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Interleukin-34 as a Robust Predictor of No-Reflow Phenomenon in ST-Elevation Myocardial Infarction: Insights into Inflammatory Mechanisms and Clinical Implications

ST-Yükselmeli Miyokard İnfarktüsünde No-Reflow Fenomeninin Güçlü Bir Belirteci Olarak İnterlökin-34: Enflamatuvar Mekanizmalar ve Klinik Sonuçlar Üzerine Bir Bakış

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ABSTRACT

Objective: ST-elevation myocardial infarction (STEMI) poses a significant challenge despite advances in reperfusion strategies. The "no-reflow" phenomenon, characterized by inadequate microvascular blood flow restoration following successful revascularization, remains poorly understood. Inflammation, particularly interleukin-34 (IL-34), is implicated in cardiovascular disease, prompting investigation into its role in no-reflow.

Methods: This observational study included 182 patients with STEMI (32 with no-reflow, 150 without) and 100 controls. Clinical and angiographic data were analyzed, and IL-34 levels were measured. Logistic regression and receiver operating characteristic (ROC) analysis assessed IL-34's predictive value for no-reflow.

Results: Patients with no reflow exhibited elevated IL-34 levels compared with controls and those without no-reflow. Logistic regression identified IL-34 as an independent predictor of no-reflow (odds ratio: 1,020, p<0.001). ROC analysis showed IL-34's significant predictive value (area under the curve: 0.972, p<0.001).

Conclusion: IL-34 emerges as a robust predictor of no-reflow in STEMI, potentially reflecting its role in macrophage activation and the inflammatory response. These findings suggest a novel avenue for understanding and mitigating no-reflow in STEMI, paving the way for targeted therapies. Early identification of high-risk patients could inform tailored interventions, ultimately improving STEMI outcomes. Further research is warranted to elucidate IL-34's mechanistic involvement and validate its predictive value in larger cohorts.

Keywords: Interleukin-34, ST-elevation myocardial infarction, no-reflow phenomenon

ÖZ

Amaç: ST-yükselmeli miyokard enfarktüsü (STEMI), reperfüzyon stratejilerindeki ilerlemelere rağmen önemli bir zorluk teşkil etmektedir. Başarılı revaskülarizasyon sonrasında yetersiz mikrovasküler kan akımının geri kazanılması ile karakterize edilen "no-reflow" fenomeni, henüz tam olarak anlaşılamamıştır. Enflamasyon, özellikle interlökin-34 (IL-34), kardiyovasküler hastalıklarda rol oynamaktadır ve bu, no-reflow'daki rolünün araştırılmasını teşvik etmektedir.

Yöntemler: Bu gözlemsel çalışmaya STEMI olan 182 hasta (32 no-reflow, 150 no-reflow olmayan) ve 100 kontrol grubu dahil edilmiştir. Klinik ve anjiyografik veriler analiz edilmiş ve IL-34 seviyeleri ölçülmüştür. Lojistik regresyon ve alıcı işletim karakteristiği (ROC) analizi, no-reflow için IL-34'ün prediktif değerini değerlendirmiştir.

Bulgular: No-reflow olan hastalar, kontrol grubuna ve no-reflow olmayanlara kıyasla yükselmiş IL-34 seviyeleri göstermiştir. Lojistik regresyon analizi, IL-34'ü no-reflow'nun bağımsız bir öngörücüsü olarak tanımlamıştır (olasılık oranı: 1.020, p<0,001). ROC analizi, IL-34'ün anlamlı prediktif değerini ortaya koymuştur (eğri altındaki alan: 0,972, p<0,001).

Sonuç: IL-34, STEMI'de no-reflow'nun güçlü bir öngörücüsü olarak ortaya çıkmakta olup, makrofaj aktivasyonu ve enflamatuvar yanıt üzerindeki rolünü yansıtıyor olabilir. Bu bulgular, STEMI'de no-reflow'yu anlama ve azaltmada yeni bir yol önererek, hedefe yönelik tedavilere kapı aralamaktadır. Yüksek riskli hastaların erken tanımlanması, özelleştirilmiş müdahaleleri bilgilendirebilir ve sonuçta STEMI sonuçlarını iyileştirebilir. Daha geniş kohortlarda IL-34'ün mekanik katılımını açıklamak ve prediktif değerini doğrulamak için daha fazla araştırma gerekmektedir.

Anahtar Sözcükler: İnterlökin-34, ST-yükselmeli miyokard enfarktüsü, no-reflow fenomeni

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INTRODUCTION

ST-elevation myocardial infarction (STEMI) represents a significant cardiovascular emergency marked by the abrupt blockage of a coronary artery, resulting in substantial and frequently irreversible harm to the heart muscle. The timely recognition and management of STEMI are crucial to mitigate its potentially severe consequences (1). The swift reinstating of blood flow to the oxygen-starved heart muscle using reperfusion methods like primary percutaneous coronary intervention (PCI), has fundamentally transformed the approach to managing STEMI. This intervention has significantly improved patient outcomes and minimized the extent of heart muscle damage in many cases (2). However, despite these advances, a vexing challenge persists - the "no-reflow" phenomenon (NRP).

"No-reflow" represents an intriguing and clinically significant complication in the treatment of STEMI (3). It occurs when, despite successful revascularization of the occluded coronary vessel, there is insufficient restoration of microvascular blood flow within the myocardium (4). This phenomenon is associated with exacerbated myocardial injury, increased infarct size, and a heightened risk of adverse cardiovascular events, making it a subject of keen interest among clinicians and researchers alike (5).

To date, the precise mechanisms underlying no-reflow in the context of STEMI remain incompletely understood. Ongoing research is shedding light on the potential impact of inflammatory processes in the pathophysiology associated with this condition (6). In particular, interleukin-34 (IL-34), a proinflammatory cytokine, has garnered attention for its potential role in cardiovascular disease (7). IL-34 operates by engaging with the colony-stimulating factor-1 receptor present on a spectrum of immune and non-immune cells. Through this interaction, it exerts influence over immune responses and modulates inflammatory processes within the body. This interplay underscores its significance in regulating the immune system and related inflammatory pathways (8). Recent investigations have suggested a potential link between IL-34 and an increased risk of the composite endpoint and cardiovascular death in the context of myocardial infarction (9,10). This finding prompts further exploration of IL-34's role in the context of no-reflow.

This research article seeks to delve into the intricate interplay between the NRP and IL-34 in the context of STEMI, unraveling the underlying mechanisms that govern microvascular dysfunction during acute myocardial infarction (AMI). By scrutinizing IL-34's impact on the coronary microcirculation and its role in associated inflammatory responses, we aim to provide valuable insights that may inform future therapeutic strategies and, ultimately, enhance the prognosis of patients experiencing STEMI.

MATERIALS AND METHODS

Study Design

In this cross-sectional observational study, data were gathered from 182 individuals with STEMI, comprising 32 patients experiencing no-reflow (NRP) and 150 without NRP, constituting the study group. Furthermore, a control group comprising 100 individuals was also incorporated into the study for comparative analysis.

Diagnostic criteria: STEMI diagnosis relied on the presence of typical myocardial ischemia symptoms and specific ST-segment elevation criteria: more than 1 mm in the inferior lead or over 2 mm in the anterior chest lead, observed in a minimum of two adjacent leads. Confirmation included the emergence of a new left bundle branch block, which was subsequently validated by elevated cardiac troponin levels. The exclusion criteria included individuals with a previous history of coronary artery bypass surgery, those experiencing cardiogenic shock, prolonged delays exceeding 12 hours from symptom onset to balloon inflation, individuals treated with fibrinolytic agents, active infectious or inflammatory conditions, and a spectrum of chronic inflammatory or autoimmune disorders.

The study received ethical clearance from the Ethics Committee of Fırat University Faculty of Medicine, ensuring compliance with the principles outlined in the Declaration of Helsinki and maintaining adherence to good clinical practices throughout the research process (approval number: 2022/07-38, date: 26.05.2022). Informed written consent was obtained all of the participants prior to study. Upon the diagnosis of STEMI, all patients received specific medications, including 300 mg of aspirin, accompanied by a loading dose of either 600 mg clopidogrel, 180 mg of ticagrelor, or 60 mg prasugrel as part of their immediate treatment regimen. Initial coronary angiography was performed using standard techniques, followed by an intravenous bolus of unfractionated heparin upon the decision for coronary intervention. Primary PCI procedures utilized 6 F or 7 F guiding catheters, and cineangiography analysis was conducted using an Artis Zee Floor workstation (Siemens Medical Solution, Erlangen, Germany).

Assessment of no-reflow phenomenon: The presence of NRP was determined by visually grading thrombolysis in my ocardial infarction (TIMI) flow grades in peri-procedure angiograms. TIMI flow grades were evaluated by two independent interventional cardiologists blinded to patient data. Grades ranged from 0 (indicating no flow after the culprit lesion) to 3 (representing normal coronary flow). Patients were divided into two distinct groups based on their final angiographic TIMI flow rates: the normal-reflow group and the no-reflow group. This categorization allowed for a comparative analysis between these two subsets based on their observed flow rates.

Laboratory assessments: Blood samples were collected from the antecubital veins before coronary intervention for various laboratory examinations, including troponin I levels, lipid profiles, platelet and white blood cell (WBC) counts, creatinine, plasma glucose, and other biochemical tests. The estimated glomerular filtration rate was determined by applying the modification of diet in renal disease equation for calculation purposes. Medication administration during the perioperative period aligned with clinical guidelines, including the discretionary use of glycoprotein IIb/IIIa inhibitors, intracoronary nitroglycerin, and adenosine, as deemed necessary by the operator.

Statistical Analysis

Statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to determine whether continuous variables were normally distributed. Normally distributed variables were given as mean ± standard deviation, and non-normally distributed variables were given as median (minimum-maximum) values. Descriptive statistics are given as percentages and absolute values. The ANOVA test was used to compare the baseline clinical characteristics of 3 groups. A post-hoc

analysis was performed for multiple comparison of groups. When homogenity of variance could not be provided in Levene's test, the Games-Howell test was applied.

Correlation analysis was applied to determine the relationship between IL-34 and NRP. Data were analyzed using logistic regression models to determine whether IL-34 was independently associated with NRP. We performed receiver operating characteristic (ROC) analysis to determine the most sensitive IL-34 cut-off level for predicting the occurrence of NRP following primary PCI in STEMI. Potential confounding factors underwent univariable regression analysis, and confounders with a p<0.25 were further tested in multivariable logistic regression. The threshold for statistical significance was established at a p-value of less than 0.05. We used G-power to detect the study power. The enrollment of 182 patients with STEMI (32 with NRP and 150 without NRP) in the study group, alongside 100 individuals in the control group was aimed at achieving a 99.5% statistical power to detect significant differences in IL-34 levels among patients with NRP, those without NRP, and control subjects.

RESULTS

Table 1 provides a detailed summary of baseline characteristics and laboratory measurements comparing control subjects with patients diagnosed with STEMI, delineating between those with and without the occurrence of the NRP. Cardiovascular risk factors and inflammatory markers appear elevated in STEMI patients, especially those with no reflow. Age did not significantly differ between control subjects (59 years), STEMI patients who underwent successful primary PCI (61 years), and those with no-reflow after STEMI (58 years). There was no statistically significant difference observed in the ratio of females to males between the groups. Body mass index showed a slight increase in both STEMI groups compared to control subjects. Glucose levels exhibited a slightly elevated trend in both STEMI groups when contrasted with the control group; however, this disparity was not significant. Median levels of blood urea nitrogen, creatinine, uric acid, hemoglobin, platelet count, and high-density lypoprotein showed no significant differences across the groups.

When compared with the control group, patients with STEMI, especially those with no reflow, had significantly higher total cholesterol levels. STEMI groups exhibited notably higher levels of triglycerides and low dencity lypoprotein (LDL), showcasing a statistically significant difference between these cohorts. High-sensitivity C-reactive protein (hs-CRP) levels displayed considerable elevation in both STEMI groups when compared with the control group, indicating a notable difference between these sets of patients.

Table 1. Baseline characteristics and laboratory measurements of the study population

Parameters	Control subjects (n=100), mean ± SD or median (min.-max.)	STEMI with successful primary PCI (n=150), mean ± SD or median (min.-max.)	STEMI with NR (n=32), mean ± SD or median (min.-max.)	p
Age, years	59±6.4	61±3.7	58±5.7	NS
Sex, female/male	44/56	69/81	13/19	NS
Body mass index, kg/m^2	28.0±4.4	29.6±4.9	30.1±4.7	NS
Glucose, mg/dL	86.5±5.2	88.3±6.1	92.2±2.7	NS
BUN, mg/dL	14.5 (10-21)	18 (11-27)	13 (9-26)	NS
Creatinine, mg/dL	0.7 (0.5-1.1)	0.7 (0.5-1.2)	0.8 (0.5-1.4)	NS
Uric acid mg/dL	7.6±1.0	7.1±1.8	7.7±1.6	NS
Total cholesterol mg/dL	**219 (111-319)**	**280 (186-366)**	**290 (191-389)**	**<0.05**
Triglyceride, mg/dL	**163.7±99.6**	**182.4±60.4**	**188.4±62.9**	**<0.05**
HDL, mg/dL	45.3±9.9	46.5±11.1	44.5±12.3	NS
LDL, mg/dL	**133.2±43.5**	**172.8±27.3**	**181.1±21.9**	**<0.05**
hs-CRP, mg/dL	**0.3 (0-0.8)**	**4.8 (4.1-6.1)**	**5.9 (4.4-7.7)**	**<0.05**
Hemoglobin, g/dL	13.4±1.0	13.1±1.0	13.7±2.0	NS
Platelet, x10^3/µL	247.4±53.0	253.9±52.7	251.9±47.5	NS
WBC, x10^3/µL	**5.8±1.1**	**8.8±1.6**	**11.4±2.8**	**<0.05**
IL 34, pg/mL	**11±0.9**	**34±5.9**	**51±7.7**	**<0.05**
DM (n)	18	27	8	NS
HT (n)	22	32	8	NS
Smoking (n)	32	48	11	NS
Gensini score, mean	-	34±7.6	37±4.4	NS
Stent length, mm, mean	-	29±3.8	30±5.2	NS
Bifurcation stenting	-	-	-	

BUN: Blood urea nitrogen, HDL: High-density lipoprotein, LDL: Low dencity lipoprotein, WBC: White blood cell, NR: No-reflow, IL: Interleukin, NS: Not significant, STEMI: ST elevated myocardial infarction, PCI: Percutaneous coronary intervention, hs-CRP: High-sensitivity-C-reactive protein.

WBC counts exhibited a notable rise in the no-reflow group compared to both the control group and the successful primary PCI group, showcasing a significant difference among these cohorts. This difference highlights a notable disparity in WBC counts among these patient subsets. IL-34 levels were significantly elevated in both STEMI groups, with the highest levels in the NRP group. There were no significant differences observed in the prevalence of diabetes mellitus, hypertension, and smoking across the groups. The Gensini score, reflecting the severity of coronary artery disease, was not significantly different between the successful primary PCI group and the no-reflow group, though this data was not available for the control group. Stent length did not display any significant differences among the groups.

Those with NRP had significantly increased average serum IL-34 values than controls and STEMI with successful primary PCI (Figure 1).

Table 2 showcases the outcomes derived from logistic regression analyses aimed at pinpointing independent predictors associated with the occurrence of the NRP within the scope of STEMI. While age [odds ratio (OR): 1.018, 95% confidence interval (CI): 0.977-1.062, p=0.388), LDL (OR: 0.940, 95% CI: 0.666-1.328, p=0.727), platelet count (OR: 1.001, 95% CI: 0.995-1.007, p=0.672), and WBC count (OR: 1.007, 95% CI: 0.997-1.018, p=0.173) did not emerge as significant predictors, hs-CRP (OR: 1.039, 95% CI: 1.018-1.060, p=0.004), and IL-34 (OR: 1.020, 95% CI: 1.010-1.030, p<0.001) demonstrated varying degrees of significance. IL-34, in particular, showed a strong association with the NRP in both univariable and multivariable analyses.

A ROC curve was employed to assess the sensitivity and specificity of IL-34 as a diagnostic marker for detecting the NRP within the study population. Results (Figure 2) indicate that plasma IL-34 levels had a significant predictive value for the identification of individuals with NRP (area under the curve: 0.972, 95% CI: 0.950-0.980, p<0.001).

DISCUSSION

In this study, we demonstrated that IL-34, a cytokine involved in macrophage differentiation and activation, emerges as a robust predictor of no-reflow in STEMI patients. The results clearly indicate significantly elevated IL-34 levels in patients who subsequently develop no-reflow following primary PCI. These findings align with a growing body of evidence that underscores the crucial involvement of inflammation in NRP development.

The phenomenon of no-reflow, which is characterized by impaired microvascular perfusion despite successful epicardial vessel reperfusion, is a complex, multifactorial process involving

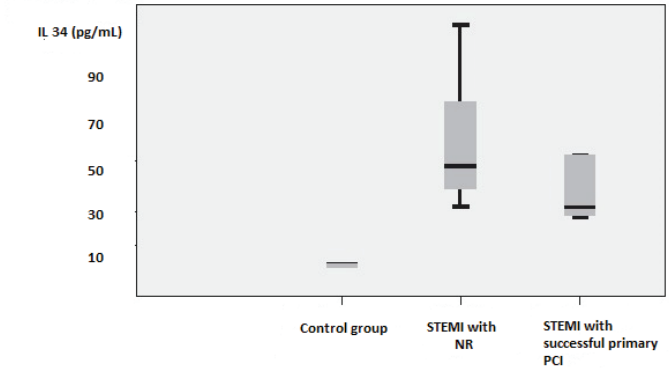

Figure 1. Comparison of IL-34 levels between the groups.

IL-34: Interleukin 34, STEMI: ST-elevation myocardial infarction, PCI: Percutaneous coronary intervention.

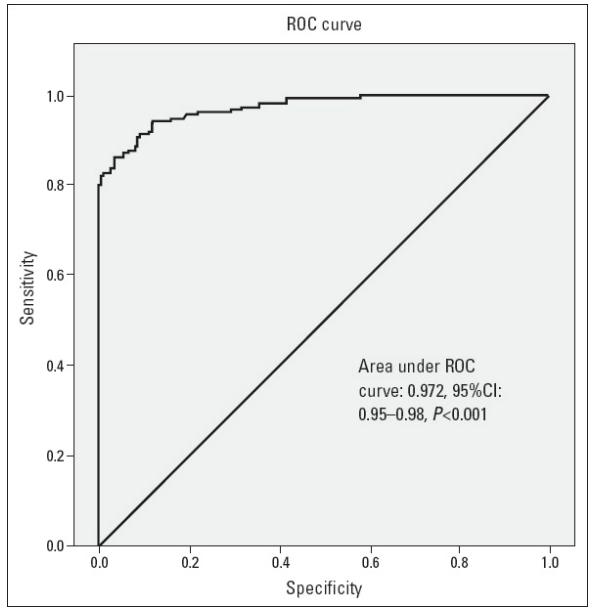

Figure 2. ROC of IL 34 and NRP.

ROC: receiver operating characteristic, NRP: No-reflow phenomenon, CI: Confidence interval.

Table 2. Univariable and multivariable logistic regression analysis representing the independent predictors of NR phenomenon

	Univariable		Multivariable	
Variables	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Age	1.027 (0.991-1.064)	0.140	1.018 (0.977-1.062)	0.388
LDL	0.831 (0.631-1.094)	0.187	0.940 (0.666-1.328)	0.727
Platelet	1.004 (0.999-1.008)	0.141	1.001 (0.995-1.007)	0.672
WBC	**1.013 (1.004-1.022)**	**0.006**	1.007 (0.997-1.018)	0.173
hs-CRP	**1.183 (1.143-1.223)**	**0.003**	**1.039 (1.018-1.060)**	**0.004**
IL-34	**1.028 (1.018-1.038)**	**<0.001**	**1.020 (1.010-1.030)**	**<0.001**

CI: Confidence interval, OR: Odds ratio, WBC: White blood cell, hs-CRP: High-sensitivity-C-reactive protein, IL-34: Interleukin 34, LDL: Low-density lipoprotein.

inflammation, endothelial dysfunction, and thrombosis (11,12). Thus, identifying reliable predictors is crucial for improving risk stratification and potentially developing targeted therapeutic interventions.

Previous studies have reported CRP and IL-6 on admission as predictors of the NRP (13). Hs-CRP has the potential to foster the development of the NRP by augmenting the expression of COX-1 and COX-2, a process that is partly regulated through ERK and JNK activity (14). AMI followed by reperfusion led to notable elevations in serum IL-6 levels and an increase in interferon gamma expression within the myocardial tissue (15). Inflammatory markers like platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), mean platelet volume, and platelet distribution width PDW have been associated with the occurrence of NRP (16-19). A recent study by Esenboğa et al. (20) demonstrated that SII is superior to NLR and PLR in NRP prediction. They also showed that SII was better than CRP for NRP prediction (20). Moreover, the present study underscores the importance of looking beyond traditional inflammatory markers in the context of no-reflow.

One possible explanation for the enhanced predictive value of IL-34 could be its direct involvement in the regulation of macrophages, which are key players in the inflammatory response following myocardial infarction. Macrophages, through their diverse phenotypes, can either exacerbate or resolve inflammation, and their imbalance may contribute to microvascular dysfunction. IL-34 plays a role in the differentiation and migration of macrophages and monocytes (21). Being a proinflammatory cytokine, IL-34 stimulates chemokines and cytokines like monocyte chemoattractant protein, IL-6, and IL-8 (22). IL-34 significantly promotes IL-6 and IL-8 expression (23). Furthermore, IL-34 levels are significantly negatively associated with PLT (24). In a study conducted in patients with rheumatoid arthritis, an increased amount of IL-34 in synovial tissue decreased neutrophil recruitment and intra-synovial neutrophil extracellular traps (25). Li et al. (26) showed that in T-lymphocytes cocultured with antigen-presenting cells, IL-34 treatment downregulates the number of effector cells. Elevated concentrations of IL-34 in patients are correlated with ESR, CRP, ds-DNA antibodies, hemoglobin, and complement levels (27).

The specificity of IL-34 to macrophage activation could make it a more relevant marker for the underlying processes that lead to no-reflow. Although, as far as we have seen, there is no study showing the relationship between NRP and IL-34, numerous studies have investigated the correlation between IL-34 and various cardiovascular diseases, aiming to elucidate its potential role and impact within this medical domain.

Xi et al. (28) demonstrated significantly increased serum IL-34 in ischemic cardiomyopathy, correlating with the presence and severity of ischemic heart failure. Preisser et al. (29) linked IL-34 to profibrotic macrophages and released transforming growth factor β, platelet-derived growth factor, and galectin-3-factors impacting heart failure development. Fan et al. (30) associated IL-34 with the presence and severity of CAD. Li et al. (31) noted elevated IL-34 in CAD patients, correlating positively with hs-CRP levels. Zorena et al. (32) underscored IL-34's enhanced discrimination over CRP for vascular diabetes complications. It is worth noting that this study has limitations, including its cross-sectional design and the need for further validation in larger, prospective cohorts. Additionally, the exact mechanisms by which IL-34 influences no-reflow require further investigation.

CONCLUSION

In conclusion, assessing the NRP in STEMI is of paramount importance in guiding clinical management and predicting patient outcomes. While several inflammatory markers have been explored as potential predictors of no-reflow, the results of this study suggest that the potential role of IL-34 in the regulation of macrophages and the inflammatory response post-myocardial infarction makes it a promising candidate for further research in this context. Identifying patients at a higher risk of no-reflow early could pave the way for more targeted therapies and improved outcomes in STEMI management.

Ethics

Ethics Committee Approval: The study received ethical clearance from the Ethics Committee of Fırat University Faculty of Medicine, ensuring compliance with the principles outlined in the Declaration of Helsinki and maintaining adherence to good clinical practices throughout the research process (approval number: 2022/07-38, date: 26.05.2022).

Informed Consent: Informed written consent was obtained all of the participants prior to study.

Authorship Contributions

Concept: H.A.B., Design: H.A.B., Süpervision: H.A.B., Resources: İ.A., Materials: İ.A., Data Collection or Processing: İ.A., Analysis or Interpretation: H.A.B., Literature Search: M.K., Writing: M.K., Critical Review: M.K.

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