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High-sensitivity cardiac troponin I and D-dimer are risk factors for in-hospital mortality of adult patients with COVID-19: A retrospective cohort study

COVID-19 tanılı yetişkinlerde yüksek duyarlıklı kardiyak troponin I ve D-dimer hastane içi mortalite için risk faktörleridir: Retrospektif kohort çalışması

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ABSTRACT

Aim: This study aimed to evaluate the impact of high-sensitivity cardiac troponin I (Hs-cTnI) and D-dimer on in-hospital mortality of adult patients with Coronavirus disease 2019 (COVID-19).

Materials and Methods: The COVID-19 outbreak, a global health disaster, has resulted in significant morbidity and mortality around the world since it emerged in December 2019. The outbreak has gradually spread nationwide. COVID-19 is associated with hemostatic abnormalities and cardiac injury. This retrospective cohort study included a total of 221 adult inpatients. The diagnosis of COVID-19 was made according to the World Health Organization's interim guideline and confirmed by RNA detection of SARS-CoV-2. Participants were divided into 2 groups, survivors and non-survivors.

Results: Hs-cTnI and D-dimer levels on admission were significantly higher in non-survivors COVID-19 patients ($p<0.05$ for each). Forward stepwise logistic regression analysis demonstrated that age (OR=1.140, 95% CI: 1.045-1.244, p=0.003), baseline hs-cTnI level (OR=1.022, 95% CI: 1.004-1.041, p=0.018), and baseline D-dimer level (OR=1.790, 95% CI: 1.078-2.972, p=0.024) were independent predictors of in-hospital mortality of adult patients with COVID-19. The receiver operating characteristic curve analysis provided a cut-off value of >18.6 ng/L for hs-cTnI to predict in-hospital mortality of adult patients with COVID-19 with 100% sensitivity and 74% specificity, and a cut-off value of > 1.41 mg/L for D-dimer with 93.3% sensitivity and 71.5% specificity.

Conclusion: High-sensitivity cardiac troponin I and D-dimer levels on admission predict in-hospital mortality of adult patients with COVID-19.

Keywords: SARS-CoV-2, cardiac troponin I, D-dimer, COVID-19, mortality.

ÖZ

***Amaç:** Bu çalışmada, yüksek duyarlıklı kardiyak troponin I (Hs-cTnI) ve D-dimerin, Koronavirus hastalığı 2019 (COVID-19) olan yetişkin hastaların hastane içi mortalite üzerine etkisinin değerlendirilmesi amaçlamıştır.*

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Gereç ve Yöntem: *Küresel bir sağlık felaketi olan COVID-19 salgını, Aralık 2019'da ortaya çıktığından bu yana dünya çapında önemli morbidite ve mortaliteyle sonuçlanarak yavaş yavaş ülke çapında yayıldı. COVID-19 hemostatik anormallikler ve kardiyak hasar ile ilişkilidir. Bu retrospektif kohort çalışmasına toplam 221 yetişkin hasta dahil edilmiştir. COVID-19 tanısı, Dünya Sağlık Örgütü'nün geçici rehberlerine göre konuldu ve SARS-CoV-2' nin RNA tespiti ile doğrulandı. Hastalar sağ kalanlar ve sağ kalımı olmayanlar olarak 2 grupta incelendi.*

Bulgular: *Başvuru esnasındaki hs-cTnI ve d-dimer düzeyleri sağ kalımı olmayan CoVID-19 hastalarında anlamlı olarak daha yüksekti (her biri için p<0.005). Lojistik regresyon analizinde; yaş (OR=1.140, %95 CI: 1.045-1.244, p=0.003), bazal hs-cTnI (OR=1.022, %95 CI: 1.004-1.041, p=0.018) ve bazal d-dimer (OR=1.790, %95 CI: 1.078-2.972, p=0.024) düzeyleri COVID-19 hastalarında hastane-içi mortalitenin bağımsız prediktörleri olarak tespit edildi. Hastane-içi mortaliteyi öngörmede hs-cTnI için %100 duyarlılık ve %74 özgüllükle 18.6 ng/L kestirim değeri tespit edilirken; d-dimer için %93,3 duyarlılık ve %71,5 özgüllükle 1,41 mg/L kestirim değeri saptandı.*

Sonuç: *Başvuru sırasındaki hs-cTnI ve d-dimer düzeyleri COVID-19 tanısı alan yetişkin hastalarda hastane-içi mortaliteyi öngörmektedir.*

Anahtar Sözcükler: *SARS-CoV-2, kardiyak troponin I, D-dimer, COVID-19, mortalite.*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1], which was first reported in December 2019[1] and has turned into a COVID-19 pandemic, spreading rapidly worldwide. At present, new confirmed cases and deaths caused by COVID-19 still have increased day-by-day around the world. Therefore, the World Health Organization has officially declared a public emergency of international concern. Risk stratification in such pandemics is extremely essential. Thus, in patients with COVID-19, timely and effective predictors of clinical outcomes are immediately needed for risk stratification.

Although SARS-CoV-2 mainly causes pneumonia, acute respiratory distress syndrome (2), cardiac injury (3-7), venous thromboembolism, and arterial thrombosis (8) were reported as complications of COVID-19. In approximately 90% of inpatients with pneumonia, coagulation activity increases markedly with increasing D-dimer concentrations (9). In addition, the association of coronary artery disease with acute cardiac events and poor outcomes was reported for patients with influenza and other respiratory viral infections (10-12). It has been reported that COVID-19 was associated with cardiac injury and hemostatic abnormalities, and that significantly elevated D-dimer and high-sensitivity cardiac troponin I (hs-cTnI) levels were associated with poor outcome (13, 14). The present study aimed to assess the impact of hs-cTnI and D-dimer on mortality of adult inpatients with COVID-19.

MATERIALS and METHODS

Study Population and Design

This retrospective cohort study included a total of hospitalized 221 adult patients. The diagnosis of COVID-19 was made according to the World Health Organization's temporary guideline and was confirmed by RNA detection of SARS-CoV-2. Hospitalization was planned according to the following criteria determined by the Republic of Turkey Ministry of Health;

»Mild-moderate pneumonia with respiratory rate ≥24 and SpO2 ≤93%

»Mild-moderate pneumonia (blood lymphocyte count <800 / µl or serum CRP> 10 x Upper limit of normal value or ferritin> 500ng / ml or D-dimer > 1000 ng / ml, etc.)

»Severe pneumonia (changes in consciousness, respiratory distress, respiratory minutes ≥ 30, SpO2 90% in room air, bilateral diffuse (> 50%) involvement in lung imaging)

»Hypotension (<90/60 mmHg, mean blood pressure <65 mmHg), tachycardia (> 100)

»Sepsis, septic shock,

»Myocarditis, acute coronary syndrome, arrhythmia, and

»Acute kidney injury

All participants diagnosed with COVID-19 were screened, and those who died or were discharged between March 10, 2019, and May10, 2020, were enrolled in the present study. Patients were divided into 2 groups, survivors and non-survivors. The study was conducted following the Declaration of Helsinki and was approved by Çukurova University Medical Faculty Ethics

Committee (99/2020). The need for written informed consent was waived due to the retrospective nature of the study.

Data Collection

Demographic, epidemiological, laboratory, clinical, treatment, and outcome data were obtained from an electronic medical record system, utilizing admission numbers that were unique to each patient. All data were checked by three physicians (GA, AQ, and HH) and a fourth researcher (AQ) adjudicated any difference in interpretation between the three primary reviewers. Mortality outcomes were followed up to May20, 2020.

Laboratory Procedures

RNA detection of SARS-CoV-2 in respiratory specimens was carried out by real-time PCR methods. The criteria for discharge were the absence of fever for at least 3 days, substantial improvement in both lungs in chest computed tomography, clinical remission of respiratory symptoms, and one throat-swab sample negative for SARS-CoV-2 RNA. Blood examinations were complete blood count, serum biochemical tests, D-dimer, and myocardial enzymes. Chest radiographs and computed tomography scans were done for all participants.

STATISTICAL ANALYSIS

Data analyses were performed using SPSS version 22.0 statistical software package (SPSS Inc., Chicago, IL, USA) and MedCalc statistical software v19.5.6 (Ostend, Belgium). Assessment of distribution was carried out using an analytical (Kolmogorov–Smirnov test) method and visual methods (histograms and probability plots). Continuous variables were expressed as mean ± standard deviation or median (minimum-maximum). Categorical variables were expressed as number (percentage). The independent samples t-test or Mann–Whitney U-test was used to compare continuous variables, as appropriate. The Chi-square test or Fisher's exact test was used to compare categorical variables. All significant parameters with a p value of < 0,1 in the univariate analysis were included in the multivariable model and a forward stepwise logistic regression analysis was used to determine the independent predictors of in-hospital mortality of adult patients with COVID-19. The odds ratio and 95% confidence interval of each independent variable were calculated. A receiver operating characteristic (ROC) curve analysis was carried out to identify the optimal cut-off level of D-dimer and hs-cTnI for predicting in-hospital mortality. The area under the curve (AUC) comparison of these predictors was performed using the DeLong method. Youden index method was utilized to establish values of independent predictors. A two-tailed p-value of less than 0.05 was considered significant.

RESULTS

A total of 221 hospitalized COVID-19 patients were enrolled in this retrospective cohort study for the final analysis. 53 patients died during hospitalization and 168 were discharged.

The mean age of the 221 patients was 60.4 ± 15.5 and 40.7% of the patients were male. Comorbidities were present in almost half of the patients, with hypertension being the most common comorbidity, followed by diabetes mellitus and coronary artery disease. The most common symptom of admission was fever, followed by cough, dyspnea, and fatigue. Leukocyte count, glucose, C-reactive protein, lactate dehydrogenase, hs-cTnI, and D-dimer levels on admission were significantly higher in non-survivors COVID-19 patients. The Comparison of demographic, clinical, laboratory, radiographic, and treatment characteristics of COVID-19 patients according to in-hospital mortality is shown in Table-1.

Forward stepwise logistic regression analysis was carried out to determine the independent predictors of in-hospital mortality. The analysis demonstrated that age (OR=1.140, 95 % CI: 1.045-1.244, p=0.003), baseline hs-cTnI level (OR=1.022, 95 % CI: 1.004-1.041, p=0.018), and baseline D-dimer level (OR=1.790, 95 % CI: 1.078-2.972, p=0.024) were independent predictors of in-hospital mortality of adult patients with COVID-19 (Table-2).

The ROC curve analysis provided a cut-off value of >18.6 ng/L for hs-cTnI to predict in-hospital mortality of COVID-19 patients with 100 % sensitivity and 74.04 % specificity, with the area under the curve being 0.919 (95% CI: 0.872-0.965, p<0.001). Also, a cut-off value of > 1.41 mg/L for D-dimer to predict in-hospital with 93.33 % sensitivity and 71.54 % specificity, with the area under the curve being 0.878 (95% CI: 0.828-0.927, p<0.001) was obtained. In the results of pairwise comparisons of the ROC curves, there was no significant difference (p=0.108) (Figure-1a-1b).

Table-1. Comparison of demographic, clinical, laboratory, radiographic and treatment characteristics of COVID-19 patients according to in-hospital mortality.

Variable	Total (n=221)	Survivor (n=168)	Non-survivor (n=53)	p-value
Demographic and clinical characteristics				
Age (year)	60.4 ± 15.5	57.6 ± 15.8	69.3 ± 10.7	**<0.001***
Gender, (male) n (%)	90 (40.7)	69 (41.1)	21 (39.6)	0.852
BMI (kg/m^2)	28.7 ± 5.0	28.6 ± 4.9	30.3 ± 6.8	0.413
Current smoker, n (%)	70 (31.7)	51 (30.4)	19 (35.8)	0.454
Durations of hospitalization (day)	8 (1-22)	8 (2-17)	7 (1-22)	0.656
Comorbidity				
DM, n (%)	79 (35.7)	59 (35.1)	20 (37.7)	0.729
HLP, n (%)	52 (23.5)	36 (21.4)	16 (30.2)	0.190
HT, n (%)	102 (46.2)	72 (42.9)	30 (56.6)	0.080
CAD, n (%)	54 (24.4)	32 (19.0)	22 (41.5)	**0.001***
HF, n (%)	20 (9.0)	13 (7.7)	7 (13.2)	0.271
COPD, n (%)	21 (9.5)	18 (10.7)	13 (24.5)	**0.012***
Stroke, n (%)	12 (5.4)	10 (6.0)	2 (3.8)	0.735
Symptom				
Fever (temperature ≥ 37,3 °C), n (%)	192 (86.9)	145 (86.3)	47 (88.7)	
Cough, n (%)	174 (78.7)	132 (78.6)	42 (79.2)	
Dyspnea, n (%)	150 (67.9)	111 (66.1)	39 (73.6)	0.636
Fatigue, n (%)	60 (27.1)	45 (26.8)	15 (28.3)	
Diarrhea, n (%)	10 (4.5)	8 (4.8)	2 (3.8)	
Laboratory Findings				
Hemoglobin (g/L)	132 (92-178)	135 (92-174)	129 (99-178)	0.329
Leukocyte count, x10^3/uL	9.1 ± 6.3	7.4 ± 3.6	14.4 ± 9.3	**<0.001***
Platelet count, x10^3/uL	229.5 ± 105.2	232.0 ± 98.1	221.5 ± 125.5	0.539
Glucose (mmol/L)	8.8 ± 5.3	7.9 ± 3.9	11.7 ± 7.9	**<0.001***
GFR (mL/min per 1.73 m2)	95.0 (70.0-99.0)	95.0 (70.0-99.0)	95 (87.0-98.0)	0.569
CRP (nmol/L)	1066.7 ± 876.2	830.5 ± 764.8	1810.0 ± 811.5	**<0.001***
LDH (nmol/L)	5216.7 (2100.0-10450.0)	5050.0 (2633.3-10266.7)	7050.0 (2100.0-10450.0)	**<0.001***
Hs-cTnI (ng/L)	12.0 (1.4-236.0)	7.0 (1.4-154.0)	77.5 (20.0-236.0)	**<0.001***
D-dimer (mg/L)	1.29 (0.01-9.58)	0.90 (0.01-5.24)	3.37 (1.12-9.58)	**<0.001***
Imaging Features				
No features, n (%)	6 (2.7)	6 (3.6)	0 (0.0)	
Consolidation, n (%)	31 (14.0)	29 (17.3)	2 (3.8)	
Ground-glass opacity, n (%)	86 (38.9)	68 (40.5)	18 (34.0)	**<0.001***
Infiltration, n (%)	23 (10.4)	21 (12.5)	2 (3.8)	
Pleural effusion, n (%)	21 (9.5)	4 (2.4)	17 (32.1)	
Mixed features, n (%)	54 (24.4)	40 (23.8)	14 (26.4)	
Lymphadenopathy, n (%)	59 (26.7)	39 (23.2)	20 (37.7)	**0.049***
Treatments				
Antibiotic treatment, n (%)	203 (91.9)	152 (90.5)	51 (96.2)	1.000
Antiviral treatment, n (%)	218 (98.6)	165 (98.2)	53 (100.0)	1.000
Hydroxychloroquine use, n (%)	221 (100.0)	168 (100.0)	53 (100.0)	-
Invasive mechanical ventilation, n (%)	99 (44.8)	48 (28.6)	51 (96.2)	**<0.001***

Data are presented as number (%), mean ± standard deviation or median (minimum-maximum).
*p-value was calculated using the Independent Samples t-test or the Mann-Whitney U-test for continuous variables and the Chi-Square test or the Fisher's exact test for categorical variables as appropriate. p value < 0.05 was considered significant.
BMI: Body mass index, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CRP: C-reactive protein, DM: Diabetes mellitus, GFR: Glomerular filtration rate, HF: Heart failure, HLP: Hyperlipidemia, Hs-cTnI: High sensitivity cardiac troponin I, HT: Hypertension, LDH: Lactate dehydrogenase

Table-2. Risk factors associated with in-hospital mortality in COVID-19 patients.

Variable	Univariate Analysis		Multivariate Analysis	
	OR (95 % CI)	**p-value**	**OR (95 % CI)**	**p-value**
Age (year)	1.061 (1.034-1.088)	**<0.001***	1.140 (1.045-1.244)	**0.003***
Oxygen saturation (%)	0.946 (0.916-0.977)	**0.001***	-	**-**
HLP, n (%)	1.586 (0.793-3.170)	0.192	-	-
HT, n (%)	1.739 (0.933-3.243)	0.082	-	-
CAD, n (%)	3.016 (1.546-5.885)	**0.001***	-	-
COPD, n (%)	2.708 (1.224-5.992)	**0.014***	-	-
Leukocyte count, $x10^3$/uL	1.230 (1.145-1.320)	**<0.001***	-	-
Glucose (mg/dL)	1.007 (1.003-1.010)	**<0.001***	-	-
CRP (mg/L)	1.013 (1.009-1.017)	**<0.001***	-	-
LDH (U/L)	1.007 (1.003-1.010)	**<0.001***	-	-
Hs-cTnI (ng/L)	1.032 (1.020-1.045)	**<0.001***	1.022 (1.004-1.041)	**0.018***
D-dimer (mg/L)	2.158 (1.680-2.771)	**<0.001***	1.790 (1.078-2.972)	**0.024***

*p-value < 0.05 was considered significant.

CAD: Coronary artery disease, CI: Confidence interval, COPD: Chronic obstructive pulmonary disease, CRP: C-reactive protein, HLP: Hyperlipidemia, Hs-cTnI: High sensitivity cardiac troponin I, HT: Hypertension, LDH: Lactate dehydrogenase, OR: Odds ratio.

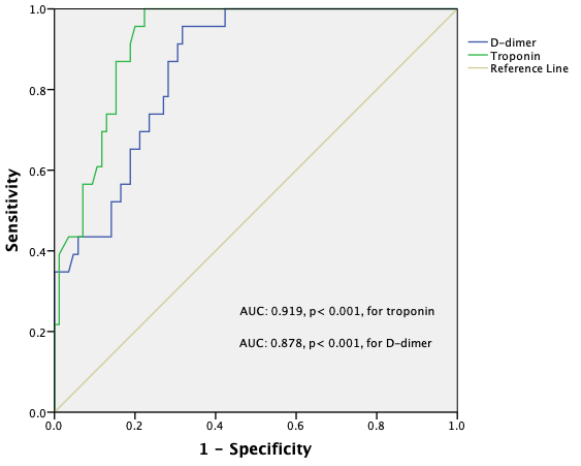

Figure-1a. Receiver operating characteristic (ROC) curve of D-dimer, and troponin for predicting in-hospital mortality (AUC: area under the curve, SE: standard error, 95% CI: 95% confidence interval) and pairwise comparison of ROC curves.

Variable	AUC	SE [a]	95% CI [b]	p value
D-dimer	0.878	0.0253	0.828 to 0.927	<0.001
Hs-cTnI	0.919	0.0238	0.872 to 0.965	<0.001

[a] DeLong et al., 1988. [b] Binomial exact.

	D-dimer (mg/dL)	**Hs-cTnI (ng/L)**
Sensitivity, %	93.33	100
Specificity, %	71.54	74.04
Youden index	0.6487	0.7404
Cut-off value*	1.41	18.6

* Cut-off values were determined from the Youden index.

Figure-1b. Pairwise comparison of ROC curves.

D-dimer ~ Hs-cTnI	
Difference between areas	0.0627
Standard Error [a]	0.0390
95% Confidence Interval	-0.0138 to 0.139
Z statistic	1.607
Significance level	P = 0.1081

[a] DeLong et al., 1988

DISCUSSION

This retrospective cohort study described certain risk factors for death in adult hospitalized patients with COVID-19 in Turkey. The major findings of our study identify that older age, hs-cTnI, and D-dimer levels on admission were associated with higher in-hospital mortality. Additionally, cut-off

values of 18.6 ng/L for hs-cTnI and 1.41 mg/L for D-dimer to predict in-hospital mortality of COVID-19 patients were well established.

Previously, advanced age has been reported as a significant independent predictor of mortality in viral infections, including severe acute respiratory syndrome (15), middle east respiratory syndrome (16-19), and COVID-19 (14, 20, 21). Our study verified that older age was associated with mortality in patients with COVID-19. The potential underlying pathophysiological mechanism of these findings may refer to altered immune responses in elderly individuals. With aging, changes occur in immunity (22, 23). As a result, the aged people are at greater risk of sustaining more severe and more durable infections with increased morbidity and mortality, such as respiratory tract infections (24). Smits et al. (25), investigated macaques inoculated with SARS-CoV and revealed that older macaques had stronger host innate responses to virus infection than younger ones, with an increase in differential expression of genes associated with inflammation, while decreased expression of type I interferon beta. Furthermore, the age-dependent defects in cellular components of the adaptive immune response and the excess production of type 2 cytokines could lead to a lack of control of viral replication and more prolonged proinflammatory responses, probably causing adverse outcome (26).

Several studies have reported a substantial association between pneumonia and cardiovascular complications (10, 27, 28). These complications have clinical implications because they can trigger acute cardiorespiratory decompensation and substantially increase risk (29, 30). Elevated troponin levels are not only associated with acute respiratory infections and sepsis but could also be used as a marker of disease severity and predicts probable cardiac events (31). Previous studies have demonstrated that up to 30% of patients with COVID-19 presented elevated cardiac troponin levels reflecting cardiac injury (2, 14, 32). In contrast to patients with normal values, individuals with elevated troponin were advanced age, had significantly higher proportion of comorbidities, including coronary artery disease, hypertension, and diabetes mellitus (32), and showed higher in-hospital mortality (14, 32) The present study confirmed that hs-cTnI level on admission was significantly higher in non-survivor COVID-19 patients and were also associated with higher rates of in-hospital mortality. Possible pathophysiology of myocardial damage in COVID-19 involve microangiopathy, viral myocarditis, unmasked coronary artery disease, and cytokine-related myocardial injury (33). However, so far, it has not been proven whether any of these mechanisms are the main mechanism of troponin elevation and / or heart damage in COVID-19 patients.

Reported to be one of the laboratory findings of hospitalized COVID-19 patients, D-dimer reflects the activation of coagulation and fibrinolysis due to cross-linked fibrin formation and lysis (34). It has been indicated that COVID-19 was correlated with hemostatic abnormalities and, that the association of markedly elevated D-dimer with adverse outcome and mortality (13, 14). Guan et al. (35), reported that non-survivor COVID-19 patients had significantly higher D-dimer levels than survivors. Similarly, Tang et al. (13), observed markedly elevated D-dimer levels in fatal cases with COVID-19. Zhou et al. (14), also found that D-dimer on admission was associated with in-hospital death in COVID-19 patients. Recent guideline on the recognition and management of coagulopathy in COVID-19 from the International Thrombosis and Hemostasis Association have defined the markedly increased D-dimer on admission as a 3-4-fold increase (36). In the present study, a D-dimer cut-off value of 1.41 mg/L was determined to predict in-hospital mortality.

The potential underlying pathophysiological mechanism of hypercoagulable state in patients with COVID-19 may refer to several aspects. An imbalance between pro-inflammatory and anti-inflammatory response in viral infections (37,39), hypoxia-related prothrombotic state in critically ill patients (40), age-related hypercoagulability (41, 42) sepsis-induced coagulopathy or even disseminated intravascular coagulation might trigger endothelial cells and stimulate thrombosis (43).

In the present study, the mortality rate was 24%. This rate was higher than that reported in previous studies (44, 45). This heterogeneity is probably due to differences in the illness severity of the patients enrolled. 44.8% of the patients were critically ill, admitted to the intensive care unit, and required invasive mechanical ventilation.

This study has certain limitations. First it might have a selection bias because of its retrospective design. Larger prospective studies are required to validate the impact of hs-cTnI and D-dimer on mortality of patients with COVID-19. Second, data regarding the time between illness onset

and hospital admission were unobtainable. This might have influenced our findings regarding the link between baseline levels of hs-cTnI and D-dimer and mortality. Third, severity scores were not attainable. Thus, the relationship between these markers and disease severity was not evaluated.

CONCLUSION

High-sensitivity cardiac troponin I and D-dimer levels on admission are independently associated with in-hospital mortality of adult patients with COVID-19. A cut-off value of 18,6 ng/L for hs-cTnI and another of 1,41 mg/L for D-dimer to predict in-hospital mortality is well established. However, further studies are warranted.

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