ORIGINAL ARTICLE

INFECTIOUS DISEASE

Prognostic value of pro-adrenomedullin, procalcitonin and C-reactive protein in predicting outcome of febrile urinary tract infection

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Abstract

Bacterial infections such as febrile urinary tract infection (fUTI) may run a complicated course that is difficult to foretell on clinical evaluation only. Because the conventional biomarkers erythrocyte sedimentation rate (ESR), leucocyte count, C-reactive protein (CRP) and procalcitonin (PCT) have a limited role in the prediction of a complicated course of disease, a new biomarker—plasma midregional pro-adrenomedullin (MR-proADM)—was evaluated in patients with fUTI. We conducted a prospective multicentre cohort study including consecutive patients with fUTI at 35 primary-care centres and eight emergency departments. Clinical and microbiological data were collected and plasma biomarker levels were measured at presentation to the physician. Survival was assessed after 30 days. Of 494 fUTI patients, median age was 67 (interquartile range 49–78) years, 40% were male; two-thirds of them had significant co-existing medical conditions. Median MR-proADM level was 1.42 (interquartile range 0.67–1.57) nM; significantly elevated MR-proADM levels were measured in patients with bacteraemia, those admitted to the intensive care unit, and in 30-day and 90-day non-survivors, compared with patients without these characteristics. The diagnostic accuracy for predicting 30-day mortality in fUTI, reflected by the area-under-the-curve of receiver operating characteristics were: MR-proADM 0.83 (95% CI 0.71–0.94), PCT 0.71 (95% CI 0.56–0.85); whereas CRP, ESR and leucocyte count lacked diagnostic value in this respect. This study shows that MR-proADM assessed on first contact predicts a complicated course of disease and 30-day mortality in patients with fUTI and in this respect has a higher discriminating accuracy than the currently available biomarkers ESR, CRP, PCT and leucocyte count.

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Introduction

Urinary tract infections (UTIs) are one of the most common bacterial infections. Febrile UTI (fUTI), reflecting acute pyelonephritis, prostatitis or urosepsis, is a potentially serious infection with a mortality rate of about 0.3%, but in bacteraemic fUTI the mortality may be as high as 7.5–30% [1,2]. Moreover, bacteraemia in fUTI is associated with prolonged hospitalization and a complicated course [3–5], and occurs in

up to 30% of those admitted to hospital and in 15% of patients treated at home [6]. Evaluation of clinical symptoms fails to provide accurate guidance to the clinician on which patients have bacteraemia or who may run a complicated course, and which patients may be safely treated at home. At present, there is a lack of robust inflammatory biomarkers that may help to determine the severity of disease in *f*UTI [7,8]. A promising new biomarker is midregional pro-adrenomedullin (MR-proADM). Adrenomedullin (ADM) has been detected in a variety of tissues including kidneys. It has immune modulating, metabolic and bactericidal activities, and is involved in regulation of complement activity [9–12]. Reliable plasma measurement of ADM is challenging because of its half-life time of 22 min [13]. MR-proADM, the more stable mid-regional fragment of adrenomedullin, has been identified in the plasma of patients with septic shock [13–15].

The aim of the present study is to assess the prognostic value of plasma MR-proADM in adult patients with *f*UTI with respect to bacteraemia, need for hospital admission and a complicated course, as compared with current available biomarkers like blood leucocyte count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and procalcitonin (PCT).

Patients and Methods

We conducted a prospective observational multicentre cohort study of patients presenting with a presumptive diagnosis of *f*UTI from January 2004 until March 2011. Participating centres were 35 primary-care centres and eight emergency departments (ED) in the Netherlands as described previously [6,8]. The local ethics committees approved the study and all participants provided written informed consent. Over 7 years, we established a cohort of 869 patients. From this database, we randomly selected (every other patient, e.g. the first, third, fifth, etc.) frozen plasma samples of 494 patients for measurement of MR-proADM.

Inclusion criteria were age ≥18 years, fever (≥38.0°C) and/or a history of fever or shaking chills within 24 h before presentation, at least one symptom of UTI (dysuria, perineal pain or flank pain) and a positive nitrite dipstick test or leucocyturia. Exclusion criteria were current treatment for urolithiasis or hydronephrosis, pregnancy, haemodialysis or peritoneal dialysis, history of kidney transplantation or presence of polycystic kidney disease. Patients were only included once.

Procedures and definitions

Clinical data and laboratory values were collected within 24 h of enrolment by standardized questionnaires and reviewing the medical record. All patients were empirically treated with antibiotics according to local and national policy. Blood cultures and clean midstream-catch urine cultures were obtained before starting antimicrobial therapy and analysed using standard microbiological methods. Bacteraemia was defined as growth of any pathogen in the blood culture, except coagulase-negative staphylococci.

Plasma EDTA blood samples were collected, centrifuged and stored at −80°C within 2 h of patient enrolment. MR-proADM and PCT levels were measured after completion of all study enrolments, using a Time Resolved Amplified Cryptate Emission technology assay (TRACE®, Kryptor Compact, MR-proADM sensitive and PCT sensitive; Thermofisher—Brahms AG; Henningsdorf, Germany). The median concentration of MR-proADM in a cohort of healthy individuals was 0.39 nM (97.5th centile: 0.55 nM) [16]. According to the manufacturer's recommendation we tested MR-proADM levels for different cut-off values [16,17]. Results of PCT measurement to predict bacteraemia have been described previously [8]. Measurements of CRP, ESR and leucocyte count were only performed at enrolment when indicated by the attending physician. All eight participating EDs applied similar techniques. CRP was measured using immunoturbidimetric assay, cut-off values varied from 6 to 10 mg/L. ESR was measured using the Westergren method, cut-off values: <20 mm/h for men and women aged ≤50 years, 30 mm/h for women >50 years and 15 mm/h for men >50 years. Leucocyte count was measured using flow cytometry, cut-off value: 10.0×10^9/L. Data on biomarkers available in our study population were: CRP ($n = 319$), ESR ($n = 158$), leucocyte count ($n = 372$) and PCT ($n = 321$).

Endpoints

MR-proADM values were evaluated for their predictive ability of primary and secondary endpoints, in comparison to that of the other biomarkers. The primary endpoint was 30-day mortality. Secondary endpoints were presence of bacteraemia at admission, need for hospital admission as estimated by the Acute Pyelonephritis Severity Index score (APSI score), and need for intensive care unit (ICU) admission. The APSI score is a prediction rule allocating points to age, sex, nursing home residency, comorbidities and vital signs at presentation (van Nieuwkoop *et al.* 2009 Prospective validation of acute pyelonephritis severity index to predict clinical outcome [abstract 982]. Program and abstracts of the 47th Annual Meeting Infectious Diseases Society of America (Philadelphia). Arlington, VA: Infectious Diseases Society of America) .

Statistical analysis

The histograms of biomarker values were skewed and log-normalized before analysis. Descriptive analysis included

means with confidence intervals or medians and ranges, as appropriate. Univariate analysis was performed using analysis of variance, Student's *t*-test or where appropriate Mann–Whitney *U*-test for continuous variables and chi-square tests for categorical variables. Continuous variables were added into the models as continuous variables (except for the APSI score) and log-normalized if data were not normally distributed. The APSI score was analysed as a binary variable, using a cut-off value of 100 points, based on previous data (van Nieuwkoop *et al.* 2009).

To assess the prognostic ability of MR-proADM compared with PCT and other conventional biomarkers in predicting the primary and secondary endpoints, area-under-the-curve (AUC) of receiver operating characteristics (ROC) curves were calculated. The main conclusion regarding the predictive ability of MR-proADM was based on this analysis. For each biomarker corresponding positive and negative predictive values and likelihood ratios were calculated for standardized cut-off values in predicting the primary endpoint. Kaplan–Meier survival curves were generated to illustrate survival probability and clinical outcome for different levels of MR-proADM. The log rank test was used to test the difference between survival curves. Survival analysis was performed on the whole cohort, ROC-analysis and sensitivity analysis were performed on the subset of patients with data on the concerning biomarkers available. A p-value <0.05 was considered to indicate statistical significance. SPSS software (version 20.0; SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

In total, 494 patients were randomly selected from our existing database resource. There were no significant differences between our study population and the remainder of the database population, except for having a significantly older population (p 0.027) with significantly more patients with diabetes (25%; p <0.001) in the selected study group (data not shown). Median age of our study population was 67 (interquartile range (IQR) 49–78) years, 40% were male and 66% had co-existing medical conditions. Of 376 patients included at the ED, 329 (88%) were hospitalized. None of the patients recruited in primary care were hospitalized (Table 1).

In the ED group, 30-day mortality was 3% (*n* = 12) versus an absence of 30-day mortality in the primary-care group. A total of 101 (22%) patients with blood cultures taken at presentation (*n* = 463) presented with bacteraemia, with significantly more patients in the ED group (*n* = 90/347, 26%, p <0.001). Nineteen (5%) of the ED patients were admitted to the ICU, of these two died. (Table 2).

TABLE 1. Baseline characteristics of 494 patients presenting with febrile urinary tract infection

Characteristic	Febrile UTI patients (*n* = 494)
Age, median years (IQR)	67 (49–78)
Male sex	198 (40)
Antibiotic pretreatment	171 (35)
Comorbidity	
Any	325 (66)
Diabetes mellitus	121 (25)
Malignancy	56 (11)
Heart failure	76 (15)
Cerebrovascular disease	73 (15)
Chronic obstructive pulmonary disease	77 (16)
Chronic renal insufficiency	54 (11)
Urological history	
Urinary tract disorder[a]	126 (26)
Indwelling urinary catheter	40 (8)
Recurrent UTIs[b]	158 (32)
Presentation	
At emergency department	376 (76)
Shaking chills	290 (59)
Dysuria[c]	366 (74)
Flank pain	283 (57)
Fever duration at presentation, median hours (IQR)	32 (16–66)
Heart rate >90 beats/min	258 (52)
Systolic blood pressure, mean mmHg ± SD	130 ± 23
Diastolic blood pressure, mean mmHg ± SD	72 ± 14

UTI, urinary tract infection; IQR, interquartile range; SD, standard deviation.
Data presented as *n* (%) unless otherwise stated.
[a]Any anatomical or functional abnormality of the urinary tract except urinary catheter and history of nephrolithiasis.
[b]Defined as three or more UTIs in the past 12 months or two or more UTIs in the past 6 months.
[c]Not recorded in patients with indwelling urinary catheter.

MR-proADM versus other biomarkers in predicting 30-day mortality

To define the prognostic accuracy of different biomarkers for predicting 30-day mortality, ROC analyses were performed. The AUC for MR-proADM (*n* = 494) was 0.83 (95% CI 0.71–0.94), leucocyte count (*n* = 372) 0.44 (95% CI 0.26–0.62), ESR (*n* = 158) 0.60 (95% CI 0.43–0.78), CRP (*n* = 319) 0.59 (95% CI 0.37–0.81) and PCT (*n* = 321) 0.71 (95% CI 0.56–0.85). Based on the constructed AUCs, MR-proADM has a higher discriminating accuracy for

TABLE 2. Overview of primary and secondary endpoints in 494 patients with febrile urinary tract infection

Endpoint	Febrile UTI patients (*n* = 494)
Bacteraemia at presentation[a]	101/463 (22)
Hospitalization duration (days), median (IQR)	4 (0–7)
ICU admission	19 (4)
APSI score >100[b]	77 (16)
Mortality	
Day 3	2/492 (0.4)
Day 30	12/485 (3)
Day 90	19/474 (4)

IQR, interquartile range; ICU, intensive care unit; APSI, Acute Pyelonephritis Severity Index.
Data are presented as *n* (%) unless otherwise stated.
[a]No blood culture performed in 31 patients.
[b]Prediction rule allocating points to age, sex, nursing home residency, comorbidities and vital signs at presentation; patients with APSI score <100 can be safely treated at home without risk of readmission and mortality.

predicting 30-day mortality compared with the other conventional biomarkers.

The 97.5th centile cut-off value of normal provided by the manufacturer is 0.55 nM but in our target group this cut-off lacks specificity. Hence, the positive and negative predictive values and likelihood ratios for different MR-proADM cut-off values were calculated (Table 3). Our data indicate that a plasma MR-proADM level of 1.00 nM was the optimal cut-off value to stratify 30-day mortality in patients with *f*UTI. Using this cut-off, we calculated a sensitivity of 91.7% with a specificity of 48.0%; negative predictive value 99.6%; positive predictive value 4.3%; positive likelihood ratio 1.8; negative likelihood ratio 0.2 (Table 3).

Need for hospital admission

In the prediction of need for hospitalization, as based on an APSI score >100 points, MR-proADM outperformed PCT (n = 321 patients with both data available) given the AUC for MR-proADM of 0.82 (95% CI 0.77–0.88) compared with 0.69 (95% CI 0.62–0.77) for PCT. For prediction of bacteraemia, MR-proADM and PCT performed about equally (MR-proADM: AUC 0.78 (95% CI 0.72–0.85) and PCT 0.81 (95% CI 0.75–0.87)). As the predictive values might have been influenced by antibiotic (pre)treatment (in 35% of the patients), analysis was also performed separately in those with and without antibiotics on study enrolment (n = 113 versus n = 208). Corresponding AUCs for MR-proADM were 0.75 (95% CI 0.65–0.85) and 0.79 (95% CI 0.70–0.88), and for PCT were 0.80 (95% CI 0.71–0.89) and 0.80 (95% CI 0.72–0.88), respectively, indicating that antibiotic pretreatment did not alter the predictive value of MR-proADM with respect to bacteraemia. In the prediction of either bacteraemia or need for hospital admission, CRP, ESR and blood leucocyte counts lacked predictive power (all AUC <0.60). For prediction of the need for ICU admission, pro-ADM and PCT performed almost identically (i.e. AUC of 0.77 and 0.75, respectively, n = 321).

MR-proADM and clinical parameters

In addition to 30-day mortality, median MR-proADM level was significantly correlated with bacteraemia (bacteraemic versus non-bacteraemic patients: 1.60 (IQR 1.01–3.28) versus 0.96 (IQR 0.61–1.37) nM), need for ICU admission (ICU versus non-ICU patients: 2.01 (IQR 1.37–4.61) vs. 1.04 (IQR 0.65–1.50) nM) and APSI score (1.95 (IQR 1.27–2.90) nM in patients with a score >100 points vs 0.94 (IQR 0.62–1.36) nM in patients with a score ≤100 points). Furthermore, MR-proADM levels increased with age and were significantly higher in patients with heart failure and chronic renal insufficiency.

The Kaplan–Meier curves showed no 30-day or 90-day mortality in patients with MR-proADM levels in the first quartile (n = 123) of the whole group. In the second quartile (n = 124) three events occurred, four in the third quartile (n = 124), and eleven in the fourth quartile (n = 123). All three events in the second quartile occurred late in the current disease episode: days 16, 27 and 33. One event in the third quartile occurred on day 3, the other three occurred late after disease onset (days 41, 42 and 66). Events in the fourth quartile occurred primarily in the early stage of the current disease episode. This suggests that events in the second and third quartile are probably due to pre-existing co-morbidity, while events in the fourth quartile occur as result of the current active disease (Fig. 1). The 30-day cumulative survival rate was 1.00 in the first quartile, 0.98 in the second quartile (log rank p 0.157), 1.00 in the third quartile (log rank p 1.00) and 0.92 in the fourth quartile (log rank p 0.001). The 90-day cumulative survival rate was 1.00 in the first quartile, 0.98 in the second quartile (log rank p 0.083), 0.97 in the third quartile (log rank p 0.046) and 0.91 in the fourth quartile (log rank p 0.001).

Discussion

The main finding of the present study is that MR-proADM, determined on first contact in a patient with presumptive *f*UTI,

TABLE 3. Sensitivity, specificity, PPV, NPV, LR+ and LR– of different infectious biomarkers for predicting 30-day mortality

	Cut-off value	No. cases under cut-off	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	LR+ (95% CI)	LR– (95% CI)
MR-proADM (nM)	0.55[a]	79 (16%)	100.0 (73.4–100.0)	15.6 (12.5–19.2)	2.9 (1.5–5.1)	100.0 (95.1–100.0)	1.2 (1.1–1.2)	0.0 (0.0–0.0)
	1.00	234 (47%)	91.7 (61.5–98.6)	48.0 (43.4–52.6)	4.3 (2.2–7.5)	99.6 (97.6–99.9)	1.8 (1.5–2.1)	0.2 (0.0–1.1)
	1.50	362 (73%)	83.3 (51.6–97.4)	74.6 (70.5–78.5)	7.7 (3.8–13.7)	99.4 (98.0–99.9)	3.3 (2.4–4.4)	0.2 (0.1–0.8)
	1.88	406 (82%)	66.7 (35.0–89.9)	83.1 (79.4–86.4)	9.1 (4.0–17.1)	99.0 (97.4–99.7)	3.9 (2.5–6.2)	0.4 (0.2–0.9)
Procalcitonin (μg/mL)	0.25	129 (26%)	72.7 (39.1–93.7)	40.7 (35.1–46.3)	4.2 (1.8–8.1)	97.7 (93.3–99.5)	1.2 (0.8–1.8)	0.7 (0.3–1.8)
C-reactive protein (mg/L)	6	6 (1%)	100.0 (73.4–100.0)	1.3 (0.5–2.7)	2.5 (1.3–4.3)	100.0 (54.1–100.0)	1.0 (1.0–1.0)	0.0 (0.0–0.0)
	8	10 (2%)	100.0 (73.4–100.0)	2.1 (1.0–3.9)	2.5 (1.3–4.3)	100.0 (69.0–100.0)	1.0 (1.0–1.0)	0.0 (0.0–0.0)
	10	13 (3%)	100.0 (73.4–100.0)	2.8 (1.5–4.7)	2.5 (1.3–4.4)	100.0 (75.1–100.0)	1.0 (1.0–1.0)	0.0 (0.0–0.0)
ESR (mm)	20	74 (15%)	91.7 (61.5–98.6)	15.0 (11.9–18.6)	2.7 (1.3–4.7)	98.6 (92.5–99.8)	1.1 (0.9–1.3)	0.6 (0.1–3.7)
Leucocyte count (×10⁹/L)	10	106 (22%)	75.0 (42.8–94.2)	21.8 (18.1–25.8)	2.4 (1.1–4.5)	97.2 (91.9–99.4)	1.0 (0.7–1.3)	1.2 (0.4–3.1)

MR-proADM, midregional pro-adrenomedullin; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio; ESR, erythrocyte sedimentation rate.
Data on biomarkers available: MR-proADM (n = 494), procalcitonin (n = 321), C-reactive protein (n = 319), ESR (n = 158), leucocyte count (n = 372).
[a]97.5th centile Brahms MR-pro-ADM Kryptor cut-off value in 144 healthy individuals.
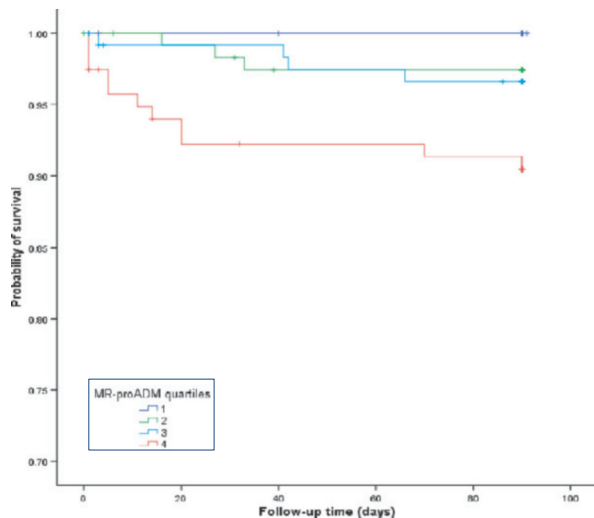
FIG. 1. Kaplan–Meier curves of 90-day mortality according to quartiles of mid-regional pro-adrenomedullin (MR-proADM).

predicts a complicated course of disease necessitating hospital admission and admission to the ICU, and a worse outcome of infection as reflected by 30-day mortality. MR-proADM more accurately predicts outcome than currently used biomarkers. Furthermore, we found significantly higher plasma MR-proADM levels in patients presenting with bacteraemia. Given these characteristics, measurement of MR-proADM in patients with a presumptive diagnosis of *f*UTI may provide the clinician with more accurate guidance than currently applied biomarkers, e.g. with respect to admission of high-risk patients, and so help to focus resources on the patients that need them most.

Strengths of this study are its prospective design in which *f*UTI patients were included in both primary care and hospital ED settings, reflecting a real-life, full spectrum of invasive UTI recognizable to every clinician. Also, the large sample size of a clinically and microbiologically well-characterized disease group is a strength. To our knowledge, this is the first large prospective study focusing on the predictive value of MR-proADM in adult patients with *f*UTI, and making a comparison to currently available biomarkers of inflammation like PCT and CRP. Travaglino *et al.* showed that in febrile ED patients, MR-proADM and PCT levels correlated with APACHE-II score and the combined use of both biomarkers might be helpful in predicting hospitalization [18].

There are also some limitations. We determined MR-proADM levels once, at first contact with the physician. This precludes the analysis of whether a rise or decline in MR-proADM levels correlates with changes in the clinical course of disease, as has been determined, for example, for PCT [19]. However, our findings show that having a single

baseline value can provide clinicians with guidance in predicting a complicated clinical course at the ED or primary care. This is where patients initially present and decisions have to be made regarding treatment and hospital admission. When interpreting MR-proADM, it should be taken into account that certain patient characteristics like age and heart failure may affect the plasma level of MR-proADM, as well as disease duration before presentation. A technical limitation might be that the measurement of MR-proADM and other biomarkers was performed afterwards, and not immediately 'at the bedside'. However, it has been shown that frozen storage and consequent freeze–thaw cycles of blood samples has no influence on the analyte and measured concentration [15,20]. Finally, it should be realized that our findings pertain to *f*UTI and need to be confirmed in other infectious conditions. Of note, similar findings have been made in other infectious states albeit usually in much smaller groups of patients and rarely prospectively [14,21–24].

We hypothesize that at least two mechanisms might be responsible for the marked increase of MR-proADM in *f*UTI. *In vitro* and *in vivo* studies have shown that the onset of inflammation is accompanied by changes in both ADM and pro-inflammatory cytokines, such as tumour necrosis factor-α and interleukin-1. Plasma ADM levels are markedly increased in patients with septic shock, supporting the hypothesis that pro-inflammatory cytokines augment ADM production and may increase plasma levels of ADM [11,25–27]. However, ADM is also capable of upregulation of interleukin-6 in non-stimulated and lipopolysaccharide-stimulated macrophages, thereby suppressing LPS-induced tumour necrosis factor-α production [28]. This suggests that ADM acts as part of a regulatory loop balancing pro-inflammatory cytokines with its anti-inflammatory actions. As LPS and cytokine levels were not measured in our study, we cannot refute or confirm this hypothesis. Second, a decreased clearance of ADM by the kidneys may be, at least in part, responsible for increased proADM levels in *f*UTI. This is supported by our data with a higher median MR-proADM in patients with chronic renal insufficiency and studies that have shown a significant correlation between MR-proADM and creatinine levels [14,29].

In conclusion, we show that MR-proADM has a strong predictive value for 30-day mortality in patients with *f*UTI compared with more conventional biomarkers. Next, studies may wish to confirm the selected cut-off value as a predictor of complicated course and evaluate using daily follow-up measurements of MR-proADM the relationship to treatment and clinical recovery. Such studies will establish whether MR-proADM could function as a new prognostic tool for guidance in risk stratification and clinical outcome in patients with *f*UTI.

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Author Contribution

WES, AV, CN and JTD were responsible for the original design. WES and SZ were responsible for data management, carried out the statistical analysis and wrote the initial draft supervised by JTD, AV and CN. WES, SZ, CN, JES, NMD, JWW, ICS, JWB, EMSL, TK and HCA. were involved in patient recruitment and data collection. AV, JES, NMD, JWW, ICS, JWB, EMSL, TK, HCA, JTD and CN critically revised the manuscript. All authors contributed to and approved the final version of the manuscript.

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Transparency Declaration

The authors declare no conflicts of interest.

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