

The effect of procalcitonin and immature granulocyte ratio in predicting the development of acute necrotizing pancreatitis: evidence from 582 cases

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Abstract. – OBJECTIVE: Acute pancreatitis (AP) is one of the diseases that surgical clinics deal with the most. While mortality rates are approximately 1% in all cases, this rate may increase to 15% in pancreatic necrosis cases. Therefore, early diagnosis and treatment are very important in necrotizing pancreatitis. Our aim in this study is to present the guiding effectiveness of procalcitonin and immature granulocyte ratios (IG%) in planning the early diagnosis and treatment of acute necrotizing pancreatitis.

PATIENTS AND METHODS: 582 patients hospitalized in our clinic with the diagnosis of acute pancreatitis were included in this study. All patients were divided into two groups as acute edematous pancreatitis (AEP) and acute necrotizing pancreatitis (ANP) according to tomography results. White blood cell (WBC) count, procalcitonin, IG%, C-reactive protein (CRP), amylase and lipase, albumin, CRP/albumin levels were recorded. The differences between the two groups were analyzed statistically.

RESULTS: According to the results of contrast-enhanced abdominal tomography (CECT), 525 patients were diagnosed with AEP and 57 with ANP. WBC, CRP, procalcitonin, IG and CRP/albumin were found to be significantly higher in ANP patients when compared to AEP ($p < 0.0001$). According to the ROC analysis result, procalcitonin (AUROC: 0.999), IG% (AUROC: 0.995), WBC count (AUROC: 0.841), CRP (AUROC: 0.947), albumin (AUROC: 0.862), and CRP/albumin (AUROC: 0.946) ratio were markers that could be used for early prediction of ANP.

CONCLUSIONS: Early diagnosis of ANP can reduce morbidity and mortality. Procalcitonin and IG% levels can be easily accessible and effective markers in the early diagnosis of ANP and in the planning of treatment.

Key Words:

Acute pancreatitis, Procalcitonin, Immature granulocyte percentage.

Introduction

Acute pancreatitis (AP) is a disease with high mortality and morbidity, which is characterized by abdominal pain, increased amylase and lipase¹. The actual incidence of AP is unknown, as it is sometimes underdiagnosed or diagnosed post-mortem. Its incidence is considered to be 5-35/100,000¹. In a study² conducted on 1,005 patients, mortality was reported as 5%. It can progress in different severity, ranging from mild clinical form such as acute edematous pancreatitis (AEP) to severe clinical form such as acute necrotizing pancreatitis (ANP). Therefore, the prognosis of the disease is highly variable¹. Especially in ANP, mortality decreases with the increase in diagnosis and treatment possibilities³.

Although various classification/scoring criteria are used to determine the prognosis in patients diagnosed with AP, we still cannot adequately detect severe pancreatitis cases at the time of diagnosis^{3,4}. Despite numerous biomarkers, prognostic classifications, and imaging studies, it is difficult to predict severe cases in advance. It is possible to detect necrosis in patients after 48 hours. Several studies⁴ are still searching for a parameter that can predict the prognosis at the time of diagnosis. Therefore, rapid and reliable biomarkers are needed for the early diagnosis of ANP.

Immature granulocyte cells consist of promyelocyte, myelocyte, and metamyelocytes and are not normally found in peripheral blood⁵. Literature⁵ show that immature granulocytes can be used as an early inflammation marker in the presence of inflammation. Recently, more studies have been carried out on this parameter, which is not used enough by clinicians. Studies⁶⁻⁸ exam-

ining the relationship between acute pancreatitis and IG% are limited^{6,7}. In these studies, the relationship between the severity of the disease and IG% was examined.

Serum procalcitonin increases in the early stages of infection and inflammation, and values above 0.5 ng/ml are considered abnormal. It is a widely used biochemical marker. Many studies^{9,10} emphasize the importance of procalcitonin in predicting the severity of AP.

Although AP has a mild course in 80-85% of patients, it is important for the physician to predict the remaining 20% that may be mortal^{1,10}. In this study, we aimed at showing the efficacy and sensitivity of procalcitonin and IG% in predicting ANP and to provide early planning of ANP treatment.

Patients and Methods

Ethics committee approval of this study was obtained from the clinical research Ethics Committee of Harran University (04.07.2022-22/13.20). In this study, 582 patients hospitalized with the diagnosis of AP in the General Surgery Clinic of S.B. Şanlıurfa Mehmet Akif Inan Training and Research Hospital between June 2019 and April 2022 were included. Contrast-enhanced abdominal computed tomography (CECT) was performed on patients when admitted at the emergency clinic. The diagnosis of AP was made based on the patient's history, physical examination findings, laboratory and typical radiological findings (CECT). For the diagnosis of AP, serum amylase and/or lipase increased three times the normal value was accepted as the diagnostic criterion.

Patients who were followed up and treated with the diagnosis of AP were evaluated with clinical, laboratory and imaging methods (CECT). Revised Atlanta Classification was used for staging of severity in acute pancreatitis⁴. According to the CECT results, the patients were divided into two groups as AEP and ANP.

There was no evidence of necrosis in the CECT reports at the time of admission. Control CECT was performed 72 and 96 hours later for the patients whose complaints, clinical and laboratory findings worsened during the follow-up and treatment. The results were evaluated together with the radiologist.

Procalcitonin, IG%, WBC, amylase, lipase, CRP, albumin, CRP/albumin levels were mea-

sured at the admission of the patient and at the 48th, 72nd and 96th hours. The average of the 4 measurement values obtained for each of these markers was statistically analyzed and the two groups were compared. The effectiveness of biomarkers in early recognition of ANP was examined and compared.

Patients presenting with chronic and recurrent pancreatitis attack, patients receiving chemotherapy, immunosuppressive patients, patients with pregnancy status, patients with hematological disorders and patients under 18 years of age were excluded from the study.

Hemogram parameters of the patients (WBC, IG%), were analyzed automatically using a Sysmex XN1000 (Sysmex Inc., Japan). Biochemistry-hormone parameters (procalcitonin, CRP, albumin, amylase, lipase) analysis was performed by Roche Cobas 6000 (Hoffmann-La Roche Ltd., Basel, Switzerland).

Statistical Analysis

Data were evaluated using the IBM SPSS Statistics 20.0 package software (IBM Corp., Armonk, NY, USA). Data were given as number of units (n), percent (%) and mean±standard deviation. Statistical analyses were performed using Fisher's exact test, unpaired *t*-test and Chi-square test, depending on the appropriate variable. Receiver operating characteristic (ROC) analysis was performed to determine the success of procalcitonin, IG%, WBC, albumin, CRP, and CRP/albumin in predicting ANP. *p*-value < 0.05 was considered significant. Statistical tests performed on the parameters are given in Tables I and II.

Results

Of the 582 patients who were admitted with the diagnosis of AP and received follow-up and treatment, 344 (59.1%) were female and 238 (40.8%) were male. In this series, 582 patients were divided into two groups according to CECT results; 525 (90.2%) were diagnosed with AEP and 57 (9.7%) with ANP. Of the patients diagnosed with ANP, 33 (57.8%) were female and 24 (42.1%) were male. The mean age was 57.9±21.05 in women and 58.06±17.34 in men (Table I).

28 of the patients diagnosed with ANP were diagnosed with CECT on the first admission, and 25 with CECT after clinical worsening. The mean age of the patients was 73.36±15.17 years in ANP and 56.78±19.80 years in AEP. The mean

Table I. Comparison of demographic data, etiology, length of hospital stays and inflammation markers between groups.

	AEP	ANP	p-value
Number of patients	525 (90.2%)	57 (19.7%)	
Gender			0.89*
Female	311 (90.4%)	33 (9.5%)	
Male	214 (89.9%)	24 (6.9%)	
Age (years)	56.78 ± 19.80	73.36 ± 15.17	< 0.0001**
Length of hospital stay (day)	6.4 ± 1.4	23.8 ± 4.3	< 0.0001**
Intensive care unit (n)			
Yes	33 (6.2%)	54 (94.7%)	< 0.0001*
No	492 (99.3%)	3 (0.7%)	
Etiology			0.344***
Biliary	512 (97.52%)	56 (98.25%)	
Non biliary	10 (1.90%)	0	
ERCP	3 (0.57%)	1 (1.75%)	
White blood cell (/μL)	11196 ± 7096	16027 ± 4966	< 0.0001**
C-reactive protein (mg/L)	16.27 ± 17.5	89.8 ± 60.6	< 0.0001**
Procalcitonin (ng/L)	0.21 ± 0.12	2.96 ± 1.40	< 0.0001**
Immature granulocyte percentage	0.24 ± 0.21	1.59 ± 0.34	< 0.0001**
Amylase (IU/L)	1151 ± 605.0	1215 ± 536.5	0.44**
Lipase (U/L)	1133 ± 591.7	1186 ± 654.6	0.53**
Albumin (g/L)	44.1 ± 175	27.37 ± 7.1	0.47**
CRP/Albumin	0.46 ± 0.52	3.83 ± 5.8	< 0.0001**

*Fisher's exact test; **Unpaired *t*-test; ***Chi-square; AEM: Acute edematous pancreatitis; ANP: Acute necrotizing pancreatitis.

age in ANP was statistically significantly higher ($p < 0.0001$). There was no significant difference between the two groups in terms of gender ($p = 0.89$; Table I).

33 (6.2%) patients from the AEP group and 54 (94.7%) patients from the ANP group were followed up in the intensive care unit. The hospital stay was 6.4 ± 1.4 days in the AEP group and 23.8 ± 4.3 days in the ANP group. A significant difference was found between the ANP and AEP groups in terms of the number of patients treated in the intensive care unit and the length of hospital stay ($p < 0.0001$; Table I).

52 (91.2%) of the ANP patients had additional disease (diabetes melitus, hypertension, coronary heart disease, cerebrovascular disease). There

was additional disease in 178 (33.9%) of the patients in the AEP group. 4 (7.1%) of 57 ANP patients and 6 (1.1%) of 525 AEP patients died. Surgical treatment was performed in 21 of ANP cases (necrosectomy, debridement, drainage).

Procalcitonin, IG%, WBC, CRP and CRP/albumin values were found to be significantly higher in the ANP patient group when compared to the AEP group ($p < 0.0001$). There was no significant difference between the two groups in terms of amylase, lipase and albumin values ($p = 0.44$, $p = 0.52$ and $p = 0.47$, respectively).

Procalcitonin, IG%, WBC, CRP, albumin, and CRP/albumin efficiency in estimating ANP were calculated using receiver operating characteristic (ROC) curves. The results obtained by

Table II. ROC analysis of inflammation markers in the prediction of acute necrotizing pancreatitis.

	AUROC	95% CI	Cut-off	Sensitivity %	Specificity %	p-value
Procalcitonin (ng/L)	0.999	0.999-1.000	> 0.75	100	98.86	< 0.0001
IG%	0.995	0.991-0.999	> 0.65	100	95.43	< 0.0001
WBC (/μL)	0.841	0.793-0.890	> 12478	80.7	72	< 0.0001
CRP (mg/L)	0.947	0.920-0.974	> 28.50	91.23	85.52	< 0.0001
Albumin (g/L)	0.862	0.814-0.909	< 33.50	85.96	72	< 0.0001
CRP/Albumin	0.946	0.908-0.984	> 0.8775	91.23	86.48	< 0.0001

AUROC: Area under ROC; CI: Confidence interval; Immature granulocyte percentage: IG%; White blood cell: WBC; CRP: C-reactive protein.

comparing the areas under the ROC curve are given in Table II and Figure 1. According to the ROC analysis results, procalcitonin > 0.75 ng/L (sensitivity 100%; specificity 98.86%) and IG% > 0.65% (sensitivity 100%; specificity 95.43%) were determined as the cut-off value for ANP estimation.

Discussion

AP is characterized by nonspecific examination findings. Therefore, the diagnosis is made by combining examination findings, laboratory values and imaging methods. The specificity and sensitivities of amylase and lipase values are not high enough to make the diagnosis on their own and change hourly. Although different scoring systems such as Atlanta criteria, Ranson cri-

teria, BISOP scoring, MARSHALL scoring and APACHE 2 criteria are used to determine the prognosis in patients diagnosed with AP, severe pancreatitis cases cannot be detected sufficiently at the time of diagnosis⁶. Despite numerous biomarkers, prognostic classifications, and imaging studies, it is difficult to predict severe cases early. It is possible to detect the formation of necrosis in patients after 48 hours. Therefore, many studies are still searching for a parameter that can predict the prognosis at the time of diagnosis^{6,7,11}. For the prognosis and treatment plan, it is essential to first determine the severity of the disease (mild form or severe form). The severe form is much more mortal and requires treatment in the intensive care unit. It is therefore important to make this distinction early^{9,10}. Although a single serum marker to determine the severity of the disease has not been found so far,

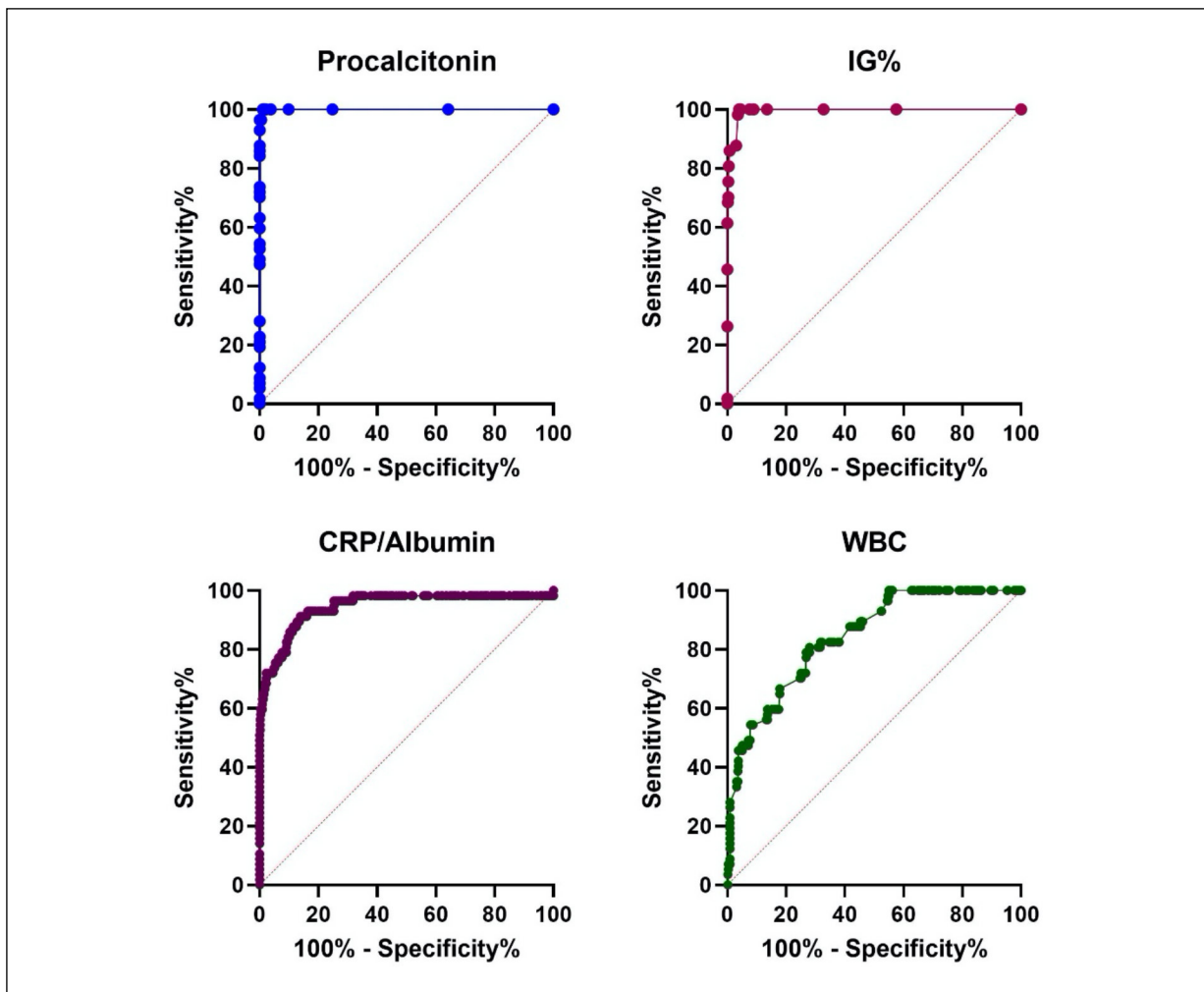


Figure 1. Receiver operating characteristic (ROC) analysis of inflammation markers to be used in the early detection of ANP.

various serum markers have been used for this purpose¹¹. The most studied of these candidate markers are procalcitonin and IG%^{6,7,12,13}. In this study, we tested procalcitonin and IG%, which are effective and easily accessible markers in the early detection of ANP, in a large patient population. We have shown that these markers can be effective in the diagnosis of ANP when used individually or in combination.

In this study, the Revised Atlanta Classification was used for staging of severity in acute pancreatitis⁴. Clinical findings, CECT results and laboratory markers of inflammation were revealed. By the help of these markers, the presence of persistent organ failure (>48 hours) with infected necrosis was determined as the mortal picture, and these patients were followed up in the intensive care unit.

ANP

It is associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis. Acute pancreatitis cases consist of 85% AEP and 15% ANP⁴. Aggressive intensive care treatments are recommended in ANP. Surgery is not recommended for the first 4 weeks in patients with infected necrosis. There is still no clear information about the timing of necrosectomy¹⁴. In a study¹⁵, AP mortality was 1-7%, and it was reported to be 20% when pancreatic necrosis developed. Early recognition of pancreatic necrosis is very important since mortality increases from 1% to 10-23% in the presence of pancreatic necrosis. CECT is the gold standard method for the diagnosis of pancreatic necrosis¹⁶. Patients with ANP may require long intensive care treatment and their mortality can reach up to 20-30%¹⁰. It can cause high costs. For this reason, markers to detect poor prognosis in acute pancreatitis before necrosis develops are important.

In this study, the rate of ANP was 9.7% and the mortality rate was 7.1%. We thought that the reason for our low mortality rate could be associated with early aggressive intensive care treatment due to the close monitoring of the patients according to the inflammation markers and evaluating patients with clinical and laboratory deterioration in the first 72-96 hours with CECT. ANP is a disease that requires long-term intensive care, is difficult to treat and still has high mortality rates¹⁰. Therefore, early prediction of ANP in patients with AP and early planning of treatment are very important in terms of reducing mortality rates and hospital costs.

Immature granulocyte cells consist of promyelocyte, myelocyte, and metamyelocytes and are not normally found in peripheral blood¹⁷. In their study, Ayres et al⁵ have shown that immature granulocytes can be used as an early inflammation marker in the presence of inflammation. There is a limited number of studies^{5,7,8} examining the relationship between acute pancreatitis and IG% immature granulocyte. In these studies, the relationship between disease severity and IG% was examined. IG% is a new marker of inflammation that can be easily measured in complete blood count and is known by very few clinicians. Park et al¹⁸ have shown that IG% increases in the early stages of inflammation much earlier than traditional parameters such as CRP and white blood cell. Another study by Ünal et al⁷ has shown that IG% in AP is related to the severity of the disease. They showed that IG% had a sensitivity of 100% and a specificity of 95% for acute necrotizing pancreatitis, and that increased IG% levels were a simple, rapid and effective marker for the early prediction of acute necrotizing pancreatitis⁷. They emphasized that further studies are needed to confirm the use of IG% in predicting severity and mortality in AP. Our study supports these findings. We think that an IG value > 0.65% (AUROC: 0.995; sensitivity: 100; specificity: 95.43) may be a marker for early detection of ANP. The most important difference between the two studies^{7,18} is the difference between the cut-off values. Ünal et al⁷ reported IG > 0.8% for ANP estimation. In our study, this value was > 0.65%. Bedel et al¹⁹ examined 269 patients and found the cutoff value for IG% as 0.65% (sensitivity: 72.7; specificity: 84.6). In these studies^{7,19}, aiming at identifying candidate markers that will enable early detection of ANP, this difference between cut-off values is beyond acceptable limits. Considering the number of patients included in the study, we think that our findings might be more realistic.

Procalcitonin is a propeptide of which is the fastest general acute phase reactant involved in many infectious and inflammatory processes²⁰. In large study groups²¹, procalcitonin was found to be more successful in showing the severity of pancreatitis and the risk of developing necrosis when compared with other inflammatory markers. The most sensitive marker for the presence of pancreatic infection is procalcitonin, and low procalcitonin levels have a strong negative predictive value for infected necrosis²². Although serum pancreatic enzyme (amylase, lipase) measure-

ments are the “gold standard” in the diagnosis of pancreatitis, both may increase in non-pancreatitis conditions; however, lipase was found to be more specific. Chen et al²³ suggested that procalcitonin may be a biomarker for ANP in their study on a large group of AP patients. However, they reported the cut-off value of procalcitonin for ANP as 1.39 ng/dL (sensitivity: 0.609; specificity: 0.750)²³. Although this study was conducted on a large patient population, its sensitivity and specificity are lower than our findings. We think that this difference is due to methodological differences. There is also a difference between their cut-off values and ours. Many studies²⁰⁻²³ have been conducted on the early recognition of ANP. Almost all of those studies reported different cut-off values for procalcitonin for the diagnosis of ANP. The main purpose of our study was to produce a solution to this problem that causes confusion. Because the number of patients included in the study is high when compared to the abovementioned studies. In addition, we think that the difference in cut-off values is usually due to the small number of patients and methodological differences. In this study, we performed the calculations by averaging the laboratory results of blood samples taken daily from patients hospitalized with the diagnosis of AP. Therefore, we consider that all the results we report are the closest to the truth.

Many markers have been found to determine severity in pancreatitis, but no early marker for severe AP has yet been found. However, a CRP level ≥ 150 mg/L on day 3 can be used as a prognostic factor for severe AP. Zrnic et al²⁴ showed that CRP levels and disease severity were correlated in patients with AP. They stated that this situation is useful in predicting the complications that may occur²⁴. Our study supports these findings. In the current study, we found the cut-off value of CRP to be > 28.5 mg/L in the diagnosis of ANP (Table II). However, we think that CRP is not effective in the differential diagnosis of ANP since its sensitivity and specificity are lower than other markers.

WBC is used in the diagnosis and follow-up of acute pancreatitis severity²⁵. White blood cells containing neutrophil and leukocyte parameters are also included in the diagnostic criteria of systemic inflammatory response syndrome. Mortality increases in cases of pancreatitis progressing with necrosis and sepsis, and since neutrophil cells are responsible for the initiation of inflammation, the follow-up of

neutrophil values in the complete blood count helps the clinician, but the specificity and sensitivity of acute pancreatitis is low²⁶. In a study by Doctor et al²⁷, suggested that CRP and leukocyte values are important distinguishing parameters in the development of infected pancreatic necrosis. However, in this study, we found that WBC was not an effective marker that could be used to detect ANP at an early stage. We think that procalcitonin and IG% may be more effective markers instead (Table II).

Limitations

Our study has some limitations as it is retrospective. Although the number of our patients was large, obtaining patient data by file scanning method caused limitations in accessing some data. There is a need for studies that will include Ranson 48th hour and other scoring systems in prognostic follow-up. Clinical studies are needed to confirm the data obtained in this study.

Conclusions

In our study, the diagnosis of ANP was predicted early in our clinical findings, inflammatory markers, and CECT follow-ups, and intensive care treatment was initiated early. As a result, a significant improvement in mortality was observed. 582 patients hospitalized with the diagnosis of AP were included in our study and the selected parameters of the patients were analyzed. For amylase and lipase values, no statistical significance was found in the early detection of ANP. Procalcitonin, IG%, WBC count, CRP, albumin and CRP/albumin values were found to be significant in determining both the severity of the disease and the development of ANP. However, among these parameters, procalcitonin and IG% are effective, simple and reliable markers in predicting the development of ANP. According to the results of this study, we think that it is appropriate to start ANP treatment when procalcitonin > 0.75 ng/L and/or IG $> 0.65\%$ in patients followed up with the diagnosis of AP. When compared with literature, we think that the results of our case series, which included a significant number of patients, are meaningful and instructive.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

None.

Informed Consent

The authors declare that the patients included in the study signed informed consent forms to use their medical information in the studies.

Ethics Approval

Ethics committee approval of the study was obtained from Harran University Clinical Research Ethics Committee (04.07.2022-22/13.20).

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