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Predictive value of ACEF score for acute kidney injury after surgical aortic valve replacement

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ABSTRACT

Objectives: Aortic stenosis is the most common form of degenerative heart valve disease. Acute kidney injury (AKI) after aortic valve replacement (AVR) is a common complication and is related to worse outcomes. Age, creatinine, and ejection fraction (ACEF) score is a simple scoring method that includes three parameters. Our study aimed to evaluate whether ACEF score could predict the development of AKI in patients who underwent AVR.

Methods: A total of 366 consecutive patients who underwent isolated AVR for symptomatic severe aortic stenosis were evaluated retrospectively. The development of AKI was the primary endpoint of the study. The ACEF score was calculated by the formula: age (years)/left ventricular ejection fraction (%) +1 (if baseline serum creatinine was >2 mg/dL). According to the ACEF score the study population was divided into two groups.

Results: AKI was developed in 66 (18%) patients. The cut-off value of the ACEF score for the prediction of AKI was 1.07 with a sensitivity of 69.7% and a specificity of 56.7% (AUC 0.663; 95% CI: 0.589-0.736; P<0.001). AKI incidence was found to be higher in patients with high ACEF score than low ACEF score [46 (26.1%) vs. 20 (10.5%); P<0.001]. In addition, ACEF score [OR: 2.599; 95% CI: 1.399-4.828; P=0.002] and hemoglobin levels (OR: 0.837; 95% CI: 0.729-0.961; P=0.012) were found to be independent predictors of AKI.

Conclusions: Our study revealed that the ACEF score is an independent predictor of AKI. ACEF score, as a simple and objective score, can be useful in predicting AKI in patients undergoing AVR.

Keywords: Acute kidney injury, aortic stenosis, aortic valve replacement, predictors, ACEF score

Aortic stenosis (AS) is an ordinary valvular heart disease, mainly in older adults, and is the leading reason for surgical valve replacement therapy, especially in developing countries. The recent data on the beneficial outcome of aortic valve replacement (AVR) may expand the indication for aortic valve intervention to a wider population of severe AS [1]. Symptomatic AS is associated with significant mortality if untreated [2].

Acute kidney injury (AKI) is an increase in serum creatinine by 1.5 times and over within seven days compared to the baseline or an increase of 0.3 mg/dL and over within 48 hours following the procedure [3]. In cardiology clinical practice, contrast-induced

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nephropathy, a particular type of AKI, has been a focus of interest for clinicians. In this regard, there are many risk classifications and searches for risk factors in different patient groups. For example, it has been reported that osmolarity and positive and negative acute phase reactants are risk factors for AKI in patients with ST-segment elevation myocardial infarction (STEMI) [4, 5]. However, in such studies, the amount of contrast material has been identified as a risk factor in addition to other risk scales and scores. On the other hand, determining the risk factors of AKI that occur in the postoperative period in cardiac surgery patients without using any contrast material is an endeavor that will significantly benefit the literature. AKI due to cardiac surgery is a serious complication. AKI is characterized by increased volume burden, electrolyte instability, and the risk of need for renal replacement therapy. Furthermore, AKI causes higher overall mortality, increased length of hospital stay, and costs. AKI complicates nearly 16% of total hospitalizations due to AVR and is associated with increased mortality and morbidity [6]. This increases the need to identify prognostic factors that predict AKI in patients undergoing AVR.

Age, creatinine, and ejection fraction (ACEF) score include three parameters associated with a higher risk of mortality in patients after elective coronary artery bypass graft (CABG) surgery [7]. Studies have shown that ACEF score is a determinant of AKI in subjects undergoing mitral valve repair, CABG, and percutaneous coronary intervention (PCI) [8-10]. Previously, the ACEF score has been found to be a marker of AKI in patients with AS undergoing transcatheter aortic valve replacement (TAVR), but not yet in patients treated with surgery [11]. We evaluated the prognostic value of the ACEF score in the prediction of AKI in patients with isolated severe degenerative AS undergoing surgical aortic valve replacement (SAVR).

METHODS

Study Population

This retrospective study assessed 750 patients diagnosed with severe degenerative AS who underwent successful SAVR at a tertiary cardiovascular surgery center from January 2012 to December 2019. All subjects were assessed by a multidisciplinary cardiac team before the procedure. Our study was carried out according to the principles of the Declaration of Helsinki with the approval of the local ethics committee of Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital (Date: 12.04.2022, decision no: 2022.04.26).

Exclusion criteria for the study: Emergency surgery for acute aortic regurgitation and known coronary artery disease, PCI, previous or simultaneous CABG or heart valve replacement surgery outside the aortic valve, postoperative aortic incompatibility, type A aortic dissection, malignancy or end-stage liver disease, receiving dialysis treatment, death, and demographic medical records not available during or within 72 hours of the procedure. Patients with significant coronary artery disease were excluded, because, after surgical implantation, additional coronary ischemia may have an effect of worsening renal functions. After excluding these patients, a total of 366 technically successful cases were considered as the study population.

Echocardiography

The target population of our study was patients with severe aortic stenosis. Aortic stenosis was defined according to current data: (1) Mean transvalvular gradient higher than 40 mmHg and (2) Aortic valve area less than 1 cm^2 [12].

Procedural Details

SAVR was carried out via traditional full sternotomy, hemisternotomy or right anterior minithoracotomy, depending on the surgeon's preference [13]. Our surgeons commonly preferred the traditional full sternotomy approach. In all median sternotomy and hemisternotomy patients, traditional central cannulation techniques were used. In case the minimally invasive approach is selected, it involves a 6 to 9 cm skin incision for the upper hemisternotomy approach was made and at the level of the fourth intercostal space the sternum was transected horizontally. At SAVR, the patient was thoroughly heparinized and the ascending aorta was evaluated by epiaortic ultrasonography for safe cannulation. Antegrade and retrograde cardioplegia were given. If there was more than mild aortic regurgitation, an aortotomy was performed for direct ostial delivery.

Data Collection

Baseline characteristics (demographic data, comorbidities, hemodynamic variables, echocardiographic parameters, and serum laboratory values), operation details and postoperative results, intensive care and inpatient follow-up records were retrospectively reviewed. Before the procedure, the estimated glomerular filtration rate (eGFR) was calculated with the Cockroft-Gault formula [14]. We measured serum creatinine level (mg/dL) 24 hours before the process, presently after the process, and day-to-day until the discharge.

We calculated the ACEF score by the formula: ACEF= age/left ventricular ejection fraction (%) + 1 (if creatinine >2.0 mg/dL) [15]. We made the diagnosis and stage of AKI according to the standards suggested in the second consensus report disseminated by the Valve Academic Research Consortium (VARC-3) [3]. The creatinine levels before and after the procedure were compared and the diagnosis of AKI was defined as follows: (a) The absolute increase in creatinine level ≥0.5 mg/dL from baseline within 48 hours (may increase throughout up to seven days) and (b) Increase of creatinine levels 1.5 times when compared to the baseline.

VARC-3 score determines acute kidney injury in four different categories [3]. We determined the optimal ACEF score threshold for predicting AKI development and subsequently categorized the patients into groups based on their ACEF scores: high ACEF scores and low ACEF scores.

Study Endpoint

The ACEF score predicts Stage-1 AKI (VARC-3 criteria) in patients who have undergone SAVR. Stage-1 AKI is defined as an increase in serum creatinine by ≥ 150–200% (≥1.5–2.0 times) within seven days compared to the baseline or an increase of ≥0.3 mg/dL (≥26.4 μmol/L) within 48 hours following the procedure [3].

Statistical Analysis

Data analysis were performed using the Statistical Package for the Social Sciences, version 24.0 (SPSS Inc., Chicago, Illinois, USA). The distribution normality of the variables was evaluated using histograms, probability curves, and Kolmogorov-Smirnov test. Normally distributed numerical variables were expressed as mean [standard deviation (SD)]. Non-normally distributed numerical variables were expressed as median (interquartile range). Categorical variables were expressed as a percentage (%) and were compared by the chi-square or Fisher exact tests. We evaluated numerical variables using Student t-tests and the Mann-Whitney U-test. Covariates, including all baseline and procedural factors indicating significant P value in the univariable analysis, were included in a logistic regression analysis model to decide the predictive characteristics of the incidence of AKI. We employed receiver operating characteristic (ROC) curve analysis to identify the optimal ACEF cut-off value for accurate AKI prediction. Statistical significance was defined as a P value below 0.05.

RESULTS

The mean age of patients was 62±11 years, 121 (33.1%) patients were female. Baseline clinical, demographic, and laboratory variables were demonstrated in Table 1. Of the patients in our study, 49.5% (n=181) had NYHA class 3-4 dyspnea, 50.8% (n=186) presented with angina, and 11.7% experienced syncope attacks. The baseline creatinine level was 0.83 (0.7-1.0) mg/dL, the postoperative 72nd hour creatinine level was 1.0 (0.8-1.4) mg/dL, and the mean ejection fraction was 57±8%. We detected acute kidney injury in 66 (18%) patients. We performed ROC analysis to determine the predictive value of ACEF score in predicting AKI in postoperative AVR patients. In ROC curve analysis, the curve intersected at 1.07, where the combined sensitivity and specificity values were highest (sensitivity: 69.7%; specificity: 56.7%). The area under the curve measured 0.663 (95% confidence interval (CI): 0.589-0.736, P<0.001) (Fig.1). Based on the ACEF cut-off value, the study population was categorized into two groups: Group 1 consisted of 190 patients with ACEF≤1.07, and Group 2 included 176 patients with ACEF>1.07. Baseline clinical, demographic, and laboratory variables were also demonstrated in Table 1. The mean age was higher in Group 2 (54±7 vs. 71±9 years; P<0.001). The incidence of angina was higher in Group 1 [108 (56.8%) vs. 78 (44.3%); P=0.017]. Hemoglobin level was lower in Group 2 [13.9 (12.4-15.1) vs. 12.1 (11.2-13.8) g/dL; P<0.001]. The baseline creatinine [0.8 (0.7-0.9)

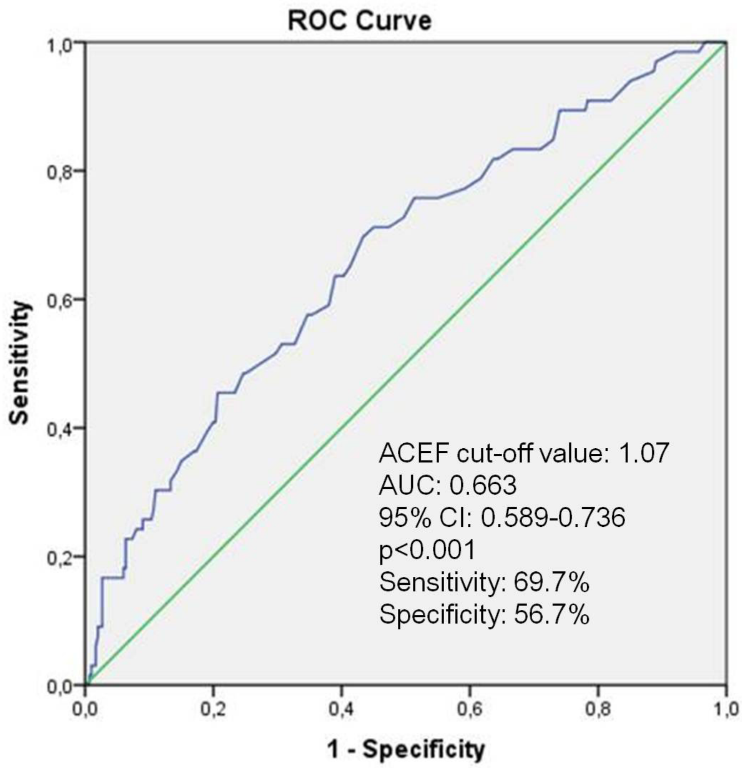

Fig. 1. Receiver operating characteristic curve showing the optimal ACEF score cut-off value to indicate acute kidney injury. ACEF=Age, creatinin, ejection fraction, AUC=Area under the curve, CI=Confidence interval, ROC=Receiver operating characteristic.

vs. 0.9 (0.8-1.1) mg/dL; P<0.001] and postoperative 72nd hour creatinine [0.9 (0.78-1.11) vs. 1.2 (0.93-1.54) mg/dL; P<0.001] were higher in Group 2. The incidence of AKI was also higher in Group 2 [20 (10.5%) vs. 46 (26.1%); P<0.001]. The incidences of diabetes mellitus [33 (17.4%) vs. 52 (29.5%); P=0.006], hypertension [68 (35.8%) vs. 108 (61.4%); P<0.001], chronic obstructive pulmonary disease [15 (7.9%) vs. 38 (21.6%); P<0.001] and peripheral artery disease [2 (1.1%) vs. 8 (4.5%); P=0.040] were higher in Group 2. The ejection fraction was lower in Group 2 (61±4% vs. 54±11%; P<0.001). Left atrium size [38 (34-41) mm vs. 41 (37-45) mm; P<0.001] and aortic valve maximal gradient [75 (65-87) mmHg vs. 78 (66-90) mmHg; P=0.048] were higher in Group 2.

We performed logistic regression, incorporating significant variables identified in the univariate analysis (Table 2). The results of the multivariate logistic regression analysis revealed that a higher ACEF score (Odds ratio (OR): 2.812; 95%CI: 1.343-4.906; P<0.001), higher leukocyte counts (OR: 1.089; 95% CI: 1.014-1.216; P=0.036) and lower hemoglobin levels (OR: 0.802; 95% CI: 0.706-0.954; P=0.002) independently served as predictors for AKI. Variables such as diabetes, hypertension, chronic obstructive pulmonary disease, peripheral arterial disease, left atrial width, and maximal gradient of the aortic valve, which we found significant differences between ACEF groups, did not significantly affect the risk of AKI development in logistic regression analysis.

DISCUSSION

We investigated the impact of the ACEF score on predicting AKI development in patients undergoing SAVR. The incidence of AKI development after SAVR was found to be higher in patients with high ACEF scores. The ACEF score independently predicted AKI in patients undergoing SAVR.

AKI is a significant post-cardiac surgery complication, with reported incidences varying from 9% to 43%. It is linked to increased mortality rates and a heightened risk of in-hospital morbidity [16, 17]. The

Table 1. **Baseline clinical, demographic, and laboratory variables**

	All patients (n=366)	ACEF ≤1.07 (n=190)	ACEF >1.07 (n=176)	P value
Age (years)	62±11	54±7	71±9	**<0.001**
Female, n (%)	121 (33.1)	56 (29.5)	65 (36.9)	0.130
Dispne, n (%)				
NYHA Class 1-2, n (%)	185 (50.5)	99 (52.1)	86 (48.9)	0.535
NYHA Class 3-4, n (%)	181 (49.5)	91 (47.9)	90 (51.1)	
Angina, n (%)	186 (50.8)	108 (56.8)	78 (44.3)	**0.017**
Syncope, n (%)	43 (11.7)	26 (13.7)	17 (9.7)	0.232
Hemoglobin (g/dL)	13.2 (11.5-14.7)	13.9 (12.4-15.1)	12.1 (11.2-13.8)	**<0.001**
Platelet (10^3/uL)	229.5 (189.75-276.25)	236 (193-278)	221 (186-275)	0.266
Leukocytes (× 10^3/mm^3)	7.9 (6.6-9.4)	8 (6.89-9.5)	7.9 (6.5-9.35)	0.376
Bazalcreatinine (mg/dL)	0.83 (0.7-1.0)	0.8 (0.7-0.9)	0.9 (0.8-1.1)	**<0.001**
GFR (mL/min/1.73 m^2)	90±25	103±21	77±20	**<0.001**
Postoperative creatinine (mg/dL) (72^{nd} h)	1.0 (0.8-1.4)	0.9 (0.78-1.11)	1.2 (0.93-1.54)	**<0.001**
Acute kidney injury, n (%)	66 (18.0)	20 (10.5)	46 (26.1)	**<0.001**
Total cholesterol (mg/dL)	175.5 (149.75-211.25)	177 (147-215)	175 (154-207)	0.920
LDL-C (mg/dL)	104 (81-132)	102 (79-135)	104.5 (83-128)	0.737
HDL-C (mg/dL)	42.5 (35-51)	43 (36-50)	42 (34-52)	1.000
Triglyceride (mg/dL)	120 (91.75-174.25)	120 (93-179)	122.5 (89-162)	0.598
Diabetes mellitus, n (%)	85 (23.2)	33 (17.4)	52 (29.5)	**0.006**
Hypertension, n (%)	176 (48.1)	68 (35.8)	108 (61.4)	**<0.001**
COPD, n (%)	53 (14.5)	15 (7.9)	38 (21.6)	**<0.001**
Cerebrovascular disease, n (%)	0 (0)	0 (0)	0 (0)	
Peripheral artery disease, n (%)	10 (2.7)	2 (1.1)	8 (4.5)	**0.040**
Smoking, n (%)	92 (25.1)	55 (58.9)	37 (21.0)	0.081
Atrial fibrillation, n (%)	30 (8.2)	12 (6.3)	18 (10.2)	0.173
Ejection fraction, (%)	57±8	61±4	54±11	**<0.001**
LVEDD (mm)	49 (45-56)	50 (46-55)	49 (45-57)	0.833
LVESD (mm)	32 (28-38)	32 (28-37)	32 (28-41)	0.162
LA (mm)	40 (35-43)	38 (34-41)	41 (37-45)	**<0.001**
Maximum gradient, (mmHg)	76 (65-89)	75 (65-87)	78 (66-90)	**0.048**
Mean gradient, (mmHg)	50 (43-56)	48 (43-55)	51 (44-58)	0.128
Aortic valve area, (cm^2)	0.67±0.11	0.66±0.11	0.68±0.12	0.178

Data are presented as a percentage, mean±standard deviation, or median (interquartile range). ACEF=Age, creatinin, ejection fraction, COPD=chronic obstructive pulmonary disease, GFR=glomerular filtration rate, HDL-C=High-density lipoprotein cholesterol, LA=Left atrium, LDL-C=Low-density lipoprotein cholesterol, LVEDD=Left ventricular end-diastolic diameter, LVESD=Left ventricular end-systolic diameter, NYHA=New York Heart Association.

Table 2. Univariable and multivariable logistic regression analysis for independent predictors of acute kidney injury

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
Gender	1.394	0.771-2.520	0.271			
Diabetes mellitus	1.152	0.603-2.200	0.669			
ACEF	3.008	1.697-5.332	**<0.001**	2.812	1.343-4.906	**<0.001**
Hemoglobin	0.789	0.694-0.897	**<0.001**	0.802	0.706-0.954	**0.002**
Leukocytes	1.107	1.012-1.211	**0.026**	1.089	1.014-1.216	**0.036**
Hypertension	1.593	0.930-2.729	0.090			

ACEF=Age, creatinin, ejection fraction, CI=Confidence interval

occurrence of AKI increases the postoperative mortality in patients requiring dialysis, exceeding 40% or even reaching 50% in series, compared to the 0.6-2% mortality rate in patients without AKI [18]. Minor changes in serum creatinine were associated with negative outcomes [19]. Compared with CABG, it is an independent risk factor with a 2.7-fold increased risk for AKI in valve surgery [20]. The kidney has the most heightened tissue perfusion rate close to body organ weight, making it sensitive to hemodynamic injury. Cellular ischemia is an important cause of AKI in AVR. This ischemia can cause tubular epithelial damage, vascular endothelial activation, and injury. Many preoperative, intraoperative, and postoperative factors, especially perioperative renal hypoperfusion, prepare the way for this injury. Many procedural factors have been associated with AKI during AVR, such as perioperative anemia, erythrocyte transfusion, and cardiopulmonary bypass. In SAVR, cardiopulmonary bypass is thought to play an essential role in developing AKI with two mechanisms: hemodilution and hypotension. Hemodilution causes a general inflammatory state. Hypotension results from low pressures and flow rates [21].

The ACEF score is easily applicable. Firstly, Ranucci *et al*. [7] revealed the association of ACEF with mortality in elective heart surgeries. Studies have shown that ACEF score was a strong predictor for AKI in patients who underwent PCI after STEMI [22]. The ACEF score has been recognized as a straightforward tool with sufficient capability to identify patients at risk for all stages of AKI following mitral valve repair [8]. Uygur *et al*. [11] reported a strong relationship between ACEF and AKI in severe AS patients who underwent TAVR. The ACEF score, in conjunction with other factors, demonstrated its reliability in predicting mortality among patients undergoing AVR [23].

In a study involving 2169 patients who underwent AVR, Najjar *et al*. [21] revealed that increasing age and preoperative creatinine levels increased the development of AKI, and this was supported by other studies [24]. In the study by Grayson *et al*. [20], valvular surgeries and preoperative creatinine levels were distinct risk factors independently associated with AKI development. Heart failure was stated as one of the most important perioperative risk factors for AKI. Hertzberg *et al*. [25] evaluated 36,403 patients after cardiac surgery and found that heart failure was an independent predictor of AKI. In patients undergoing AVR, proven by clinical studies, these three basal clinical variables are independent risk factors for postoperative AKI. These parameters are not only risk factors for the development of AKI but also interacting parameters. The process leading to AKI in postoperative AVR patients is not a simple process due to changing a single parameter. It is an outcome achieved by the joint interaction of mechanisms such as inflammation, hemodilution, and hypotension [21]. Therefore, it would be misleading to evaluate the development of AKI in postoperative AVR patients by measuring a single parameter. ACEF score offers us the chance to combine analysis of variables previously proven to be risk factors for AKI development in this patient group by clinical studies. Thus, with these three important parameters, we have a better chance to make more accurate predictions for the prediction of AKI development in postoperative AVR patients. Evaluating these parameters separately may result in under-evaluation of the AKI process. Hence, incorporating various parameters enhances the precision of risk models.

ACEF score offers notable benefits regarding straightforward accessibility and rapid, uncomplicated calculation. Our study corroborates existing literature by revealing significantly lower hemoglobin levels in the AKI-developing group. Furthermore, low hemoglobin levels emerged as an independent predictor of AKI. Callejas *et al*. [26] revealed in a multicenter prospective study that peri-procedural anemia was an independent predictor for AKI. In our study, we adhered to the original version of the ACEF score. But this result is promising that the ACEF score can be modified in the future, and thus its diagnostic power can be further increased.

ACEF score was demonstrated to be useful in various patient groups, however, it has not been applied to the patients who underwent cardiac surgery. Our objective was to assess the utility of ACEF score in predicting AKI among patients who underwent a major cardiac surgery, specifically surgical aortic replacement, and it has proven to be effective. If we try to adapt these results to our clinical practice: (i) In older patients with low ejection fraction, even if their renal functions are normal; (ii) In patients older than 1.07 times the ejection fraction (e.g., a patient with an ejection fraction of 60% would be over 64 years of age), we recommend that renal protective measures be taken, as in patients with pre-SAVR renal dysfunction.

Limitations

Our retrospective study was conducted at a single center and involved a relatively modest patient cohort. Consequently, it is imperative to conduct comprehensive prospective cohort investigations to validate and substantiate our findings. Additionally, it should be noted that we were unable to calculate the STS (Society of Thoracic Surgeons) score and EuroSCORE II (European System for Cardiac Operative Risk Evaluation II) for this group due to data unavailability. Thus, we could not compare the effectiveness of predicting AKI by using three different methods. Not least of all, this majority of the patient group consists of female patients, gender variance may have an additional effect on results. Further trials are needed to determine the long-term efficacy of ACEF score in mortality and second endpoints, including long-term renal insufficiency, in this patient group.

CONCLUSION

Our study illustrates the effectiveness of the pre-procedural ACEF score in predicting acute kidney injury in patients undergoing surgical aortic valve replacement. Patients with higher ACEF scores may require additional renal function precautions compared to patients with lower ACEF scores.

Authors' Contribution

Study Conception: GD, ARD, SK; Study Design: GD, ARD, SK; Supervision: GD, ARD, SK; Funding: N/A; Materials: N/A; Data Collection and/or Processing: GD, ARD, SK; Statistical Analysis and/or Data Interpretation: GD, ARD, SK; Literature Review: GD, ARD, SK, SÇ, EY; Manuscript Preparation: GD, ARD, SK, SÇ, EY and Critical Review: GD, ARD, SK, SÇ, EY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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