



The return visit, outcome and predicting factors of return visit among suspected COVID-19 outpatients

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Abstract

Rate of return visit, predicting factors of return visit and occurrence of adverse events in suspected to be or likely cases of COVID-19 patients who received outpatient treatment. This is a retrospective observational cohort study on patients (> 16 years), suspected to be or likely cases of COVID-19 who were visited in a respiratory emergency department and subsequently discharged home. Patients' baseline characteristics were extracted from medical charts. All patients were followed-up for 7 days after their first visit. Patients' outcomes during the 7-day follow-up, as well as the severity of pulmonary involvement based on imaging were recorded. A total number of 601 patients (350 men and 251 women) were recruited. The rate of return visit was 27.74% (144 patients) with 6.74% (34 patients) experiencing a poor outcome. Six factors with a significant odds ratio were predictors of poor outcome in patients who received outpatient treatment, namely, older age [odds ratio = 3.278, 95% confidence interval: 1.115–9.632], days from onset of symptoms [1.068, 1.003–1.137], and history of diabetes [6.373, 2.271–17.883]. Predictors of favorable outcome were female gender [0.376, 0.158–0.894], oxygen saturation > 93% [0.862, 0.733–1.014], smoking habit [0.204, 0.045–0.934]. The findings of this study demonstrate that the rate of return visit with poor outcome in patients who received outpatient treatment was reasonably low. Age, male sex, diabetes mellitus and pulmonary disease are predicting factors of poor outcome in these COVID-19 patients who received outpatient management.

Keywords COVID-19 · Outpatient management · (poor) Outcome predictors

Introduction:

Since the first report of Coronavirus 2019 (COVID-19) in December 2019, this acute contagious infectious disease has spread throughout the globe, infecting more than 164 million people as of May 19, 2021. While about 20% of infected patients develop severe and critical form of the disease, the majority are asymptomatic or have mild-to-moderate symptoms. Although some countries such as China [1] admit all patients, including mild and asymptomatic confirmed cases,

to be isolated, monitored and treated in designated hospitals, limited capacity of in-hospital beds, especially at the time of pandemics, makes it practically impossible to admit all symptomatic cases of COVID-19. In many countries, the response capacity of healthcare systems has already been overwhelmed by the influx of patients with signs and symptoms of COVID-19. According to the Centers of Disease Control and Prevention (CDC) and World Health Organization (WHO) guidelines, asymptomatic patients and patients with mild symptoms in the absence of viral pneumonia and hypoxia can be isolated in outpatient settings to receive home care [2, 3]. Some countries such as Iran, United States of America (USA) and England consider outpatient management even for patients with moderate infections if clinically appropriate according to national guidelines [4]. This approach helps them decrease the pressure on the hospitals and create surge capacity for medical centers to focus on severe and critically ill patients. However, concerns have been raised regarding this approach, stating that these

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patients may return to the hospital with worsened symptoms requiring admission.

During this pandemic, prediction models have focused mostly on the risk of critical illness among admitted patients. Few studies mentioned the incidence of return hospital admission and the associated patient characteristics [5]. Therefore, in this cohort study, we evaluated the outcome of COVID-19 patients who were assessed in the emergency department and discharged home. We specifically focused on the rate of return visit and the occurrence of adverse events in order to disclose their predictors.

Materials and methods

Study design

We carried out this retrospective observational cohort study to assess the rate of return visit and the adverse events in patients who were examined in the “Respiratory ED” (ResED) and discharged to receive only home treatment. The study protocol was approved by the university ethics committee (IR.TUMS.VCR.REC.1399.074).

Study setting

This study was conducted at a large university-affiliated tertiary care hospital, during March 2020 to April 2020. Following COVID-19 pandemic, a ResED was set up for patients with signs and symptoms suggestive of COVID-19. It is staffed 24/7 by board-certified specialists from the departments of emergency medicine and infectious diseases and had an average daily census of about 500 patients during the study period. The national protocol for management of COVID-19 patients is (Table 1) not mandatory, such that patients are admitted or discharged at the discretion of the physicians.

Participants

All patients (older than 16 years), suspected to be or likely cases of COVID-19 according to WHO definition [6], who were evaluated and subsequently discharged home from our ResED were eligible for this study. Based on the hospital guideline and at the discretion of the treating physician, these patients were discharged either on conservative treatments or antiviral/antibacterial treatment plus conservative management. Exclusion criteria included pregnancy and a known history of pulmonary disease independent from a hospital admission during the previous month.

Study protocol and measurements

One of the researchers (E.N.) extracted the list of all consecutive patients older than 16 who had been discharged from our ResED between March 2020 and April 2020. The researcher then screened the charts of the patients for inclusion and exclusion criteria. All data were recorded, including age, gender, primary vital signs, severity of primary illness, past medical history (including diabetes mellitus [DM], hypertension [HTN], ischemic heart disease [IHD], respiratory disease, and immune deficiency), medication history in the data collection sheet.

The severity of pulmonary involvement in chest CT scan of the patients who had undergone imaging was assessed by a board-certified radiologist who was blinded to the outcomes.

Then, one of the researchers (A.A.) compared the discharge criteria followed by the treating physician to those of the Iranian national flowchart, adding these results to the checklist. The same researcher also checked the hospital registration system to find any return visit of patients during the 7 days that followed the index examination. If no data were found, the patient was contacted to assess the outcome. If the

Table 1 Outpatient management criteria for COVID-19 according to the Iranian National flowchart

Out patient management criteria:	<p>Patient with a chief complaint of cough, dyspnea, chills with/without fever and without any past medical history of DM^a; BMI^b> 40; HTN^c; IHD^d; respiratory disease and immune deficiency: patients with RR^e< 30/min or SatO₂^f> 93% can be discharged home with conservative management</p> <p>Patient with a chief complaint of cough, dyspnea, chills with fever and with any past medical history (as mentioned above) with normal chest imaging of the chest, who has RR^e< 30/min or SatO₂^f> 93% can be discharged home with both antiviral and conservative treatment. Patients with immunodeficiency will also undergo imaging even though they do not have any fever</p>
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^aDiabetic mellitus

^bBody mass index

^cHypertension

^dIschemic heart disease

^eRespiratory rate

^fO₂ saturation

first call failed, the researcher made follow-up phone calls for 3 consecutive days. Respondents were enquired regarding re-admission or the occurrence of adverse outcomes during the follow-up period.

Definitions

The diagnosis of Human Immunodeficiency Viruses (HIV) infection, of malignancy, any history of chemotherapy and transplantation, prednisone treatment > 12.5 mg/ day for > 2 weeks were considered as immunodeficiency.

The severity of COVID-19 was classified into four categories according to the Guidelines for the Diagnosis and Treatment of New Coronavirus Pneumonia [7]: (1) mild type: no complaints to mild clinical symptoms without any chest CT involvement; (2) moderate type: patients with fever and signs of respiratory infections with chest CT scan involvement; (3) severe type: any of these criteria: (a) a respiratory distress, respiratory rate ≥ 30 /min; (b) finger oxygen saturation $\leq 93\%$ in resting condition; (c) arterial partial pressure of oxygen (PaO₂)/oxygen concentration (FiO₂) ≤ 300 , (4) critical type: any of these criteria: respiratory failure, needing Intensive Care Unit (ICU) admission, shock.

The severity of pulmonary involvement on chest CT scan was assessed by a semi-quantitative 0 to 5 scoring system [8] for each of the 5 lung lobes. The scoring system was based on the percentage lung involvement: Score 1, 1–5%; Score 2, 6–25%; Score 3, 26–50%; Score 4, 51–75%; Score 5, 76–100%. The sum of individual lobar scores was assumed as total CT scores and ranged from 0 (no involvement) to 25 (maximum involvement).

For the purpose of this study, patient outcomes were divided into poor or good. Patients were considered to have a good outcome if they did not return for an unscheduled visit during the first 7 days of follow-up period, if admission was not deemed necessary at the hospital examination during the same period. Poor outcome was defined as any hospital admission either to ward or to ICU, intubation or any cause of death during these 7 days.

Outcomes

The primary outcome in our study was return visit to our hospital or any other medical center and occurrence of adverse events including admission to ward, ICU, intubation, or all-cause mortality.

Study size

Sample size required for the present study was calculated to be 600 cases, considering 10% relative error, $d=0.04$ with confidence interval of 95% and $\alpha=0.05$.

Statistical analysis

Analyses were done using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, N.Y., USA). We used either chi-square or Fisher's exact test for categorical variables. Shapiro–Wilk test was used to evaluate the normality of the scale distributions of the variables and we tested these variables with the Mann–Whitney *U* test. We performed binomial logistic regression to measure the relationship between dependent variables and the outcome of the patients (odds ratios).

Results

During the study period, 601 patients, suspected or probable cases of COVID-19, were assessed and discharged from our ResED. We did not succeed in reaching 82 cases and, therefore, completed the follow-up for 519 patients. Participants' flow in the study is demonstrated in Fig. 1.

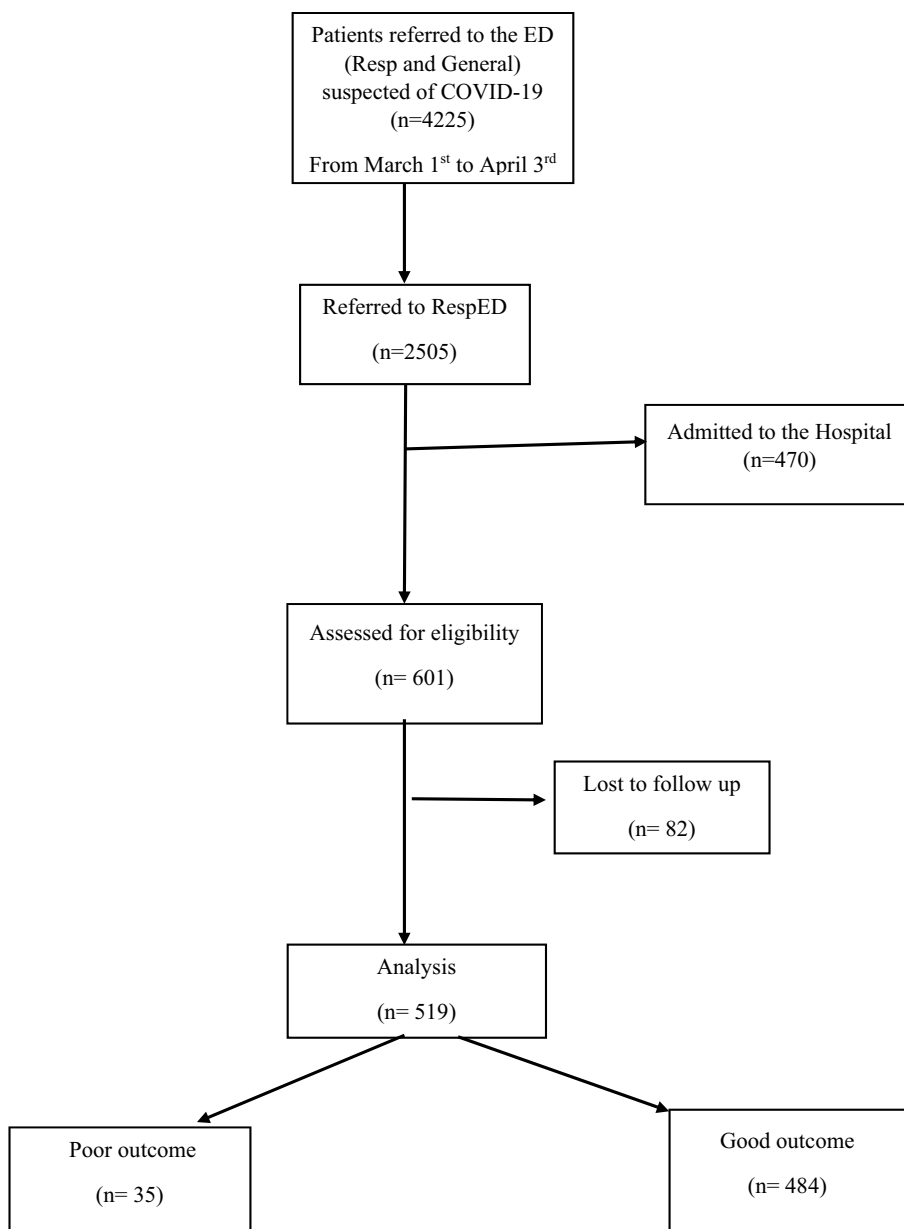
Among 519 patients for whom the 7-day follow-up was completed, 484 (93.26%) patients had good outcome: 375 (77.48%) had no return visit and 109 (22.52%) had a return visit but admission was not deemed necessary. Only 35 (6.74%) patients experienced poor outcome; 27 (77.14%) were admitted to the ward, 2 (5.71%) required ICU admissions, 1 (2.86%) underwent intubation, and 5 patients (14.30%) died.

Demographic and baseline characteristics of all patients as well as those experiencing good or poor outcome are shown in Table 2.

Forty-seven patients (9.96%) were 65 years of age or older, 9 (19.15%) of them had poor outcome. On the other hand, among 472 patients (90.94%) younger than 65, only 26 (5.51%) had poor outcome (P -value = 0.002).

As can be seen in Table 2, there is a significant difference between the two groups of patients (those with poor and those with good outcome) regarding their age, sex, days from symptoms onset, oxygen saturation on room air, body temperature, past history of IHD and DM, as well as severity of the disease. Although oxygen saturation and body temperature showed a statistically significant difference between the two groups, we do not consider this of importance in treating these patients.

Based on the available data from patients' charts and the Hospital Information System (HIS), we managed to determine the adherence to our national protocol for disposition in 484 patients. We noted that in 397 cases (82.02%), discharge was in accordance with the national protocol, while in 87 cases (17.98%) the decision of outpatient management basis was made at the discretion of the treating physician, but not in strict compliance with the national protocol. Among the former group, 20 patients (5.04%) experienced poor

Figure 1 Participants' flowchart

outcome, while in the latter group, 12 (13.79%) had poor outcome. (P value = 0.007). The analysis of the patients who were discharged home based on national protocol revealed that poor outcome was seen more likely in patients aged 65 or older (P value = 0.040) and those who had pulmonary disease (P value = 0.044).

When logistic regression model was applied to obtain odds ratios, several factors were found to be related to poor outcome. Odds ratios based on final output model are presented in Table 3. As noted in the table, from 14 factors entered into the model, only 6 had a significant odds ratio (namely, age [odds ratio = 3.278, 95% confidence interval: 1.115–9.632], gender [0.376, 0.158–0.894], oxygen saturation [0.862, 0.733–1.014], number of days from

onset of symptoms [1.068, 1.003–1.137], smoking [0.204, 0.045–0.934], and history of DM [6.373, 2.271–17.883]).

Discussion

The result of this retrospective observational cohort study revealed that the overall rate of return visit in patients who were visited in our ResED and received outpatient treatment was about 27.74% (144 patients) with 6.74% (35 patients) experiencing adverse events. There were factors which predicted poor outcome in patients who received outpatient management.

Table 2 Baseline characteristics and demographics of patients with coronavirus disease-2019

Characteristics	Total	Poor outcome	Good outcome	P-Value
Age in years mean \pm SD ^a	43.0 \pm 14.2	50.0 \pm 16.3	42.4 \pm 13.9	0.005
Gender N ^b				
Men	303 (58.4)	26 (74.3)	277 (57.2)	0.048
Women	216 (41.6)	9 (25.7)	207 (42.8)	
Vital signs mean \pm SD				
PR ^c	94.7 \pm 16.1	97.4 \pm 15.7	94.5 \pm 16.2	0.476
RR ^d	19.4 \pm 2.6	20.1 \pm 3.5	19.3 \pm 2.5	0.218
O ₂ Saturation	96.0 \pm 2.1	94.7 \pm 3.0	96.1 \pm 2.0	0.005
Temperature	36.7 \pm 1.3	37.1 \pm 0.7	36.7 \pm 1.4	0.012
Days from onset of symptoms to hospital examination mean \pm SD	4.7 \pm 4.4	6.4 \pm 5.3	4.5 \pm 4.3	0.018
Smokers N (%)	94 (18.1)	2 (5.7)	92 (19.0)	0.049
Co-existing factors N (%)				
HTN ^e	70 (13.5)	8 (22.9)	62 (12.8)	0.119
Cardiovascular disease	42 (8.1)	7 (20.0)	35 (7.2)	0.016
Pulmonary disease	23 (4.4)	3 (8.6)	20 (4.1)	0.197
DM ^f	45 (8.7)	10 (28.6)	35 (7.2)	<0.001
Immune deficiency	10 (1.9)	1 (2.9)	9 (1.9)	0.506
Severity of the disease N (%)				
Mild	225 (43.4)	8 (22.9)	217 (44.8)	0.005
Moderate	138 (26.6)	12 (34.3)	126 (26.0)	
Severe	33 (6.4)	6 (17.1)	27 (5.6)	
Missing	123 (23.7)	9 (25.7)	114 (23.6)	
Radiologic severity score mean \pm SD	2.5 \pm 3.7	4.7 \pm 6.2	1.9 \pm 3.4	0.065

^aStandard deviation^bNumber^cPulse rate^dRespiratory rate^eHypertension^fDiabetic mellitus

As in almost any other hospital, our ED was flooded by many patients who experienced signs or symptoms suggestive of COVID-19. A national protocol was in place to help clinicians identify those patients who did not require admission. We noted that the protocol worked fairly well in our setting. Only about 5 percent of patients who had been discharged based on the national protocol experienced a poor outcome during 7-day follow-up. Therefore, our national protocol seems to be successful in selecting patients for outpatient treatment.

We reviewed the predicting factors of poor outcome in those patients who had been treated on outpatient basis. Age (older than 65 years), male sex, past medical history of DM, and days from symptom onset were all independent predictors of poor outcome during the 7-day follow-up. Furthermore, predicting factors of poor outcome in a subset of patients for whom discharge disposition was in compliance with the national protocol were also assessed. Age (older than 65 years), pulmonary disease, DM and

immune deficiency were found to predict poor outcome in these patients. Revising the national protocol by incorporating these predictors may lower the rate of poor outcome even further.

To the best of our knowledge, no prior study has evaluated the prognostic factors specifically in COVID-19 cases in outpatient setting. However, most of the factors identified in our study to predict a poor outcome were comparable to those reported in other COVID-19 populations and settings (including inpatients [9]).

In several studies [1, 8–12], age was mentioned as a predicting factor for death and respiratory failure in hospitalized patients with COVID-19.

Male sex was a predicting factor for poor outcome in our patients. In other studies [8, 12, 13], male sex was shown to be a predicting factor for respiratory failure or death in COVID-19 patients admitted to the hospital. In a single study [11], gender was not considered a predicting factor.

Table 3 Predicting factors of poor outcome in patients with coronavirus disease-2019

Predictors	OR	95% CI		P- Value
		Lower	Upper	
Age \geq 65	3.278	1.115	9.632	0.031
Female sex	0.376	0.158	0.894	0.027
PR ^a	1.010	0.985	1.037	0.431
SatO ₂ ^b	0.862	0.733	1.014	0.074
RR ^c	1.087	0.954	1.234	0.212
Temp ^d	0.999	0.971	1.028	0.949
Days from onset of symptoms to follow-up hospital examination	1.068	1.003	1.137	0.039
Smoking	0.204	0.045	0.934	0.041
HTN ^e	0.546	0.165	1.803	0.321
Cardiovascular disease	1.753	0.580	5.294	0.320
Pulmonary disease	2.233	0.546	9.122	0.263
DM ^f	6.373	2.271	17.883	<0.001
Immune deficiency	2.371	0.246	22.834	0.455

^aPulse rate^bO₂ saturation^cRespiratory rate^dTemperature^eHypertension^fDiabetic mellitus

In our study, patients' vital signs at first presentation to ResED did not independently predict poor outcome during the 7-day follow-up. In a study by Yang and his colleagues [11], respiratory rate in patients with severe COVID-19 was significantly higher than that of the patients in the mild group, while the blood oxygen saturation was significantly lower in the former group. We had the same result in our study, but in the regression model, these were not found to independently predict poor outcome, although there was a trend for oxygen saturation being lower in those with poor outcomes (P value = 0.074). In the study by Yang et al., days from symptom onset to visit was also a predictive factor in the group with severe disease, which was similar to the results of our study.

One of the unexpected findings of our study was the higher rate of smokers (19% vs 5.70%) in patients with good outcome. In fact, based on our findings, being nonsmoker was a predicting factor of poor outcome in our patients (OR = 0.2, P value = 0.041). Although some anecdotal reports and initial studies on COVID-19 patients admitted to the hospital in China [14], England [13] and France [15] with COVID-19 revealed that the proportion of smokers was smaller in these patients, another study [16] which reviewed 8 meta-analysis or systematic reviews, supported the WHO [17] position on smoking which considered smoking as

an important factor in increasing the risk of mortality and morbidity in hospitalized COVID-19 patients. The pathophysiology of the effect of smoking on this virus is not well described. Some scholars pointed out that smoking and nicotine could reduce the amount of Angiotensin-Converting Enzyme-2 (ACE2) receptors, which are used by coronavirus to enter the cells and mitigate the cytokine storm, while some other studies mentioned the upregulation of ACE2 inhibitors in smokers [18]. On the other hand smokers have destroyed ciliary apparatus and their survival is linked to coughing, caused by the irritation of the airways; therefore, by coughing they manage to clear their bronchial secretion somehow and avoid pneumonia. If COVID-19 impairs the ciliary system (as Influenza virus does) then smokers might still be able to clear their secretions, limiting the access of the virus to the small airways. In our study, only 98 patients (18.50%) were smokers; therefore, our study might be underpowered for finding any correlation between smoking and the prevalence or severity of COVID-19.

Severe underlying disease was the predictor of mortality and respiratory failure of COVID-19 patients especially, DM and severe pulmonary disease based on a large cohort study on 17 million COVID-19 patients in the United Kingdom [8, 13]. According to Chinese CDC reports IHD, HTN, DM, respiratory disease, and cancer were also associated with high mortality in these patients [19]. Also in a retrospective cohort study in Iran [11] on 62,955 COVID-19 patients who were admitted to the hospital, patients with a history of cardiovascular disease, DM, pulmonary disease, active cancer or chronic liver disease had a higher rate of mortality compared to others. In our study, pulmonary disease, DM and immunodeficiency were predictors for poor outcome in patients who were discharged based on national protocol. The number of patients with immunodeficiency was very low in the study population, therefore, we should be cautious when considering this as predicting factors of poor outcome.

In several studies, higher severity score of lung involvement in chest CT scan was found to be associated with severe and critical forms of the disease [11, 20]. We also reported the severity score in our patients. The mean radiological severity score was low (2.0 ± 3.7). A significant difference was not found between the severity score of the two groups of patients (poor vs good outcome), although there was a trend toward higher score in patients with poor outcome (4.7 ± 6.2 vs 1.9 ± 3.4 , P -value = 0.065).

Limitations

This study faces several limitations. First, our study was a single-center low population study, conducted in a tertiary care hospital. Thus, reproducing it on larger sample will improve its generalizability. Secondly, our relatively high

proportion of patients lost to follow-up might underestimate the result of poor outcomes. Third, admitted patients were not included in our study; therefore, we cannot calculate the sensitivity of our national protocol for detection of patients eligible for outpatient management. Actually, our guideline for admission was breached in a large proportion of patients due to capacity concerns in the hospitals, hence the discharge/admit guideline was not tested adequately for sensitivity and specificity. Our patients received different treatment regimens and their adherence to treatment was variable; this could have also affected the results. Limited availability of real-time PCR kit in our country made health care providers to perform the test only on admitted patients. However, considering the clinical, radiological and epidemiological factors the cases were very likely to be COVID-19.

Conclusion

The rate of return visit with poor outcome in patients who received outpatient treatment was reasonably low, especially in those who had been discharged in adherence to the national protocol. Age, male sex, DM, pulmonary disease and immunodeficiency are predicting factors of poor outcome in these COVID-19 patients who received outpatient management. We might consider age and pulmonary disease in our national protocol discharge criteria. There are a number of gaps in our study; therefore, further research should be considered to elaborate discharge predicting score for ED patients with COVID-19.

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Declarations

Ethical approval The study protocol was approved by the university ethics committee (IR.TUMS.VCR.REC.1399.074).

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest The author(s) declare that they have no conflict of interest.

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