CIN development in the current study. The inclusion of EF in the AGEF score provides a crucial dimension of risk assessment that many other CIN prediction models lack.

The practicality of AGEF lies in its simplicity and ease of use. Unlike more complex scoring systems that require numerous laboratory and clinical variables, AGEF relies on three routinely assessed parameters, making it highly accessible in real-world settings. Its strong predictive capability, combined with its ease of calculation, positions it as a valuable tool for risk stratification in patients undergoing LEAD interventions. Considering all these factors, the AGEF score may be a useful tool for clinicians in pre-evaluating patients undergoing peripheral procedures for CIN risk and, in appropriate cases, in planning preventive therapies, optimize contrast use, close follow-up and improve patient outcomes. Additionally, it may be useful for referring high-risk patients to safety procedure such as carbon dioxide angiography for CIN.

In conclusion, our study underscores the need for accurate CIN risk assessment in LEAD interventions. The AGEF score, with its strong predictive performance, offers a practical and reliable tool for risk stratification in this high-risk population. Further prospective studies are warranted to validate these findings and optimize preventive strategies for CIN in patients undergoing LEAD revascularization.

Conclusion

LEAD is a prevalent condition in society, and its treatment is crucial due to its associated morbidity and mortality. CIN poses a common and potentially life-threatening complication in interventions performed for LEAD. Predicting this prevalent complication is essential for implementing preventative measures in suitable patient groups. Our study underscores that various scoring systems can effectively estimate acute kidney injury, with AGEF exhibiting superior predictive abilities for CIN in patients with LEAD undergoing endovascular interventions.

Limitations

The main limitations of this study are that it is single center, the lack of external validation and retrospective and comprises a relatively small sample size. Additionally, other limitations of the study include the absence of long-term renal outcomes and the potential for unmeasured confounding in retrospective data. Morover, the core

institutional protocol for LEAD endovascular intervention and CIN prevention strategies remained consistent throughout the study period, minor changes — including the adoption of newer devices and gradual increases in operator experience — did occur. These factors may have had a limited, although unlikely substantial, impact on CIN incidence or the performance of the scoring systems. Further studies could develop a LEAD-dedicated CIN risk score, which can contribute to the prevention of frequent and ominous complications. Finally, our results are not validated in different hospitals or with different patient populations, which could include specific risk conditions based on epidemiological or geographical factors.

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None to declare.

Authors' contributions
D.I. developed the analysis plan and wrote the paper. I.A. ve T.O. undertook the data analysis. A.A., M.K., O.D., E.G. and O.K. collected the dataset and provided advice on its analysis. Y.K. and I.R. guided the analysis and made substantial improvements to the paper. All authors reviewed the manuscript. Finally, all authors read and approved the manuscript.

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Data availability
Data are from Kafkas University Health Research and Application Center and are not available to the public as it may compromise the privacy of research participants. Further enquiries can be directed to the corresponding author (D.I.) upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Research Ethics Committee of Kafkas University (Approval number 80576354-050-99/448). Since the study was a retrospective study, informed consent was waived by the Ethics Committee. This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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