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Research Article

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Relationship Between Antivirals Therapy and Mortality of Moderate and Severe COVID-19 Patients

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Abstract

Background: *Coronavirus disease 2019 (COVID-19) is a viral infection that has become a Pandemic with more than 394 million confirmed cases in 223 countries and more than 5.7 million deaths as of February 2022. Although there have been many studies on the effectiveness of antivirals until now the data in Indonesia is still very limited.*

Objectives: *This study aims to know the relationship between antiviral therapy with mortality of moderate and severe COVID-19 patients.*

Methods: *This study used an observational method using secondary data from medical records of COVID-19 patients at the Wahidin Sudirohusodo Hospital and Hasanuddin University Teaching Hospital from January to June 2021. The relationship between antiviral therapy and mortality was assessed by the chi-square statistical test, where the results of the test were statistically significant if the p-value < 0.05.*

Results: *In moderate-severity COVID-19 patients receiving the antiviral oseltamivir, favipiravir, and remdesivir had no effect on mortality (p = 0.061). In patients with severe COVID-19 who received remdesivir, mortality was 17.1% higher than in subjects receiving favipiravir (p = 0.000; 95% CI 0.063-0.462). Comorbid diabetes in patients with severe COVID-19 increased mortality 2,395 times compared to non-DM (p = 0.030; 95%CI 0.846-3.253). Comorbid hypertension had no effect on mortality in severe COVID-19 patients (p = 0.07). Patients with severe COVID-19 who received remdesivir, comorbid DM increased mortality 2.527 times compared to non-DM subjects (p = 0.018; 95%CI 1.153-5.540).*

Conclusions: *Moderate severity of COVID-19 patients receiving the antiviral oseltamivir, favipiravir, and remdesivir had no effect on mortality. Patients with severe COVID-19 who received remdesivir had a higher mortality risk than favipiravir, which was influenced by the presence of comorbid DM.*

Keywords: COVID-19, Severity, Antiviral, Mortality.

Introduction

Coronavirus disease 2019 (COVID-19) is an infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is a single-stranded ribonucleic acid (RNA) beta coronavirus virus. The virus has a 79% resemblance to SARS-CoV and 50% to the Middle East respiratory syndrome coronavirus (MERS-CoV) [1]. At the end of December 2019, there was an outbreak of COVID-19 which started in the Wuhan region in China and spread rapidly to various countries, so that on March 2020 the World Health Organization (WHO) designated COVID-19 as a pandemic [2].

Based on data from WHO in February 2022, more than 394 million positive confirmed cases of COVID-19 were reported in 223 countries with a death rate of 5.7 million people [3]. In Indonesia, based on data from the Ministry of Health, it is reported that as of February 2022, 4.5 million positive confirmed cases of COVID-19 have been recorded with 144,719 cases of patients declared dead [4, 5]. In South Sulawesi alone, 110,803 positive confirmed cases and 2,247 (2%) deaths have been recorded until February 2022 [6].

COVID-19 patients based on their severity are divided into asymptomatic, mild, moderate, severe, and critical. Asymptomatic is the mildest condition, the patient is asymptomatic [7]. Mild severity is patients with symptoms without evidence of viral pneumonia or hypoxia. Symptoms that appear such as fever, cough, fatigue, anorexia, shortness of breath, myalgia. Moderate severity is patients with clinical signs of pneumonia (fever, cough, shortness of breath, rapid breathing) but no signs of severe pneumonia including oxygen saturation 93 - 95% with room air [8]. Severe severity is a patient with clinical signs of pneumonia (fever, cough, tightness, rapid breathing) plus one of breathing frequency > 30 times/minute and severe respiratory distress with oxygen saturation < 93% of room air. While critical patients are patients with acute respiratory distress syndrome (ARDS), sepsis, or sepsis shock [4].

The severity of disease and mortality of COVID-19 patients are determined by several factors; such as age 65 years and over, male gender, active smokers, the presence of comorbidities (hypertension, diabetes mellitus, cardiovascular disease, chronic kidney disease, chronic liver disease, previous lung disease, malignancy, and immunodeficiency disease), speed of treatment, and type of therapy given [9, 10]. The administration of antiviral therapy is known to have a significant relationship with the clinical outcome of patients [11].

Pharmacological therapy of mild severity COVID-19 patients includes administration of antivirals (one of oseltamivir or favipiravir), azithromycin antibiotics, vitamin C and vitamin D. Pharmacological therapy of moderate severity COVID-19 patients includes administration of antivirals (one of favipiravir or remdesivir), antibiotics (one of azithromycin or levofloxacin) and vitamin C with/without added anticoagulants. In severe severity COVID-19 patients, pharmacological therapy given is antiviral (either favipiravir or remdesivir), antibiotics, corticosteroids, vitamin C, B vitamins, and vitamin D with/without added anticoagulants and other additional therapies (anti-IL6, convalescent plasma, IVIG, or MSCs) [8].

Antiviral therapies such as remdesivir, represent another type of antiviral that promises to effectively inhibit the work of the virus and the course of the disease [12]. Despite numerous studies on the effectiveness of antivirals against COVID-19, data is still very limited in Indonesia. There is no definitive antiviral therapy for COVID-19 and still varies in some guidelines, so further research needs to be done on the relationship between the type of antiviral given and the mortality of COVID-19 patients.

Materials and Methods

Study Design

This study was designed with observational research with a cross-sectional approach. The research was conducted from January to June 2021 at Wahidin Sudirohusodo Hospital Makassar. The population of this study consisted of moderate and severe COVID-19 patients, as determined by the results of the RT-PCR examination, who were undergoing hospital treatment. The inclusion criteria were patients with confirmed COVID-19 infection undergoing hospital treatment and over the age of ≥18 years.

Subjects who meet the criteria should receive antiviral therapy in the following forms: 1) oseltamivir 75 mg daily orally for five days; 2) favipiravir 1600 mg every 12 hours orally for the first day, followed by 600 mg every 12 hours orally for the second day to fifth day; or 3) remdesivir 200 mg daily intravenously for the first day and then 100 mg daily intravenously for the second day to fifth day. The antiviral oseltamivir was administered in this study to subjects with moderate COVID-19 because these subjects have impaired renal function, and favipiravir and remdesivir are not recommended.

Case Definition and Variable Measurement

Patients with confirmed COVID-19 infection were positive for SARS-CoV-2 using the real-time polymerase chain reaction (RT-PCR) method. Subjects with moderate severity COVID-19 have clinical signs of pneumonia (fever, cough, shortness of breath, rapid breathing) but do not have signs of severe pneumonia, such as oxygen saturation levels of 93-95% with room air. subjects with severe COVID-19 have clinical signs of pneumonia (fever, cough, shortness of breath, rapid breathing) and one of the following: respiratory rate > 30 breaths per minute, severe respiratory distress, or oxygen saturation < 93 percent on room air. Patients who are classified as critical are those who have ARDS, sepsis, or septic shock.

Statistical Analysis

The analysis technique used is a combination of descriptive analysis and statistical tests. Univariate analysis was used to conduct the statistical analysis, which was performed using SPSS version 25 for Windows. The number of cases is used to describe qualitative data (percentage). The chi-square test analyzed antiviral therapy and risk factors for gender, age, and comorbidities that affect patient mortality. If the p-value was < 0.05, the results were considered significant. The obtained results will be presented in the form of a narrative with a table.

Ethical Issues

Every action taken during this study had been declared to meet ethical eligibility by a letter from the Biomedical Research Commission on Humans, Faculty of Medicine, Hasanuddin University number: 535/UN4.6.4.5.31/PP36/ 2021.

Result

Characteristics of the Subjects

From January 1 to June 30, 2021, 806 subjects with confirmed diagnoses of COVID-19 were admitted to the hospital. Among these subjects, 383 were excluded because they did not meet the inclusion criteria. Finally, 423 subjects were included in the study (Fig 1).

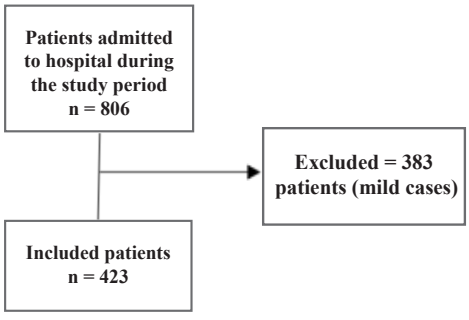

Figure 1: Flowchart of participants.

Among the 423 subjects included in the study, 232 subjects (54.8%) with moderate severity, and 191 subjects (45.2%) with severe severity. Males outnumbered females, with 127 subjects (54.7%) with moderate severity and 111 subjects (58.1%) with severe severity. The majority of subjects in this study were < 60 years old, with 173 subjects (74.6%) with moderate severity and 113 subjects (59.2%) with severe severity.

The most common comorbidities were hypertension, with 70 subjects (36.6%) with moderate severity and 63 subjects (27.2%) with severe severity. 37 subjects with moderate severity were given the antiviral oseltamivir (15.9%). Favipiravir was given to 104 subjects (44.8%) with moderate severity and 22 subjects (11.5%) with severe severity. Remdesivir was given to 91 subjects (39.2%) with moderate severity and 169 subjects (88.5%) with severe severity (Table 1).

Table 1: Characteristics of the Subjects

Parameters	Moderate Severity (n = 232)	Severe Severity (n = 191)
Gender		
Male	127 (54.7%)	111 (58.1%)
Female	105 (45.3%	80 (41.9%)
Age (years)		
< 60 years	173 (74.6%)	113 (59.2%)
≥ 60 years	59 (25.4%)	78 (40.8%)
Comorbidity		
Diabetes Mellitus	49 (21.1%)	52 (27.2%)
Hypertension	63 (27.2%)	70 (36,6%)
Antiviral Agents		
Oseltamivir	37 (15.9%)	0 (0%)
Favipiravir	104 (44.8%)	22 (11.5%)
Remdesivir	91 (39.2%)	169 (88.5%)

Analysis of the Relationship between Antiviral Therapy and Mortality of the Moderate Severity Subjects

Table 2 shows that the percentage of the subject with moderate severity who received oseltamivir therapy had a clinical outcome of death 81.1% compared to a clinical outcome of recovery 18.8%. The percentage of the subject who received favipiravir therapy had a clinical outcome of death of 94.2% compared with a clinical outcome of recovery of 5.8%. The percentage of the subject who received remdesivir therapy had a clinical outcome of death 87.9% compared with a clinical outcome of recovery 12.1%. This difference was not statistically different (p>0.05).

Table 2: Analysis of the Relationship between Antiviral Therapy and Mortality of the Moderate Severity Subjects

Antiviral Therapy	Clinical Outcome		Total	P
	Death	Recovery		
Oseltamivir	**7 (18.9%)**	**30 (81.1%)**	**37 (100%)**	**0.061**
Favipiravir	**6 (5.8%)**	**98 (94.2%)**	**104 (100%)**	
Remdesivir	**11 (12.1%)**	**80 (87.9%)**	**91 (100%)**	

Analysis of the Relationship between Antiviral Therapy and Mortality of the Severe Severity Subjects

Table 3 shows that the percentage of the subject with severe severity who received favipiravir therapy had a clinical outcome of recovery of 72.7% compared to a clinical outcome of death of 27.3%. The percentage of the subject who received remdesivir therapy had a clinical outcome of death of 68.6% compared with a clinical outcome of recovery of 31.4%. This difference was statistically meaningful. When the risk is calculated, severe COVID-19 subjects who are given remdesivir have a higher mortality of 17.1% than subjects who get favipiravir (p = 0.000; 95%CI 0.063-0.462).

Table 3: Analysis of the Relationship between Antiviral Therapy and Mortality of the Severe Severity Subjects

Antiviral Therapy	Clinical Outcome		P	OR	95%CI
	Death	Recovery			
Favipiravir	**6 (27.3%)**	**16 (72.7%)**	**0.000**	**0.171**	**0.063 – 0.462**
Remdesivir	**116 (68.6%)**	**53 (31.4%)**			

Analysis of the Relationship between Gender, Age, and Comorbidities with Mortality of the Moderate Severity Subjects.

In this study, an analysis of the relationship between sex, age, and comorbidity with mortality was carried out in subjects of moderate and severe severity. In subjects with moderate severity, there was no association between sex, age, and comorbidity with mortality (p>0.05) (table 4.1).

Table 4.1: Analysis of the Relationship between Gender, Age, and Comorbidities with Mortality of Moderate Severity Subjects.

Characteristics	Clinical Outcome		Total	P
	Death	Recovery		
Gender				
Male	12 (9.4%)	115 (90.6%)	127 (100%)	0.622
Female	12 (11.4%)	93 (88.6%)	105 (100%)	
Age				
< 60 years old	17 (9.8%)	156 (90.2%)	173 (100%)	0.657
≥ 60 years old	7 (11.9%)	52 (88.1%)	59 (100%)	
Diabetes Mellitus				
Yes	4 (8.2%)	45 (91.8%)	49 (100%)	0.572
No	20 (10.9%)	163 (89.1%)	183 (100%)	
Hypertension				
Yes	10 (15.9%)	53 (84.1%)	63 (100%)	0.091
No	14 (8.3%)	155 (91.7%)	169 (100%)	

Table 4.2 shows that in the subjects with severe severity, the analysis showed no association between sex, age, and comorbid hypertension (p>0.05). On the other hand, comorbid diabetes mellitus is associated with mortality (p = 0.003).

Table 4.2: Analysis of the Relationship between Gender, Age, and Comorbidities with Mortality in Severe Severity Subjects.

Characteristics	Clinical Outcome		Total	P
	Death	Recovery		
Gender				
Male	68 (61.3%)	43 (38.7%)	111 (100%)	0.376
Female	54 (67.5%)	26 (32.5%)	80 (100%)	
Age				
< 60 years old	68 (60.2%)	45 (39.8%)	111 (100%)	0.200
≥ 60 years old	54 (69.2%)	24 (30.8%)	80 (100%)	
Diabetes Mellitus				
Yes	42 (80.8%)	10 (19.2%)	52 (100%)	0.005
No	80 (57.6%)	59 (42.4%)	139 (100%)	
Hypertension				
Yes	51 (72.9%)	19 (27.1%)	70 (100%)	0.070
No	71 (58.7%)	50 (41.3%)	121 (100%)	

Because comorbid diabetes mellitus affects mortality, further analysis was carried out on the effect of antiviral types on mortality of severe COVID-19 patients.

Analysis of the Relationship of Antiviral Therapy Type and Comorbidity with Mortality of Severe Severity Subjects.

Table 5 shows multivariate analysis using logistic regression to assess the association of antiviral type and DM comorbidity with mortality in severe severity subjects showed that severe severity subjects who received remdesivir increased mortality by 0.79 (p = 0.003; 95%CI 0.076-0.583) and with comorbid DM increased mortality 2.395 times (p = 0.030; 95%CI 0.846-3.253).

Table 5: Analysis of the Relationship of Antiviral Therapy Type and Comorbidity with Mortality of Severe Severity Subjects

Parameters	p	OR	95%CI
Remdesivir	0.003	0.211	0.076 – 0.583
Diabetes Mellitus	0.030	2.395	1.088 – 5.272
Hypertension	0.140	1.659	0.846 – 3.253

Analysis of the Relationship of Diabetes Mellitus with Mortality of Severe Severity Subjects Receiving Favipiravir Therapy.

Table 6 shows the severe severity of subjects who received favipiravir, 8 had comorbid diabetes mellitus, and 14 without diabetes mellitus. The percentage of severe severity subjects with comorbid diabetes mellitus who received favipiravir therapy had a clinical outcome of death of 87.5% compared to the clinical outcome of recovery of 12,5%. The percentage of subjects without diabetes mellitus who received favipiravir therapy had a clinical outcome of death of 85.7% compared to a clinical outcome of recovery of 14.3%. This difference was not statistically different (p>0.05).

Table 6: Analysis of the Relationship of Diabetes Mellitus with Mortality of Severe Severity Subjects Receiving Favipiravir Therapy.

Diabetes Mellitus	Clinical Outcome		Total	P	OR	95%CI
	Death	Recovery				
Yes	7 (87.5%)	1 (12.5%)	8 (100%)	0.000	0.171	0.063 – 0.462
No	12 (85.7%)	2 (14.3%)	14 (100%)			

Analysis of the Relationship of Diabetes Mellitus with Mortality of Severe Severity Subjects Receiving Remdesivir Therapy.

Table 7 shows the severe severity subjects who received remdesivir were 51 with comorbid diabetes mellitus and 118 without comorbid diabetes mellitus. The percentage of severe severity subjects with comorbid diabetes mellitus who received remdesivir therapy had a clinical outcome of death of 80.4% compared to a clinical outcome of recovery of 19.6%. The percentage of severe severity subjects without comorbid diabetes mellitus who received remdesivir therapy had a clinical outcome of death of 61.9% compared to a clinical outcome of recovery of 38.1%. This difference is statistically meaningful. When calculating the risk of severe COVID-19 subjects receiving remdesivir, the presence of comorbid diabetes mellitus increased mortality by 2.527 times compared to subjects without diabetes mellitus (p = 0.018; 95%CI 1.153-5.540).

Table 7: Analysis of the Relationship of Diabetes Mellitus with Mortality of Severe Severity Subjects Receiving Remdesivir Therapy.

Diabetes Mellitus	Clinical Outcome		Total	P	OR	95%CI
	Death	Recovery				
Yes	7 (87.5%)	1 (12.5%)	8 (100%)	0.000	0.171	0.063 – 0.462
No	12 (85.7%)	2 (14.3%)	14 (100%)			

Discussion

Based on the COVID-19 Management Guidelines, antivirals favipiravir, and remdesivir can be administered to moderate and severe COVID-19 patients [8]. In this study, subjects with moderate COVID-19 received oseltamivir, favipiravir, and remdesivir. Favipiravir and remdesivir are adenosine analogs that broadly inhibit viral RDRP, both of which are effective as COVID-19 antivirals [13-24]. Meanwhile, oseltamivir is an effective neuraminidase inhibitor drug for influenza therapy. However, as neuraminidase is not found in the SARS-CoV-2 virus, oseltamivir is not considered useful against COVID-19 [25-30].

In subjects with moderate severity of COVID-19 who were given antivirals oseltamivir, favipiravir, and remdesivir, there was no statistical difference in mortality (P>0.05). This finding supports previous studies which revealed that no antiviral therapy, including oseltamivir, has demonstrated efficacy and effectiveness in reducing the mortality of COVID-19 patients [12, 31]. In this study, oseltamivir was administered moderately to COVID-19 patients with impaired renal function who are not recommended to receive favipiravir and remdesivir [8]. Furthermore, another prior study has reported that favipiravir is not superior to other antivirals; patients receiving favipiravir are found to be ineffective in controlling cytokine storms and have more severe symptoms, more comorbidities, and more complications [32].

On the other hand, remdesivir shows efficacy in reducing recovery time, but the results are inconsistent across trials [12]. A systematic review and meta-analysis by Chidambaram et al. found that COVID-19 patients presenting with shortness of breath, bilateral lung involvement on imaging, leukocytosis, and lymphopenia on hospital admission, as well as having elevated levels of CRP, LDH, and d-dimer, have a higher chance of severity and risk of mortality [10]. Similarly, another systematic review conducted by Izcovich et al. has also discovered that the severity and mortality of COVID-19 patients are not only influenced by comorbid factors but also by physical factors (respiratory failure, low blood pressure, hypoxemia, tachycardia, etc.), laboratory factors (increased levels of procalcitonin, troponin, leukocytes, blood lactate, plasma creatinine, d-dimer, LDH, and CRP, as well as decreased platelets, albumin, and IL-6), radiological factors (lung consolidation and pleural effusion), and a high SOFA score [33, 34].

In this study, the mortality rate of subjects with severe COVID-19 who received remdesivir is found to increase by 17.1%, compared to those taking favipiravir (p = 0.000; 95%CI 0.063-0.462). This is in line with the result of a study by Damayanti et al. that patients with severe/critical COVID-19 who were given favipiravir showed better clinical improvement than those receiving remdesivir and oseltamivir (79.2% vs 56.3%; adjusted RR = 2.196; 95%CI 1.084-4.451).34 Other studies also reported that the mortality of patients taking remdesivir was 13% higher than that of patients taking favipiravir [32, 34, 35].

The risk factors of sex, age, and comorbid hypertension are revealed in this study to be statistically unrelated to the mortality of subjects with moderate and severe COVID-19 (p>0.05). This finding confirms prior studies which proved that patients' characteristics such as age and sex, as well as comorbid hypertension, do not have a significant relationship with their clinical outcomes [11, 36]. Meanwhile, comorbid diabetes mellitus is associated with mortality (p = 0.003) of subjects with severe COVID-19, as reported by Chidambaram et al. found that

COVID-19 patients with comorbid diabetes mellitus have a 1.59 times higher mortality than those without comorbid diabetes mellitusm [10]. In addition, diabetes mellitus is the highest risk factor for death from COVID-19, which is 4,384 times greater than subjects without diabetes mellitus (p = 0.000) [36]. A meta-analysis done by Kumar et al. also discovered that diabetes mellitus is significantly associated with the mortality risk of COVID-19, with a pooled odds ratio of 1.90 (95% CI: 1.37-2.64; p<0.01) [36]. Diabetes mellitus is also found to be correlated with the risk of ARDS, longer intensive care, and the use of invasive ventilation [37].

This study revealed that for subjects with severe COVID-19 who were given remdesivir, comorbid diabetes mellitus increased mortality by 2,527 times, compared to those without comorbid diabetes mellitus (p = 0.018; 95%CI 1.153-5.540); 80.4% of all subjects who took remdesivir and had diabetes mellitus died, whereas the remaining 19.6% recovered. Meanwhile, 61.9% of subjects without comorbid diabetes mellitus died and 38.1% recovered. In other words, COVID-19 patients administering remdesivir have a higher mortality rate than those taking favipiravir. This is most likely not due to the influence of antivirals, but because of diabetes mellitus.

People with diabetes mellitus are susceptible to infection due to phagocytic cell dysfunction. DM patients have elevated ACE-2 receptors, which can increase the risk of COVID-19 or aggravate COVID-19 infection [38]. Additionally, patients with diabetes mellitus also have high expression of furin, an enzyme involved in viral entry into the host by reducing the dependence of COVID-19 on human proteases [39]. The COVID-19 S-protein attaching to ACE-2 receptors is activated by high levels of furin. Such reactivation of this S-protein allows the virus to enter cells and escape the immune system [40]. Irregular immune response to increased ACE -2 receptors and furin expression leads to higher lung inflammation and can lower insulin levels [38, 39]. Furthermoe, impaired T-cell function and elevated IL-6 levels also play a crucial role in the development of COVID-19 disease in people with diabetes [41].

Despite contributing to the literature on this topic, this study has a limitation as it does not include the analysis of confounders which have theoretically been shown to affect mortality, such as other comorbidities (chronic kidney disease, heart disease, impaired liver function, malignancy, autoimmune disease, history of pulmonary disease, HIV infection, obesity, and smoking status), acquired supportive therapy, nutritional status, and CT values. Therefore, further studies are highly needed to overcome this limitation.

Conclusion

Administration of antivirals oseltamivir, favipiravir, and remdesivir in patients with moderate severity of COVID-19 has no effect on mortality. Meanwhile, patients with severe COVID-19 who receive remdesivir have a higher mortality risk than those who are given favipiravir, which is also influenced by comorbid diabetes mellitus.

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Authors Contributuion

FJG, HI, and SB were the principal investing ators of the study and drafted the manuscript; FJG and AAZ collected and analyzed the data; SK, HR, MI, dan FP contributed to the concept and design of the study; HI and SB revisited the manuscript and critically evaluated the intellectual contents. All authors participated in the final draft preparation, manuscript revision, and critical evaluation of the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

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Institutional Review Board Statement

Approval number 535/UN4.6.4.5.31/PP36/2021 of the Ethics Committee of Dr. Wahidin Sudirohusodo General Hospital, Makassar, Indonesia.

Data Availability Statement

No new data were created or analyzed in this study. Data sharing is not applicable in this article.

Ethical Considerations

The authors have observed all ethical issues (including plagiarism, data fabrication, and double publication).

Conflicts of Interest

The authors declare no conflict of interest.

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