# Diagnostic Use of Interleukin-33 Levels in Patients with Acute Cholangitis Requiring Early or Emergency Biliary Drainage

## İnterlökin-33 Düzeylerinin Erken veya Acil Safra Drenajı Gerektiren Akut Kolanjitli Hastalarda Tanısal Kullanımı

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## ABSTRACT

**Objective:** Treatment of cholangitis is life-saving in patients with severe acute cholangitis (AC). We aimed to investigate usefulness of interleukin-33 (IL-33) to discriminate need of early or urgent biliary drainage in patients with acute cholangitis according to Tokyo Guidelines 2018 (TG18) grading system.

**Material and Methods:** The study population consisted of a total of 79 subjects (48 AC and 31 healthy controls). Patients with AC were categorized based on TG18, and the IL-33 levels and laboratory markers were measured.

**Results:** IL-33 level was significantly higher in the AC group (p <0.0001). ROC curve analysis was performed to distinguish patients with AC from normal healthy patients and to determine a cut-off value for IL-33. As a result of this analysis, the cut-off value for serum IL-33 was 0.59 pg / mL (sensitivity: 83.3% (95% CI: 69.8-92.5), specificity: 90.3% (95% CI: 74.2-98.0)) and the area under the ROC curve (AUC) was found to be 0.902 (p <0.0001; 95% CI: 0.814-0.957). The median IL-33 level was significantly higher in patients who needed early/emergency biliary drainage (moderate or severe AC) compared to patients with mild AC (0.79 vs 0.60, p = 0.01).

**Conclusion:** This study showed that IL-33 increased significantly in patients with moderate/severe AC who need immediate biliary drainage.

**Keywords:** Acute cholangitis, Biliary drainage IL-33, ST-2, Tokyo guideline

## ÖZ

**Amaç:** Şiddetli akut kolanjiti (AK) olan hastalarda kolanjit tedavisi hayat kurtarıcı öneme sahiptir. Bu çalışmada akut kolanjitli hastalarda IL-33'ün erken veya acil biliyer drenaj ihtiyacını ayırt etmek için kullanılabilirliğini 2018 Tokyo kılavuzu (TG18) derecelendirme sistemine göre araştırılmasını amaçladık.

**Gereç ve Yöntemler:** Çalışma popülasyonu toplam 79 kişiden oluşmaktaydı (48 AK ve 31 sağlıklı kontrol). Akut kolanjitli hastalar TG18'e göre kategorize edildi ve hastaların IL-33 düzeyleri ve laboratuvar belirteçleri ölçüldü.

**Bulgular:** IL-33 düzeyi AK grubunda anlamlı olarak yüksekti (p <0.0001). Akut kolanjitli hastaları normal sağlıklı hastalardan ayırt edilmesi ve IL-33 için bir cut-off değeri belirlemek için ROC eğrisi analizi yapılmıştır. Bu analiz sonucunda serum IL-33 için cut-off değeri 0.59 pg/mL (duyarlılık:% 83.3 (% 95 CI: 69.8-92.5), özgüllük:% 90.3 (% 95 CI: 74.2-98.0) bulundu ) ve ROC eğrisinin altındaki alan (AUC) ise 0.902 (p <0.0001;% 95 CI: 0.814-0.957) olarak bulunmuştur. Erken/acil biliyer drenaja ihtiyaç duyan (orta veya şiddetli AK) hastalarda, hafif akut kolanjitli hastalara göre ortanca IL-33 düzeyi anlamlı olarak daha yüksek bulunmuştur (0.79 vs 0.60, p = 0.01).

**Sonuç:** Bu çalışmada IL-33'ün acil safra drenajına ihtiyaç duyan orta/şiddetli AK hastalarında önemli ölçüde arttığı gösterilmiştir.

**Anahtar Sözcükler:** Akut kolanjit, Biliyer drenaj, IL-33, ST-2, Tokyo kılavuzu

## INTRODUCTION

Acute cholangitis (AC) is an acute inflammation and infection of the bile duct which requires prompt treatment and can cause significant morbidity/mortality (1). Development of cholangitis is the result of biliary obstruction with bile infection. The most common cause of AC is choledocholithiasis, while any condition that leads to stasis or obstruction of bile in the common bile duct (CBD), including benign or malignant stricture, parasitic infection, or extrinsic compression of CBD, can result in AC (1,2).

Severe cases (grade III) in Tokyo Guideline 2018 (TG18) refer to those who have organ dysfunction and require intensive care. Urgent biliary drainage is essential in such patients to prevent morbidity and/or mortality. Moderate cases (grade 2) describes the patients with acute cholangitis who do not have organ failue but require early biliary drainage (3,4).

In cases of severe AC, if a prompt biliary drainage is not performed, a sudden worsening in overall conditions of patients can occur which can result with mortality (5,6). Biliary decompression decreases cholangio-venous reflux and subsequently lowers bile and serum endotoxin levels. Early biliary drainage improves organ failure and shorten hospital stay times via aforementioned effects (7-9). Therefore, a rapid determination of the severity of AC and an appropriate action is essential to decrease morbidity and/or mortality rates for AC. For that, it is extremely important to identify biomarkers that can accurately predict the presence of sepsis and/or organ failure in AC which guides physicians for an urgent or early biliary drainage requirement.

The binding of IL-33 and its receptor ST2 plays a key role in the development of cardiovascular diseases, chronic inflammation, allergic diseases and fibrosis related diseases (10). Previous clinical and experimental studies have documented that IL-33 is elevated in patients with sepsis and endotoxemia (11,12). Acute cholangitis is also a serious infectious disease and can cause sepsis. Because of that we propose the hypothesis that IL-33 will increase in patients with AC.

In this study we aimed to investigate the diagnostic yield of IL-33 for AC. We also aimed to compare IL-33 levels in patients with moderate/severe cholangitis and mild cholangitis to discriminate the requirement of early or urgent biliary drainage in such patients.

## MATERIAL and METHODS

The study population included a total of 79 subjects (48 with AC and 31 healthy control). At the time of admission physical examination findings (temperature, blood pressure, pulse, oxygen saturation, neurologic examination) were recorded. In the laboratory, leucocyte count, platelet count, C-reactive protein (CRP), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (γ-GTP), alanine aminotransferase (ALT), billirubin, international normalized ratio (INR), albumin and creatinine were measured.

For the differential diagnosis of obstructive jaundice, different imaging methods such as abdominal ultrasound, abdominal computed tomography (CT) or magnetic resonance cholangiopancreatography (MRCP) were used. Diagnosis of AC was made and graded according to TG18 (4).

### *Measurement of Assay*

The number of microwell strips required to test was established. The microwell strips were washed twice with 400 µl Wash Buffer. After the last wash step, 50 µl of sample diluent was added to all wells and 50 µl of prepared standard dilutions in duplicate was added to standard wells. Fifty µl Calibrator Diluent was added to the blank wells. After that 50 µl µl of each sample in duplicate was added to the sample wells. Microwell strips was covered with an adhesive film and incubated (400 rpm) at room temperature (18° to 25°C) for 2 hours. One hundred ml Biotin-Conjugate was added to all wells. Adhesive film and empty wells were removed. Microwell strips were washed 6 times and 100 µl of Biotin-Conjugate was added to all wells. Samples were covered with an adhesive film and incubated (400 rpm) at room temperature (18° to 25°C) for 1 hour. After that adhesive film and empty wells were removed again. Microwell strips were washed 6 times and 100 µl of diluted Streptavidin-HRP was added to all wells. Samples were covered with an adhesive film and incubated (400 rpm) at room temperature (18° to 25°C) for 1 hour. Adhesive film and empty wells were removed and microwell strips were washed 6 times. Pipette 100 µl of TMB Substrate Solution was pipetted to all wells and microwell strips were incubated at room temperature (18° to 25°C) for about 30 min. One hundred µl of stop solution was added into each well. Results were read on a spectro-photometer using 450 nm as the primary wave length and 620 nm as the reference wave length.

### *Statistical Method*

Statistical Package for the Social Sciences (SPSS) Version 16 (SPSS, Chicago, IL) was used for the statistical analysis of this study. Kolmogorov-Smirnov test was used to determine normality of the distribution for the data. Comparisons between groups were performed by the Kruskal-Wallis test for nonparametric variables and One-Way ANOVA test for parametric variables. Mann-Whitney *U* test was used for subgroup analysis. The group characteristics were compared using the "Fisher exact test" and the Chi-square test. A receiver operating characteristic (ROC) curve was built to determine diagnostic ability of IL-33 for AC.

### *Approval of Ethics Commitee*

Informed consent was obtained from all participants. The study was conducted according to the ethical standards stated in the 1964 Helsinki Declaration. In our study, research and publication ethics were followed. Ethical approval for the study was taken from Türkiye Yüksek İhtisas Training and Research Hospital ethics committee with the number 29620911-929 and date 23.05.2017.

## RESULTS

This study included 48 patients with AC (60.8%) and 31 healthy subjects (39.2%). Mean age of the participants was 54.0 ± 20.2 and 60.8 % (n=48) were female. IL-33 level was significantly higher in AC group compared to control group [median, (min-max): 0.73 (0.70-14.01) vs. 0.40 (0.30-0.86), p<0.0001]. Also leucocyte, AST, ALT, ALP, GGT, billirubin, creatinine and INR values were higher while albumin and platellet levels were lower in AC group compared to control group. Table I shows comparison of demographic and laboratory findings of the study groups.

The most common etiology of the AC was choledocholithiasis (33 patients, 69%). Ten of the patients had malign biliary obstruction (21%). Moderate or severe cholangitis (TG18, Grade 2-3) was observed in 28 patients (58%). Table II demonstrates clinical characteristics of patients with AC.

A ROC curve analysis was built to determine the cut-off value of IL-33 to differentiate acute cholangitis from normal patients and the cut-off value of serum IL-33 was found to be 0.59 pg/mL [sensitivity: 83.3% (95%CI: 69.8-92.5),

**Table I:** Comparison of demographic and laboratory findings of patients.

| | **Demographic Findings of Participants** | | | |
|---|---|---|---|---|
| | **Cholangitis (+) (n=48)** | **Cholangitis (-) (n=31)** | **p value** | **Total (n=79)** |
| Age, Mean±SD | 55.9 ± 9.5 | 56.6 ± 7.5 | 0.4 | 56.2 ± 8.7 |
| Female Gender, n (%) | 24 (50) | 17 (54) | 0.6 | 41 (52) |
| ***Laboratory Findings of Participants*** | | | | |
| WBC ($10^3$/µL), Median (min-max) | 15250 (11.000-49100) | 6460 (4780-10800) | <0.001 | 12000 (4780-49100) |
| Platellet ($10^3$/µL), mean (SD) | 229729 (116204) | 281645 (60828) | <0.001 | 250101 (101047) |
| INR, Median (min-max) | 1.3 (0.9-2.4) | 1.0 (0.9-1.1) | <0.001 | 1.1 (0.9-2.4) |
| Creatinine (mg/dL), Median (min-max) | 1.09 (0.59-3.20) | 0.73 (0.50-1.19) | <0.001 | 0.81 (0.50-3.20) |
| CRP (mg/L), Median (min-max) | 126.0 (3.7-314.4) | 1.8 (0.1-8.4) | <0.001 | 82.0 (0.1-314.4) |
| AST (U/L), Median (min-max) | 129 (20-808) | 11 (11-58) | <0.001 | 75 (11-808) |
| ALT (U/L), Median (min-max) | 149 (23-619) | 17 (7-61) | <0.001 | 59 (7-619) |
| ALP (U/L), Median (min-max) | 234 (86-2112) | 67 (41-158) | <0.001 | 163.5 (41-2112) |
| GGT (U/L), Median (min-max) | 346 (57-1896) | 19 (5-44) | <0.001 | 177 (5-1896) |
| T.Billirubin (mg/dL),Median (min-max) | 5.2 (1.0-31.1) | 0.3 (0.1-1.2) | <0.001 | 2.5 (0.1-31.1) |
| Albumin (g/dL), Median (min-max) | 3.6 (1.9-5.5) | 4.5 (4.0-4.9) | <0.001 | 4.0 (1.9-5.5) |
| IL-33 (pg/mL), Median (min-max) | 0.73 (0.70-14.01) | 0.40 (0.30-0.86) | <0.001 | 0.70 (0.30-14.01) |

Table II: Clinical characteristics of patients with acute cholangitis (n=48).

| | |
|---|---|
| **Severity of AC (TG18)** | |
| ***Grade 1 (Mild), n (%)*** | 20 (41.7) |
| ***Grade 2 (Moderate), n (%)*** | 11 (22.9) |
| ***Grade 3 (Severe), n (%)*** | 17 (35.4) |
| **Etiology** | |
| ***Choledocholithiasis, n (%)*** | 33 (84.6) |
| ***Malign Biliary Obstruction, n (%)*** | 10 (12.7) |
| ***Benign Biliary Stricture, n (%)*** | 3 (3.8) |
| **Duration of Hospitalization, *median days (min-max)*** | 2.0 (1.0-28.0) |
| **Mortality, *n (%)*** | 6 (12.5) |

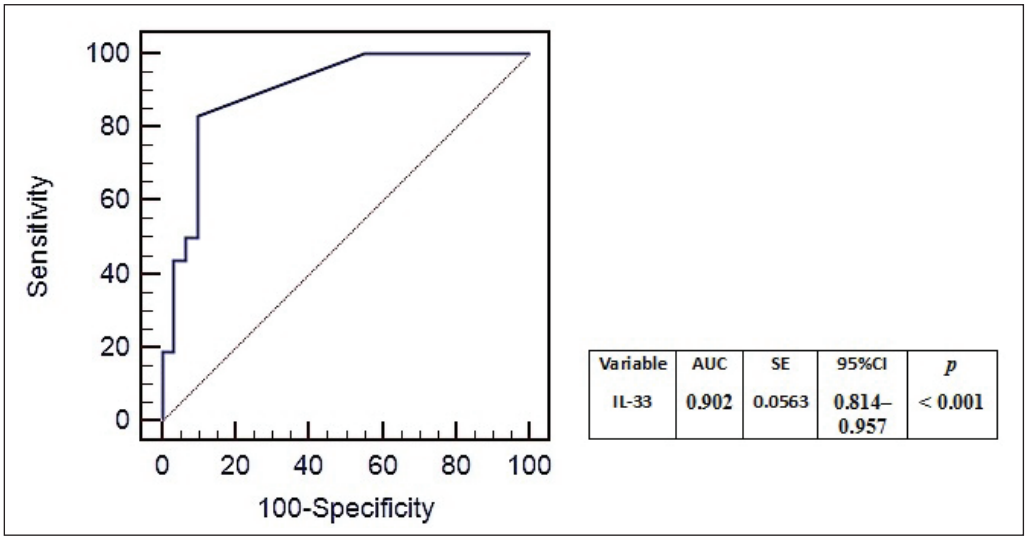
specificity: 90.3% (95%CI: 74.2-98.0), PPV: 93.0 (95%CI: 80.9-98.5), NPV: 77.8 (95%CI: 74.2-98.0) ] and the area under the ROC curve (AUC) was 0.902; $p< 0.0001$; 95% CI: 0.814–0.957) (Figure 1). A ROC curve analysis was built to compare CRP, albumine and IL-33 for diagnostic accuracy of AC. According to this analysis, CRP has the highest AUC value compared to albumin and IL-33 (Figure 2.

Median interleukin-33 levels were significantly higher in patients with severe AC than patients with moderate or mild AC (0.85 vs 0.75 and 0.60, subsequently, p=0.03) (Figure 3). When patients divided into two groups as mild and moderate/severe AC according to the early/urgent biliary drainage requirement, median IL-33 level was significantly higher in moderate/severe AC group (0.79 vs 0.60, p=0.01) (Figure III).

## DISCUSSION

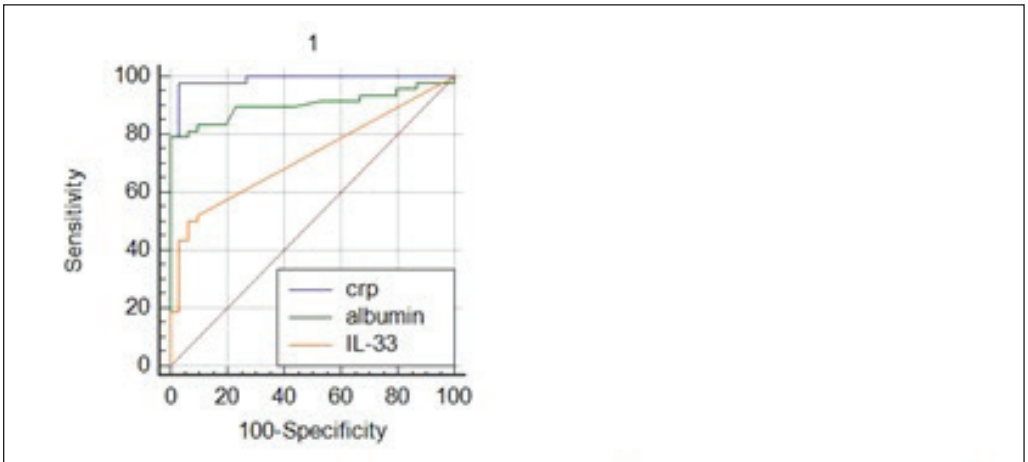
To our best knowledge, this is the first study documenting that IL-33 increases in patients with acute cholangitis. It was showed that IL-33 increased significantly in patients with moderate/severe cholangitis according to TG18 who need immediate biliary drainage.

Appropriate management of acute cholangitis is essential especially in patients with severe acute cholangitis. In particular, if a rapid and an accurate treatment is not performed during acute severe condition, it can cause mortality. In severe acute cholangitis, increased intrabiliary pressure promotes migration of bacteria and endotoxins from the cholangioles to resulting the blood or lymph streams and causes organ damage accompanying sepsis or disseminated intravascular coagulation (DIC) (4,13). Therefore, to




| Variable | AUC | SE | 95%CI | p |
|---|---|---|---|---|
| IL-33 | 0.902 | 0.0563 | 0.814–0.957 | < 0.001 |

**Figure 1:** A Receiver operating Characteristic Curve for determining the cut-off value of IL-33 to differentiate acute cholangitis from normal patients. (AUC:0.902 (95% CI: 0.814–0.957), sensitivity: 83.3% (95% CI: 69.8-92.5), specificity: 90.3% (95% CI: 74.2-98.0), PPV: 93.0 (95%CI: 80.9-98.5), NPV: 77.8 (95%CI: 74.2-98.0)).




| Variable | AUC | SE [a] | 95% CI [b] |
|---|---|---|---|
| IL_33 | 0,722 | 0,0445 | 0,609 to 0,817 |
| albumin | 0,903 | 0,0364 | 0,815 to 0,959 |
| crp | 0,988 | 0,00903 | 0,932 to 1,000 |

**Figure 2:** A receiver operating characteristic curve for compression of CRP, albumin and IL-33.

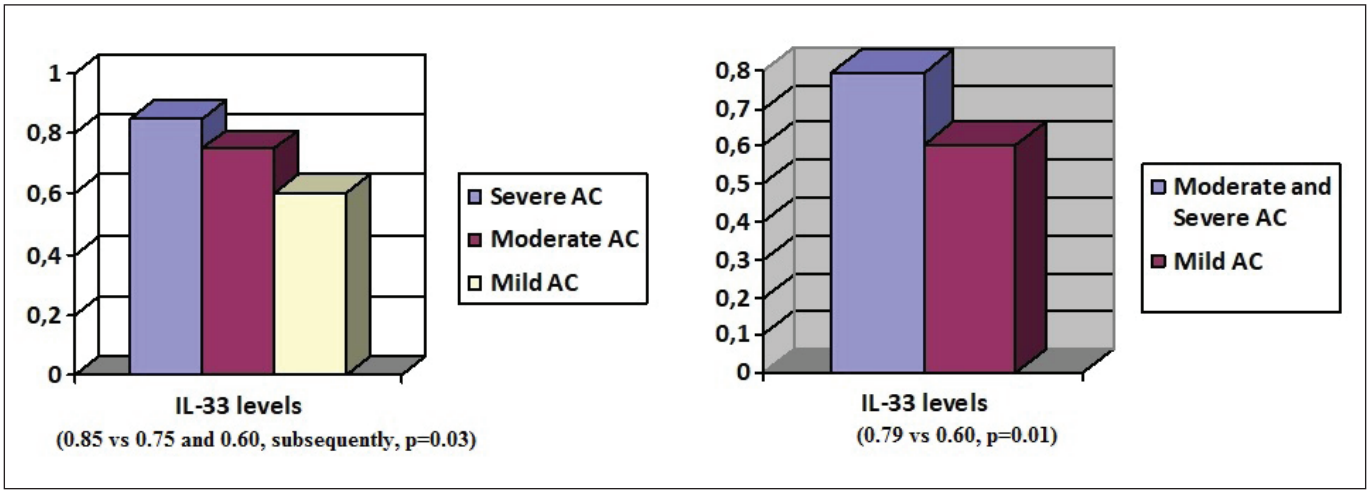



**Figure 3:** Comparison of IL-33 levels according to the severity of acute cholangitis.
Mild AC vs. Moderate AC vs. Severe AC
Mild AC vs. Moderate/Severe AC

prevent morbidity and mortality in patients with AC, the diagnostic criteria for AC and the treatment guidelines by degree of severity were clearly defined in the TG18.

Tokyo Guideline 2018 (4) recommends urgent/emergent biliary drainage for Grade II/III cholangitis, without a specified time frame (14). TG18 seems to be a more appropriate practical guideline when compared with TG07 to detect severity assessment of acute cholangitis and to make an immediate biliary drainage treatment decision. However, the severity of the AC can be underestimated in some AC patients who require urgent/early biliary drainage.

TG13 and TG18 are similar in identifying patients requiring emergency drainage. In the study of Shinya S et al. 22.2% of the patients who required emergent biliary drainage due to positive purulant bile or hemoculture was categorized as Grade I or Grade II AC due to TG13 (13). The authors in the same study concluded that TG13 (also smilarly TG 18) has limitations to exactly detect severe AC cases who require immediate biliary drainage and emphasized the importance of biomarkers that can be easily used to accurately diagnose the presence of sepsis and organ damage in AC patients (13).

IL-33 is a member of the IL-1 family that binds the heterodimeric receptor complex consisting of ST2 and IL-1 receptor accessory protein (15-17). Epithelium of injured or necrotic tissues caused by mechanical trauma, infections, smoke, aeroallergens or endogenous triggers may release IL-33. These triggers may also cause the activation and upregulation of receptors that recognize IL-33 such as ST2 and TLRs both of which result in an increase in the release of IL-33 from epithelial cells (18). Necrotic cells release biologically active Il-33 suggesting that IL-33 may act as an endogenous danger signal; thus, it has been named as alarmin (18-20). Recent data have shown that IL-33 may serve as a biomarker associated with the severity of some infectious diseases (21). During infection, IL-33 levels are highly depend on the type or stage of infectious diseases. In support of this data, several studies documented that IL-33 levels increased in the patients with sepsis (22). Significantly higher IL-33 receptor ST-2 levels were found on admission and within the first 48 hours of the diagnosis of sepsis when compared with healthy controls (23,24). In another study, mortality rate was found to be higher in septic patients who had elevated serum concentrations of ST2 (25). Also in different experimental studies, specific role of IL- 33-ST2 axis in sepsis has been observed. For instance, in abdominal sepsis, it has been showed that IL-33 accumulated neutrophil recruitment with more efficient bacterial clearance and improved survival in animal studies (22,26).

To date, there is limited data in the literature concerning the correlation of biomarkers and the severity of AC. In a recent study, Suwa et al. showed that low IL-7 and high procalcitonin levels were correlated with severity and 28-day mortality in patients with AC (27). In another recent prospective study, procalcitonin was found to be increased significantly in either moderate or severe AC (28). Another inflammatory marker Presepsin was found to be significantly higher in patients with severe AC than in patients with moderate AC or with mild AC (29). In our study we found that IL-33 increased significantly in patients with moderate/severe AC who need immediate biliary drainage.

The major limitation of our study was limited patient number. Our study was the first study that investigating the relationship between IL-33 and AC, we think that the number of patients was sufficient. Also the patient number was sufficient for statistical analysis.

In conclusion, recognition of an accurate biomarker to categorise patients with AC is essential since timely biliary drainage improves clinical outcome in patients with moderate/severe AC. We suggest that measurement of serum IL-33 on admission might ensure early categorization of patients with moderate/severe AC who need immediate biliary drainage. Large volume prospective studies are required to confirm this promising result to improve outcomes of such patients.

**Conflict of Interest:** None Declared.

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