ORIGINAL ARTICLE

A Framework to Tackle Risk Identification and Presentation Challenges in Sepsis

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Introduction: Sepsis trajectories, including onset and recovery, can be difficult to assess, but electronic health records (EHRs) can accurately capture sepsis as a dynamic episode.
Methods: Retrospective dataset of 276,722 clinical observations (4,726 unique patients) during a two-month period in 2015 were extracted from the EHRs. A Cox proportional hazard model was built to test hazard ratios of risk factors to the first sepsis episode onset within 72 hours for patients with presumed infection. Predisposition, infection, response, and organ failure (PIRO) score-based framework was used in a logistic regression to identify factors associated with in-hospital mortality within the sepsis population.
Results: 47.54% of patients with an infection episode experienced at least one sepsis episode (N=1,044 out of 2,196) within 72 hours of admission. The mortality rate was higher for patients with sepsis episodes (7.24%) compared to patient with only organ dysfunction episodes (4.84%) or only with infection episodes (3.96%). Analysis identified factors associated with the first sepsis episode onset and those associated with in-hospital mortality.
Discussion: Our study addresses identification of infection, organ dysfunction, and sepsis as dynamic episodes utilizing EHR data and provides a systematic approach to detect risk factors related to sepsis onset and in-hospital mortality.

Keywords: Sepsis, electronic health records, dynamic sepsis episodes, risk prediction

INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by a dysregulated response to infection with increasing incidence and mortality rate that make it a high cost, high mortality condition that puts a significant burden on the healthcare systems.[1,2,3,4] Sepsis has been widely studied using categorization and prediction methods based on patient-level clinical observations;[5,6] however, risk prediction methods commonly rely on a fixed time window for capturing input parameters. For example, the Quick Sequential Organ Failure Assessment (qSOFA) uses variables measured from 3-12 hours before/ after the onset of infection to predict in-hospital

mortality[7] or and studies utilizing administrative claims data that define sepsis markers as static events at the hospitalization level using International Classification of Diseases (ICD) diagnosis codes.[8]

In clinical practice, infections and sepsis develop and are treated dynamically over time.[9] Established guidelines such as the *Surviving Sepsis Campaign: 2016 International Guidelines for Management of Sepsis and Septic Shock* highlight that sepsis and septic shock,[7] defined as a subset of sepsis with circulatory and cellular/ metabolic dysfunction, require immediate resuscitation and continuing treatment guided by appropriate reassessment of patient's condition.[9] Data-driven screening of factors associated with the dynamics of sepsis has the potential to detect sepsis onset earlier and improve prognosis.[10,11]

Considering the uncertainties associated with sepsis diagnosis and treatment dynamics, hospitalized patients with a presumed infection may exhibit various sepsis-induced deterioration and recovery episodes over time. Utilization of electronic health records (EHRs) provides an opportunity to explore quantitative methods to identify factors associated with the onset of sepsis and the development of sepsis-related organ dysfunction. Furthermore, capturing sepsis-induced dynamic deterioration through the utilization of EHRs promises enhanced understanding of risk for sepsis-induced adverse outcomes including mortality during the hospitalization. The objectives of this study are to present a systematic approach to identify sepsis episodes based on clinical physiology, predict onset of sepsis episodes in infected populations, and identify factors associated with in-hospital mortality in these patients.

METHODS

Study Population

Christiana Care Health System (Christiana Care), located in Delaware, has more than 1,100 patient beds across two hospitals (Christiana Hospital and Wilmington Hospital) with over 53,000 annual admissions. The study population comprised of adult patients (18 and older) admitted to Christiana or Wilmington Hospital between January and July 2015. Pediatric, elective surgery and outpatient populations (i.e., individuals who were discharged from the emergency department without being admitted to the hospital) were excluded. The study was approved by Christiana Care's Institutional Review Board.

Study Design and Episode Definitions:

This retrospective, observational cohort study aimed to determine the association between patient-level data derived from the EHRs and patient-level outcomes: (i) onset of a sepsis episode in infected patients, and (ii) in-hospital mortality in septic patients. Infection, organ dysfunction, sepsis, and septic shock were defined as dynamic episodes using established clinical criteria as outlined below. In-hospital mortality was defined as a discharge disposition documented in the medical chart as expired.

Infection episode was defined as an administration of an antibiotic, antiviral, or antifungal (i.e., antimicrobial) with accompanying body fluid cultures (e.g. blood, urine, cerebrospinal fluid). Time windows based on Seymour el al.'s definition[8] were selected regarding antimicrobial treatment and culture sampling. If the antimicrobial treatment was administered first, the culture sampling must have been obtained within 24 hours. If the culture sampling was first, the antibiotic must have been ordered within 72 hours. The *onset of infection episode* was defined as the time at which the first of these two events (antimicrobial treatment or culture sampling) occurred.

Sepsis episode was defined utilizing the Third International Consensus definitions[1] including suspected infection and organ dysfunction. *Organ dysfunction episode* was derived from the EHRs using systolic blood pressure (SBP) measurement less than 90 mmHg, mean arterial pressure (MAP) less than 65 mmHg, decrease in SBP greater than 40 mmHg from an initial value, lactate greater than or equal to 2 mmol/L, platelet count less than 100 $\times 10^3/\mu L$, creatinine greater than 2 mg/dL or a 50% increase from baseline, or the use of a ventilator as part of the oxygen source. The *onset of organ dysfunction episode* was defined as the time at which the first of the listed organ dysfunction criteria occurred. Organ dysfunction-related measures were carried forward for 8 hours in case the other organ dysfunction criteria are met during the next 8 hours based on clinical input. To define the onset of a sepsis episode, organ dysfunction criteria must have been met 48 hours prior or 24 hours after the onset of an infection episode. *Septic shock* was defined as receiving vasopressor(s) as well as the tested serum lactate over 2 mmol/L.[12]

Figure 1 illustrates the infection, organ dysfunction, and sepsis episodes. In this hypothetical example (Figure 1), the patient first experiences an infection episode with simultaneous organ dysfunction. In other words, the first sepsis episode is caused by an infection followed by organ dysfunction. The patient recovers from the first sepsis episode when the first infection episode ends. The second sepsis episode is caused by a new onset organ dysfunction followed by an infection episode (Figure 1).

Data Processing

The dataset contained 127 patient-level data elements with a total of 276,722 clinical observations. Data elements included demographics (e.g. age, gender), visit-level data (e.g. discharge disposition), vital signs (e.g. heart rate, temperature, respiration rate, oxygen saturation, SBP, MAP), cultures and lab values (e.g. lactate, blood urea nitrogen (BUN), platelets, creatinine, bilirubin, white blood cell (WBC), bands, oxygen source, Glasgow Coma Score (GCS), antibiotic and vasopressor administration). For lab values, binary variables (i.e., normal and abnormal) were created by using clinically relevant thresholds defined a priori.

The initial longitudinal dataset contained extreme values within the vital signs and lab results. Established clinical cut-off points were used to pre-process the data and eliminate medically infeasible values. Further, every data entry into the EHRs was represented as a new row in the retrospective dataset with a corresponding

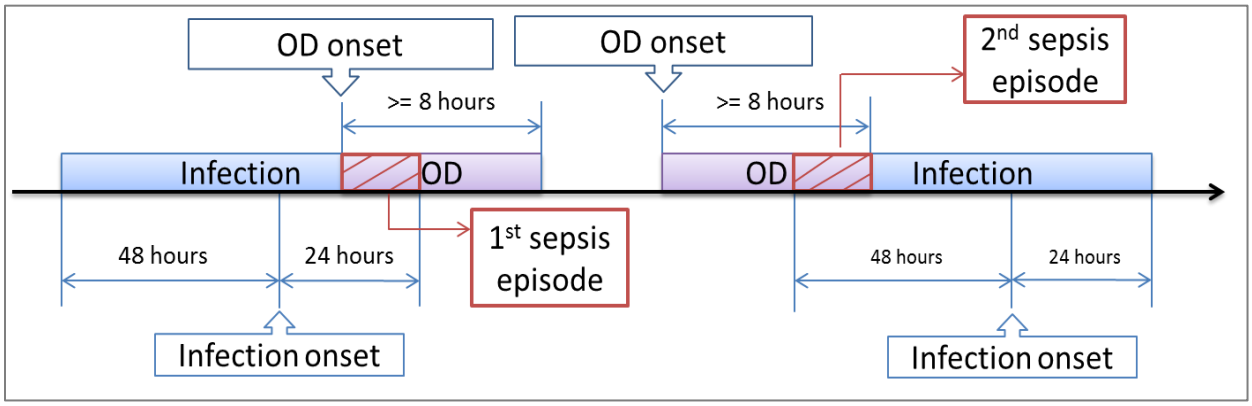

Figure 1. Dynamic definition of infection, organ dysfunction (OD) and sepsis episodes using a hypothetical patient example.

time stamp. Creating rows based on each new measurement resulted in missing values because data elements are not always measured and entered into the EHRs at the same time. Methods to deal with missing data relied on understanding the type and cause of missing data in the EHR system.[13] The last observation carrying-forward (LOCF) method was applied for the time-dependent data elements within a clinically relevant time window.

Statistical Methods

We used descriptive statistics including mean with standard deviation (SD) and frequencies to describe the population. A univariate analysis was performed by using Fisher's exact test or Mann-Whitney U test where appropriate. Any covariate with a p-value of less than or equal to 0.1 was eligible for inclusion in the logistic regression and survival model. The observational data were analyzed using multivariable logistic regression and survival analysis. Logistic regression was used for in-hospital mortality in the sepsis population, and a Cox proportional hazard model was developed for sepsis onset within 72 hours in the infection population. Discrimination of the regression model was assessed by using the area under the receiver operator characteristics curve (AUROC).

RESULTS

Descriptive Statistics

The dataset contained 4,726 inpatients at Christiana Care during the study period. Patient demographics and populations based on observed episodes during hospitalization are shown in Table 1. Results showed that 47.54% of patients with an infection episode experienced at least one sepsis episode during their hospitalization within 72 hours after admission (N=1,044 out of 2,196). Of 2,196 suspected infected patients, 27 met criteria for septic shock (1.2%). The mortality rate in the study population was 2.4% (N=112 out of 4,726).

Table 1: Patient demographics and populations based on observed episodes during hospitalization (N= 4,726 unique patients).

Characteristics	
Age, mean (SD)	63.7 (18.2)
Gender, male, n (%)	2,284 (47.6)
Race, n (%)	
White	3,476 (73.5)
African American	1,081 (22.8)
Asian	61 (1.3)
Other	107 (2.2)
Groups	
Patient with at least one infection episode, n (%)	2,196 (46.4)
Patients with at least one organ dysfunction episode, n (%)	2,168 (45.8)
Patients with at least one sepsis episode, n (%)	1,044 (23.9)
Patients who met septic shock criteria, n (%)	27 (0.5)
Length of stay, median (IQR)	4 (2.3-6.3)
Intensive care unit (ICU) admission, n (%)	648 (13.7)
Mortality, n (%)	112 (2.4)

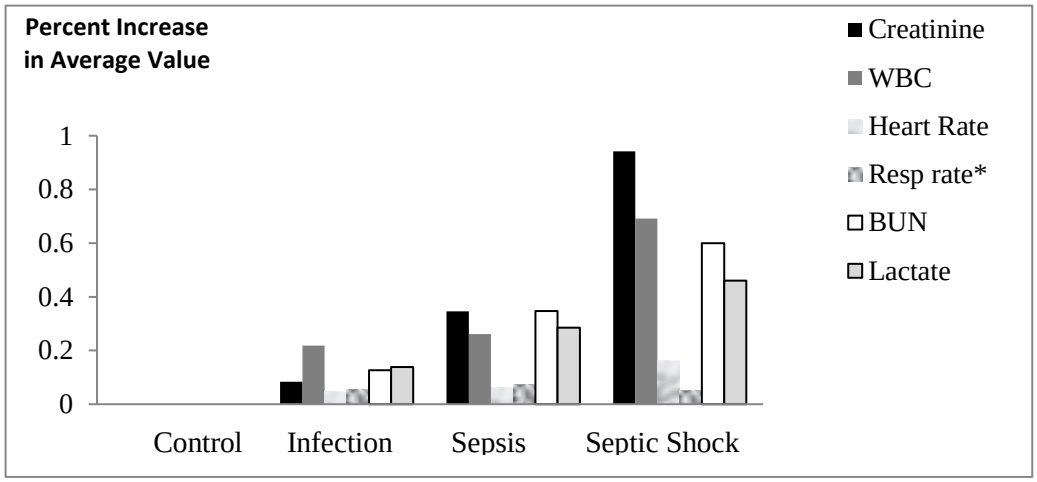

Figure 2: Percent increase in average values of sepsis-related vital signs and labs in patients with an episode of infection, episode of sepsis, and septic shock compared to the control group (i.e., patients that did not have any infection or organ dysfunction episodes). Resp rate* stands for respiratory rate.

The percent differences in average values of sepsis-related vital signs and labs were quantified at the hospital visit level. The patients that did not have any infection or organ dysfunction episodes were used as control group (Figure 2).

A comparison between patients with an infection episode, a sepsis episode, septic shock and the control group revealed an upward trend of average heart rate, temperature, respiratory rate, WBC, BUN, and lactate in patients with infection, sepsis, and septic shock (Figure 2). Patients with at least one sepsis episode during their hospitalization experienced a 28% increase in average lactate, 30% increase in average WBC, a 34.7% increase in BUN, and a 35% increase creatinine compared to control group. Patients with septic shock experienced a 94% increase in creatinine, a 70% increase in average WBC, and a 60% increase in average BUN compared with the control group. Based on the definition of sepsis episodes, patients can experience multiple sepsis episodes during the same hospitalization visit. For simplicity of the comparison of vital signs and lab values in Figure 2, we only consider the first sepsis episode during each hospitalization given potential dependency structures when multiple episodes are considered.

Figure 3 illustrates the mortality rate in different patient populations including patients with at least one or more infection, organ dysfunction or sepsis episode, and patients with septic shock during their hospitalization. The mortality rate was higher for patients with sepsis episodes (7.24%) compared to patients with only organ dysfunction episodes (4.84%) or only with infection episodes (3.96%). The highest mortality rate was observed for patients who met the septic shock criteria (29.63%). The patient groups illustrated in Figure 3 are not mutually exclusive. In other words, a patient can have multiple episodes of infection, organ dysfunction, and sepsis during the same visit.

Sepsis Model Development

For the patients who experienced at least one infection episode during their hospitalization, the developed model identified the risk of first sepsis episode onset within 72 hours by utilizing a Cox Proportional Hazard model. We selected 72

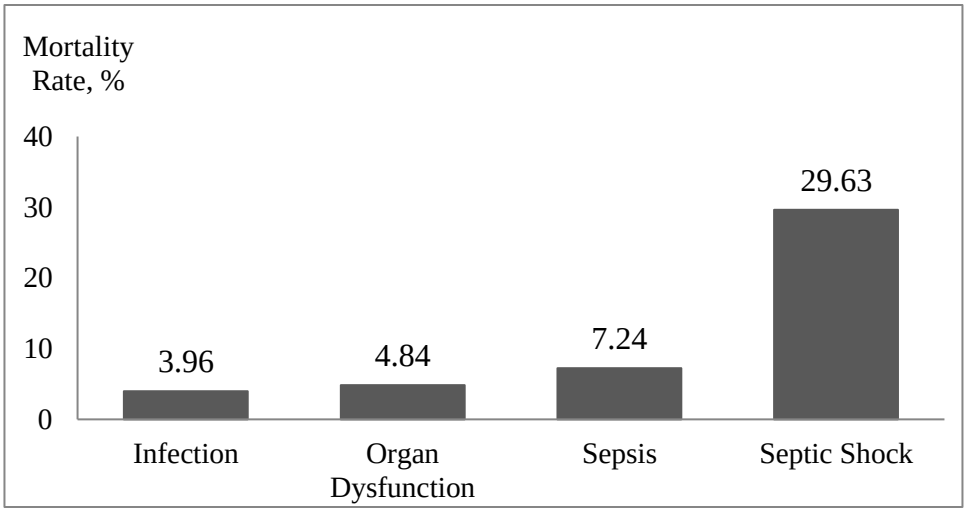

Figure 3: Mortality rate by patients with infection, organ dysfunction and sepsis episodes and patients who meet the septic shock criteria.

hours as the end point since it contains majority of episodes and patterns of outcome variation within the study dataset. Based on the empirical survival and hazard curves, the majority (92.23%) of episodes are observed within the first 8 to 12 hours. The patients who did not experienced any sepsis episodes during their visit were considered as right-censored. If multiple sepsis episodes existed during a single visit, the response referred to the onset of the first sepsis episode. When the time to the first sepsis episode onset was greater than 72 hours, it was treated as a right-censored outcome. The model identified renal disease, malignancy, heart rate, respiratory rate, and gender (female) as factors associated with the first sepsis episode onset during hospitalization (Table 2). Table 2 shows that the 95% confidence intervals for renal disease, malignancy, and gender (female) do not include 1, whereas the rest of the confidence intervals include 1. This suggests that the hazard ratios associated with experiencing renal disease, malignancy, and gender (female) are significant. BUN is another variable that has been identified to significantly influence the time to the first sepsis onset. As only 10% of patients (223 out of 2,196) have observed BUN value, it has not been included in the final model to avoid unstable and less powerful estimation.

Mortality Model Development

Each component of the predisposition, infection, response, and organ failure

Table 2. Independent predictors associated with first sepsis episode onset within 72 hours after admission to the hospital. Reference level 0 refers to non-existence of the considered condition.

Parameter (Reference level)	Estimate	Hazard Ratio	95% Confidence Intervals
Renal (0)	-0.64085	0.527	[0.462, 0.600]
Malignancy (0)	-0.23233	0.793	[0.677, 0.928]
Heart rate	0.01180	1.012	[1.009, 1.015]
Respiratory rate	0.04003	1.041	[1.028, 1.054]
Gender (Female)	-0.14969	0.861	[0.760, 0.975]
Blood urea nitrogen	0.0159	1.005	[1.000, 1.010]

Table 3. Independent significant predictors of model with age, vital signs and lab values as continuous variables where * refers to p-value <0.05; ** refers to p-value <0.001; and *** refers to p-value <0.0001.

Covariate	Coefficient	Odds Ratio	95% Confidence Interval
Predisposition Model (AUROC: 0.643)			
Age ***	0.0363	1.037	[1.014-1.06]
Liver disease*	-0.7338	0.480	[0.238-0.968]
Infection Model (AUROC: 0.602)			
Any Infection ***	1.7693	5.867	[2.452-14.037]
Response Model (AUROC: 0.813)			
Temperature **	-0.8665	0.420	[0.268-0.659]
Heart Rate ***	0.0301	1.031	[1.013-1.048]
Respiratory rate ***	0.1888	1.208	[1.145-1.274]
SBP *	-0.0164	0.984	[0.969-0.999]
Organ Dysfunction Model (AUROC: 0.837)			
WBC count **	0.0722	1.075	[1.025-1.127]
Platelets *	-0.00553	0.994	[0.989-1.000]
Lactate ***	0.4781	1.613	[1.292-2.014]
BUN *	0.0159	1.016	[1.001-1.031]

(PIRO) score was used to develop four independent logistic regression models (P, I, R, and O models) where age, vital signs, and lab values have been treated as continuous variables. The covariates identified the factors that were independently correlated with risk of death derived from the univariate analysis (Table 3).

PIRO is a well-established sepsis classification score that was developed and presented at the International Sepsis Definitions Conference in 2001 and validated by Howell et al.'s study in 2011 identifying the association between PIRO score and mortality.[5,6] PIRO score assigns numeric weights between 0 and 4 to sepsis characteristics within four dimensions: predisposition, infection, response, and organ failure. The characteristics are selected using a logistic regression method which provides the framework for our mortality model that has the same outcome of interest (in-hospital mortality). Predisposition includes categorical variable age (categorized as <65, 65-80 and >80), and binary variables chronic obstructive pulmonary disease (COPD), liver disease, nursing home resident, and malignancy. Infection includes binary variables pneumonia, skin/soft tissue infection, and any other infection. Response includes dichotomized continuous variables respiratory rate, bands, and heart rate with cut-off points. Organ failure includes dichotomized continuous variables BUN, lactate, platelet counts, categorical variable SBP (categorized as <70, 70-90 and >90), and binary variable respiratory failure/hypoxia. The sum of weights from all four dimensions results in the PIRO score.

The PIRO framework allowed us to develop logistic regression models using the elements in each of the four P, I, R, O dimensions which is aligned with how the original PIRO score was developed and validated for mortality. Our final logistic regression model was performed to predict the probability of in-hospital mortality using all significant variables from the P, I, R, O models (Table 4).

The cross-validated AUROC of the final regression model was 0.89. The model

Table 4. Odds ratio and 95% confidence interval of the covariates included in the final in-hospital mortality model where * refers to p-value <0.05; ** refers to p-value <0.001; and *** refers to p-value <0.0001.

Covariate	Odds Ratio	95% Confidence Interval
Age *	1.024	[1.003-1.045]
Liver	0.741	[0.294-1.867]
Temperature	0.780	[0.567-1.072]
Heart Rate **	1.027	[1.012-1.041]
Respiratory rate ***	1.119	[1.068-1.172]
SBP *	0.987	[0.975-0.999]
WBC count *	1.038	[1.001-1.075]
Platelets *	0.996	[0.992-1.000]
Lactate ***	1.555	[1.296-1.866]
BUN *	1.016	[1.003-1.029]

for in-hospital mortality indicated no evidence of poor fit assessed by the p-value of Hosmer-Lemeshow Goodness-of-Fit test (0.53 in the training dataset, and 0.26 in the validation dataset).

DISCUSSION

Sepsis is an infectious disease process and a major cause of morbidity and mortality in hospitalized patients.[12] However, sepsis lacks a gold-standard diagnostic test, resulting in inconsistencies in the recognition of sepsis in clinical settings. Many septic patients are not diagnosed at an early stage when aggressive treatment has the potential to reverse the course of infection.[14] Early recognition and response can reverse the inflammatory response and improve patient outcomes.[15] Failure to initiate appropriate therapy is strongly correlated with an increased morbidity and mortality.[16] For every one-hour delay in administration of an antibiotic treatment for severe sepsis or severe shock, patient survival decreases incrementally.[17] A central unresolved challenge is timely and consistent recognition of factors impacting diagnosis and treatment of sepsis.[16]

Utilizing EHR data of hospitalized patients during the study period, we developed a Cox model to predict the first sepsis episode onset within 72 hours after admission in the infected population and logistic regression models with a PIRO score-based framework to predict in-hospital mortality in those septic patients. The analysis results identified 5 factors associated with sepsis episode onset within 72 hours in infected patient population (renal disease, malignancy, heart rate, respiratory rate, and gender), and 10 factors associated with in-hospital mortality in the septic patient population (age, liver disease, temperature, heart rate, respiratory rate, SBP, WBC, platelets, lactate and BUN). Our findings showed that patients with at least one sepsis episode during their hospitalization experienced higher average lactate, WBC, BUN, and creatinine compared to control patients without any infection or organ dysfunction episodes during their hospitalization. This result suggested that these laboratory tests are important clinical indicators that could potentially be used for electronic decision support systems. As expected, mortality rate was higher for patients with sepsis episodes (7.24%) compared to patient with only organ dysfunction episodes (4.84%) or only with infection episodes (3.96%). This finding highlights the time-sensitivity of

interventions that can change the patient trajectory at the early stages of infection and organ dysfunction when the physiological deterioration is reversible, and the risk for adverse outcomes, such as in-hospital mortality, is lower compared to later stages of sepsis.

Our study has several limitations. The main limitations of this study include compromised generalizability due to the data being derived from a single health system, small sample size associated with rare events, assumptions in data processing (e.g., clinically reasonable cut-off points for data cleaning), and modeling (e.g., dynamic definition of sepsis events). Additionally, this dataset included missing values, for which we took the LOCF method to fulfill the number of missing values; it may introduce bias to the predicting model.

CONCLUSIONS

Predictive methods aim to identify and guide intervention before a patient deteriorates.[18] Data-driven screening of risk factors can ensure early recognition and treatment with goals of reducing sepsis-induced deterioration. Specific to sepsis, such methods have demonstrated increased adherence with sepsis resuscitation and management bundle elements.[19] However, sepsis trajectories are multidimensional, complex, and require in-depth interdisciplinary approaches to accurately capture the time-based dynamics and translate the findings into actionable decisions. This research demonstrates a quantitative methodology to utilize the EHRs with the goal of representing the dynamics of sepsis-induced deterioration ad recovery at the point of care.

Notes

Author contributions: All authors have seen and approved the manuscript, and contributed significantly to the work.

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