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# Biomarker guided triage can reduce hospitalization rate in community acquired febrile urinary tract infection

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SUMMARY

*Objectives:* Febrile urinary tract infections (fUTI) can often be treated safely with oral antimicrobials in an outpatient setting. However, a minority of patients develop complications that may progress into septic shock. An accurate assessment of disease severity upon emergency department (ED) presentation is therefore crucial in order to guide the most appropriate triage and treatment decisions.

*Methods:* Consecutive patients were enrolled with presumptive fUTI across 7 EDs in the Netherlands. The biomarkers mid-regional proadrenomedullin (MR-proADM), procalcitonin (PCT), C-reactive protein (CRP), and a clinical score (PRACTICE), were compared in their ability to predict a clinically severe course of fUTI, initial hospital admission and subsequent readmission using area under the receiver operating characteristic (AUROC) curves.

*Results:* Biomarker concentrations were measured in 313 patients, with 259 (83%) hospitalized upon ED presentation, and 54 (17%) treated as outpatients. Of these outpatients, 12 (22%) were later hospitalized. MR-proADM had the highest diagnostic accuracy for predicting a complicated fUTI (AUROC [95% CI]: 0.86 [0.79–0.92]), followed by PCT (AUROC [95% CI]: 0.69 [0.58–0.80]). MR-proADM concentrations were unique in being significantly elevated in patients directly admitted and in outpatients requiring subsequent hospitalization, compared to those completing treatment at home. A virtual triage algorithm with an MR-proADM cut-off of 0.80 nmol/L resulted in a hospitalization rate of 66%, with only 2% secondary admissions.

*Conclusion:* MR-proADM could accurately predict a severe course in patients with fUTI, and identify greater patient numbers who could be safely managed as outpatients. An initial assessment on ED presentation may focus resources to patients with highest disease severities.



## Introduction

Urinary tract infections (UTI) are amongst the most common infectious diseases found in the emergency department (ED),

*Abbreviations:* BP, blood pressure; BPM, beats per minute; CRP, C-reactive protein; ED, emergency department; FUTI, febrile urinary tract infection; CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; PCT, procalcitonin; PRACTICE, Prediction Rule for Admission policy in Complicated urinary Tract InfeCtion LEiden; MR-proADM, mid-regional proadrenomedullin; ROC, receiver operating characteristics curves; AUC, area under the curve; SD, standard deviation.

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and usually result in a mild, low severity illness. Nevertheless, these conditions may rapidly develop in a minority of patients into a life-threatening condition, such as septic shock or multiple organ failure. Due to this potential risk, many patients are initially hospitalized, leading to a potential over treatment of low severity patients and increased healthcare costs.[1,2] Previous studies, however, have found that uncomplicated pyelonephritis in women can be safely treated at home with oral antibiotics,[3] whilst elderly patients, men and those with comorbidities may also be potentially eligible for outpatient treatment.[4]

It is therefore surprising that no tools have been established to rapidly identify UTI disease severity on ED admission, unlike the specialized scores such as CURB-65 and PSI developed for community acquired pneumonia.[5] Recently, we assessed the use of a clinical score – the Prediction Rule for Admission policy in Complicated urinary Tract InfeCtion LEiden (PRACTICE) – to guide admission policy in a randomized clinical trial of fUTI patients. Although implementation of this score resulted in a decrease in hospital admissions, a subsequent readmission rate of more than 25% was observed in patients who were initially discharged.[6] Consequently, more accurate tools of disease severity are required to not only assess the requirement for initial hospitalization, but to also prevent subsequent readmissions.

The use of blood biomarkers has shown considerable promise in resolving this unmet clinical requirement in several infectious diseases. In adults with community acquired UTI, procalcitonin (PCT) has been shown to be an accurate marker of bacteremia,[7–9] whilst mid-regional proadrenomedullin (MR-proADM) has been shown to strongly predict a complicated course of treatment, the need for ICU admission, as well as identifying patients at risk of mortality.[10,11] Consequently, a combination of these biomarkers, or their use in isolation, may aid in determining the most appropriate setting for treatment.

This study therefore enrolled patients presenting to the emergency department with febrile urinary tract infections (fUTI), and aimed to compare the performance of biomarkers (MR-proADM, PCT and CRP) with the existing clinical score (PRACTICE) in order to (i) assess initial fUTI disease severity, (ii) predict the requirement for hospitalization, and (iii) predict the readmission rate in patients initially selected for outpatient treatment.

## Methods

### *Design and study population*

This was a secondary analysis of the *Hospitalization for community-acquired febrile urinary tract infection: validation and impact assessment of a clinical prediction rule* study[6]; a stepped wedge cluster-randomized trial involving consecutive patients presenting with a presumptive diagnosis of fUTI at the emergency departments of 7 hospitals in the Netherlands, between January 2010 and June 2014.

All participating centers started with a control period, in which routine clinical practice regarding hospitalization policy was applied. The intervention (use of the PRACTICE) was introduced at the participating centers sequentially, in random order. By the end of the allocation all sites, except one, used the PRACTICE to guide admission policy. The PRACTICE is a prediction rule allocating points to age, sex, nursing home residency, comorbidities, and vital signs at presentation (see Supplementary Table 1). The score ranges from 8 to >125 points and is divided into the following risk classes: low <75 points (recommendation towards ambulant care); intermediate 75–100 points (consider ambulant care); high >100 points (recommendation towards hospital admission), based on the validation cohort.[6]

Inclusion criteria were age ≥18 years, fever (≥38.0 °C) and/or a history of fever or shaking chills within 24 h before presentation, a positive nitrite dipstick test or leukocyturia, and at least one symptom of UTI (dysuria, perineal pain or flank pain). Exclusion criteria included pregnancy, hemo- or peritoneal-dialysis, and a history of kidney transplantation or polycystic kidney disease. In the current analysis, only patients with blood samples available for biomarker analysis were included (Supplementary Appendix Fig. S1). The study protocol was approved by the local ethical committee, and written informed consent was obtained from all participants. The original study was monitored by a data safety monitoring board and was stopped prematurely on their advice, due to the rate of secondary admissions in the interventional group exceeding the predefined stopping criterion.[6]

### *Biomarker and clinical score measurements*

CRP was measured at the local laboratories upon patient enrollment using an immunoturbidimetric assay, with cut-offs varying from 5 to 10 mg/L. Surplus EDTA plasma samples were additionally collected, centrifuged and stored at −80 °C within 2 h of patient enrollment. MR-proADM and PCT were batch-measured in a blinded fashion by TRACE technology (Time Resolved Amplified Cryptate Emission) using a new sandwich immunoassay (Kryptor Compact Plus Analyzer, BRAHMS, Hennigsdorf, Germany), with a limit of detection of 0.05 nmol/L and 0.02 ng/L, respectively. The PRACTICE score (Supplementary Appendix Table S1) was calculated in the total patient population, regardless of whether they were enrolled as part of the control or interventional group in the original study.[6]

### *Endpoints*

Severe course of febrile urinary tract infection was defined as a composite of all-cause 30-day mortality, intensive care unit (ICU) admission, and extended hospitalization (>10 days). Patient disposition was noted upon initial ED presentation, and classified as either being (i) admitted for hospital treatment, (ii) discharged for outpatient treatment, or (iii) admitted for treatment after initial outpatient therapy.

### *Statistical analysis*

Descriptive statistics are expressed as counts (percentage), means (standard deviation) or medians [first quartile – third quartile], as appropriate. Biomarker values were log-normalized before analysis. Univariate analysis was performed using ANOVA, Student's *t*-test or Mann–Whitney *U* test for continuous variables, and Chi-square test for categorical variables. Area under the receiver operating characteristics (AUROC) curves with 95% confidence intervals [95% CI] were used to compare the predictive value of the biomarkers and clinical score. Differences between AUROCs were assessed using DeLong's test for significance.[12]

Based on disease severity observations, biomarker suitability for guiding triage decisions was further investigated. Biomarker concentrations in relation to predetermined cut-offs allowed patients to be allocated to either virtual hospitalization or outpatient treatment groups. Patients allocated to outpatient care who were later hospitalized were counted as readmissions. The virtual admission and readmission rates, as well as instances of bacteremia, ICU admission and 30-day mortality were subsequently calculated. A *p*-value of <0.05 was considered statistically significant. SPSS software (SPSS Inc. Chicago, version 23.0) was used for statistical analysis.

**Table 1**
Patient characteristics and outcome.

| Patient characteristics | Control group ($N$ = 185) | Intervention group ($N$ = 128) | Total ($N$ = 313) |
|---|---|---|---|
| Age in years; median (IQR) | 58 (40–73) | 61 (42–76) | 58 (40–75) |
| Sex – female | 117 (63) | 69 (54) | 186 (59) |
| Febrile uncomplicated UTI | 45 (24) | 28 (22) | 73 (23) |
| Antimicrobial pre-treatment at inclusion | 73 (39) | 41 (32) | 114 (36) |
| *Urologic history* | | | |
| Present urinary catheter | 11 (6) | 9 (7) | 20 (6) |
| History of urinary tract disorder | 58 (31) | 33 (26) | 91 (29) |
| *Co-morbidities* | | | |
| Any | 94 (51) | 76 (59) | 170 (54) |
| Diabetes mellitus | 24 (13) | 29 (23) | 53 (17) |
| Malignancy | 10 (5) | 11 (9) | 21 (7) |
| Heart failure | 22 (12) | 12 (9) | 34 (11) |
| Cerebrovascular disease | 10 (5) | 20 (16) | 30 (10) |
| Cirrhosis | 1 (0) | 2 (2) | 3 (1) |
| Renal insufficiency | 8 (4) | 20 (16) | 28 (9) |
| Immunocompromised | 11 (6) | 10 (8) | 21 (7) |
| *Presentation* | | | |
| Shaking chills | 124 (67) | 92 (72) | 216 (69) |
| Systolic BP (mmHg), mean ± SD | 130 ± 22 | 132 ± 22 | 130 ± 22 |
| Diastolic BP (mmHg), mean ± SD | 71 ± 14 | 74 ± 14 | 72 ± 14 |
| Heart rate (b.p.m.), mean ± SD | 96 ± 18 | 98 ± 18 | 97 ± 14 |
| Fever duration at presentation, median hours [IQR] | 28 [12–72] | 24 [12–48] | 24 [12–72] |
| Need for percutaneous nephrostomy | 5 (3) | 4 (3) | 9 (3) |
| **Outcome** | | | |
| *Hospitalization* | | | |
| Total hospitalization | 169 (91)* | 102 (80)* | 271 (87) |
| – Primary admission | 167 (90)* | 92 (72)* | 259 (83) |
| – Outpatient treatment | 18 (10)* | 36 (28)* | 54 (17) |
| – Readmission | 2/18 (11) | 10/36 (28) | 12/54 (22) |
| *Mortality* | | | |
| – 30-day mortality | 2 (1) | 3 (2) | 5 (2) |
| – 90-day mortality | 3 (2) | 5 (4) | 8 (3) |
| Need for ICU admission | 8 (4) | 1 (1) | 9 (3) |
| Hospital admission > 10 days | 11 (6) | 10 (8) | 21 (7) |
| Length of hospital stay [median; IQR] | 5; 4–7 | 5; 3–6 | 5; 4–7 |
| Severe course of fUTI | 22 (9) | 12 (9) | 34 (9) |
| Bacteremia | 44/177 (25) | 30/125 (24) | 74/302 (24) |
| Clinical cure | 146/165 (79) | 94/117 (80) | 240/282 (85) |
| Microbiological cure | 139/154 (90) | 102/108 (94) | 241/262 (92) |

Data are presented as $n$ (%) unless stated otherwise. BP: blood pressure. SD: standard deviation. Bpm: beats per minute. IQR: interquartile range. Readmission: after initial outpatient treatment. ICU: intensive care unit.
* $p < 0.05$. Severe course: composite of 30-day mortality, need for ICU-admission or > 10 days hospitalization. Clinical and microbiological cure: assessed at day 30. *$p < 0.01$.

## Results

A total of 313 patients with a presumptive diagnosis of fUTI were analyzed (details provided in the Flowchart in the Supplementary Appendix Fig. S1). Patient characteristics in terms of urologic history, comorbidities and presenting symptoms are outlined in Table 1. The 30-day mortality rate across the total population was 2% ($N$ = 5), with 114 (36%) patients undergoing existing antimicrobial treatment prior to ED presentation. Patients had an average age of 58 (40–75) years, with females comprising the majority of enrolled patients ($N$ = 186; 59%).

Upon presentation to the ED, 259 (83%) patients were hospitalized, with 54 (17%) selected for outpatient treatment. Of these outpatients, 12 (22%) subsequently re-presented to the ED and were hospitalized. Bacteremia was found in 74 (24%) patients (Supplementary Appendix Table S2), and 9 (3%) patients were admitted onto the ICU. Median biomarker concentrations across the total patient population were as follows: MR-proADM: 1.0 [0.71–1.54] nmol/L; PCT: 0.60 [0.16–2.5] $\mu$g/mL; and CRP: 115 (52–199) mg/L. Both MR-proADM and PCT were significantly correlated to the PRACTICE score ($p < 0.001$), albeit weakly ($R^2$ = 0.28 and 0.05, respectively; Supplementary Appendix Fig. S2). There was no significant correlation between the PRACTICE score and CRP concentrations.

### *Disease severity: the prediction of severe course of fUTI*

The performance of individual biomarkers and the PRACTICE score in predicting a severe course of treatment was assessed using AUROC analysis (Fig. 1). MR-proADM exhibited the strongest performance (AUROC [95% CI]: 0.86 [0.79–0.92]), which was significantly greater than that of PCT (AUROC [95% CI]: 0.69 [0.58–0.80]; $p < 0.001$) and CRP (AUROC [95% CI]: 0.55 [0.44–0.66]; $p < 0.001$). There were no significant differences between the performance of MR-proADM and the PRACTICE score (AUROC [95% CI]: 0.80 [0.74–0.87]). The combination of MR-proADM, PCT or PRACTICE with one another did not significantly increase predictive ability more than the use of MR-proADM alone (e.g. MR-proADM + PRACTICE: AUROC [95% CI]: 0.88 [0.82–0.93]; Supplementary Appendix Table S3).

### *Prediction of the need for hospital admission in the total population*

Biomarker measurements upon presentation to the ED (Fig. 2) found significantly higher concentrations of MR-proADM and PCT in patients who were hospitalized compared to those who were treated as outpatients (MR-proADM: 1.05 [0.73–1.61] vs. 0.83 [0.57–1.15] nmol/L, $p < 0.01$; PCT: 0.68 [0.20–2.69] vs. 0.29 [0.13–1.07] $\mu$g/mL, $p < 0.05$). Conversely, there were no significant differences in CRP concentrations between the two groups.

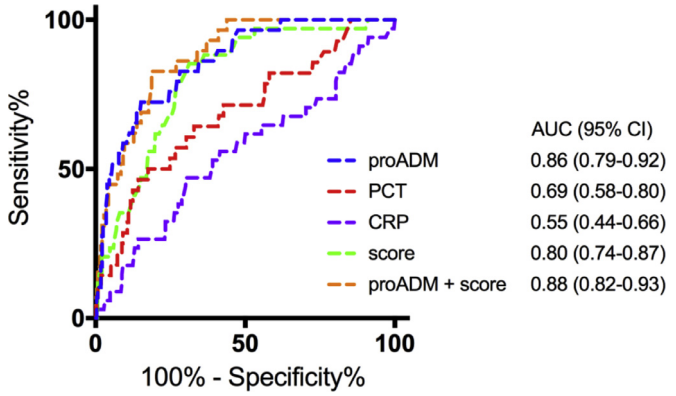


**Fig. 1.** Biomarker and clinical score accuracy in the prediction of a severe course of fUTI.
*proADM*: Mid-regional proadrenomedullin; *PCT*: Procalcitonin; *CRP*: C-reactive protein; *fUTI*: febrile urinary tract infection; *AUC*: area under the curve.

AUROC analysis indicated that the PRACTICE score had the highest accuracy in predicting the need for hospitalization (AUROC [95% CI]: 0.72 [0.64–0.79]), although there were no significant differences compared to the performance of either MR-proADM or PCT (AUROC [95% CI]: 0.68 [0.60–0.76] and 0.63 [0.54–0.72], respectively; Supplementary Appendix Fig. S3). Furthermore, there were no significant improvements in accuracy when MR-proADM, PCT or the PRACTICE score were combined in any order (Supplementary Appendix Table S4).

*Prediction of hospitalization in the outpatient population*

Interestingly, in the subgroup of patients that were initially treated as outpatients but who later re-presented to the emergency department and were hospitalized, MR-proADM concentrations were significantly elevated upon initial presentation (1.21 [0.81–1.86] nmol/L) compared to those who completed outpatient treatment at home (0.78 [0.55–1.02] nmol/L; $p < 0.01$). There were no significant differences in either PCT or CRP concentrations between the two groups.

AUROC analysis for the prediction of hospitalization in patients who were initially deemed suitable for outpatient treatment found that MR-proADM had the greatest performance (AUROC [95% CI]: 0.74 [0.58–0.90]) followed by the PRACTICE score (AUROC [95% CI]: 0.72 [0.52–0.91]), although differences were not significant (Supplementary Appendix Fig. S4). There was no significant association using either PCT or CRP.

*Potential effects on triage decisions*

Based on the previous analysis, MR-proADM was chosen for the virtual biomarker guided treatment allocation. Four different cut-off values were subsequently used based on those found in the literature, which included: 0.55 nmol/L[13]; 0.80 nmol/L; 1.0 nmol/L[10]; and 1.25 nmol/L.

The potential impact of this virtual triage algorithm on both hospitalization and outpatient treatment decisions is shown in Fig. 3. Compared to the actual hospitalization rate of 83% ($N = 259$), a decreased hospitalization rate of 66%, 49% and 34% could be found at MR-proADM cut-offs of 0.80, 1.0 and 1.25 nmol/L, respectively. Only at the lowest cut-off of 0.55 nmol/L, did the hospitalization rate (86%) exceed that of the actual hospitalization rate. Interestingly, the secondary admission rate at all MR-proADM cut-offs did not exceed 3%, compared to the actual readmission rate of 22%. PCT and CRP had less value in the virtual triage, since commonly used cut-off points did not lower the primary admission rate when compared to MR-proADM,

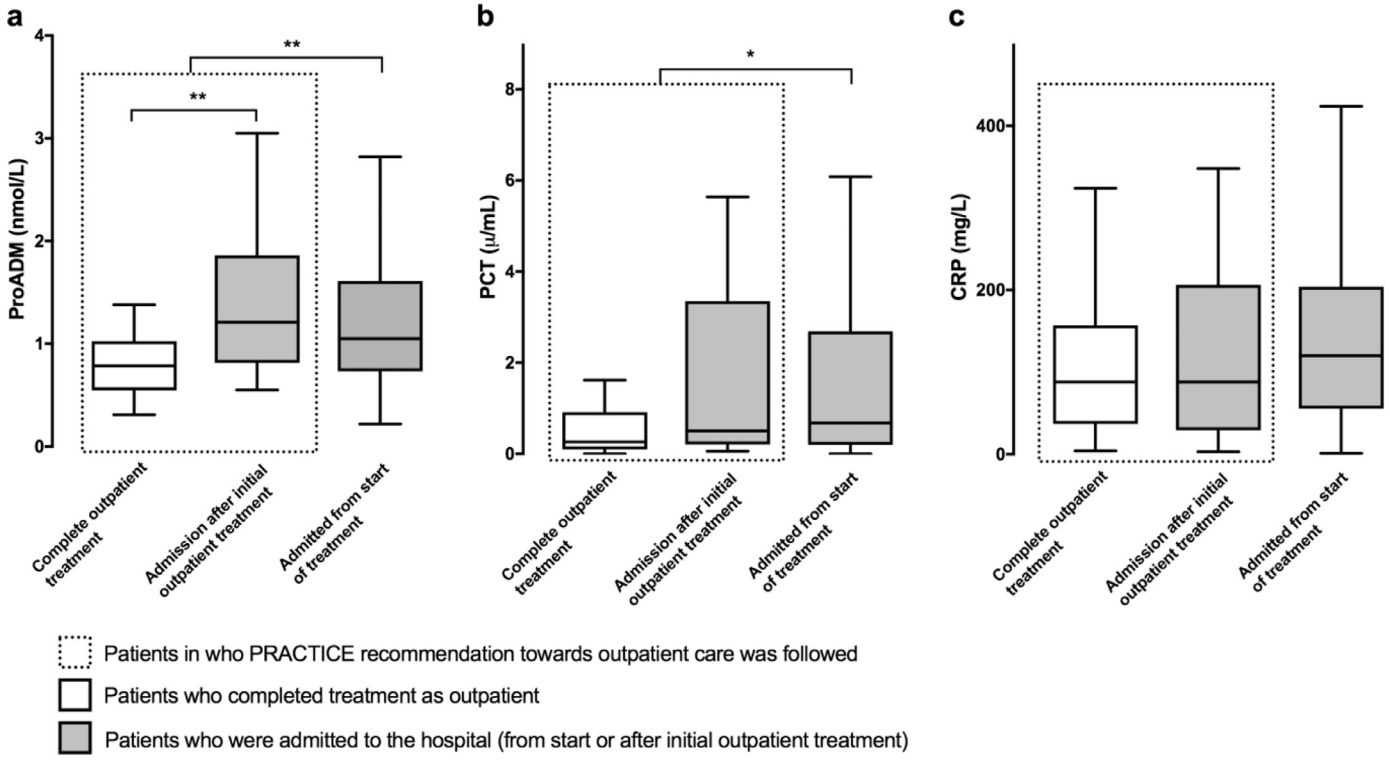


**Fig. 2.** Biomarker concentrations in different patient treatment settings.
Distribution of (a) MR-proADM, (b) PCT and (c) CRP in patients treated as who completed treatment as an outpatient, patients who were hospitalized after initial outpatient treatment, and patients who were hospitalized from the start of treatment. * $p < 0.05$; ** $p < 0.01$.

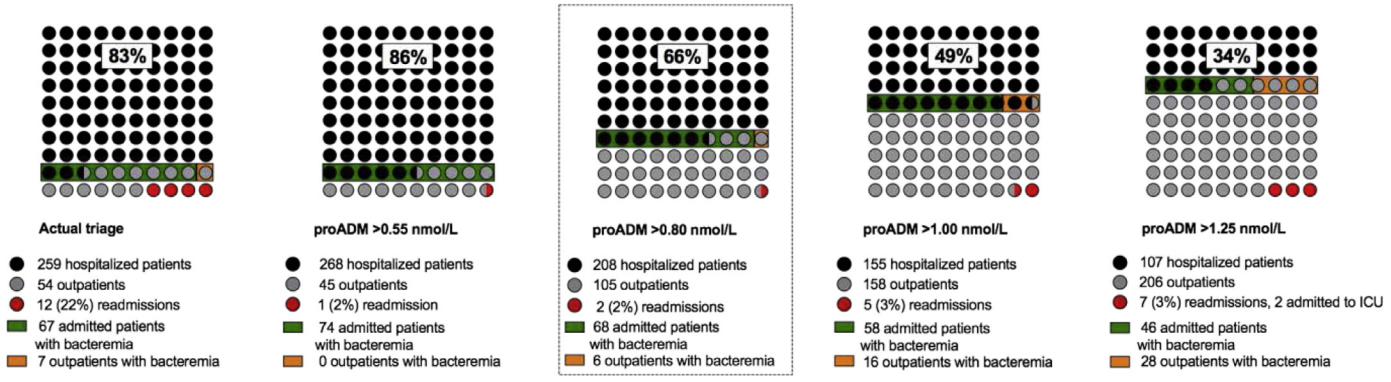


**Fig. 3.** 10 × 10 dot plot of virtual triage based on MR-proADM at different cut off levels.
Data are presented as *n*. Admission: hospitalization after initial outpatient treatment; $n = 12$ in all patients. Bacteremia: $n = 74$ in all patients. ICU: admission on Intensive Care Unit, $n = 9$ in all patients. Mortality: assessed at day 30; $n = 5$ (all admitted to hospital in each of the triage scenarios). *proADM*: mid-regional proadrenomedullin.

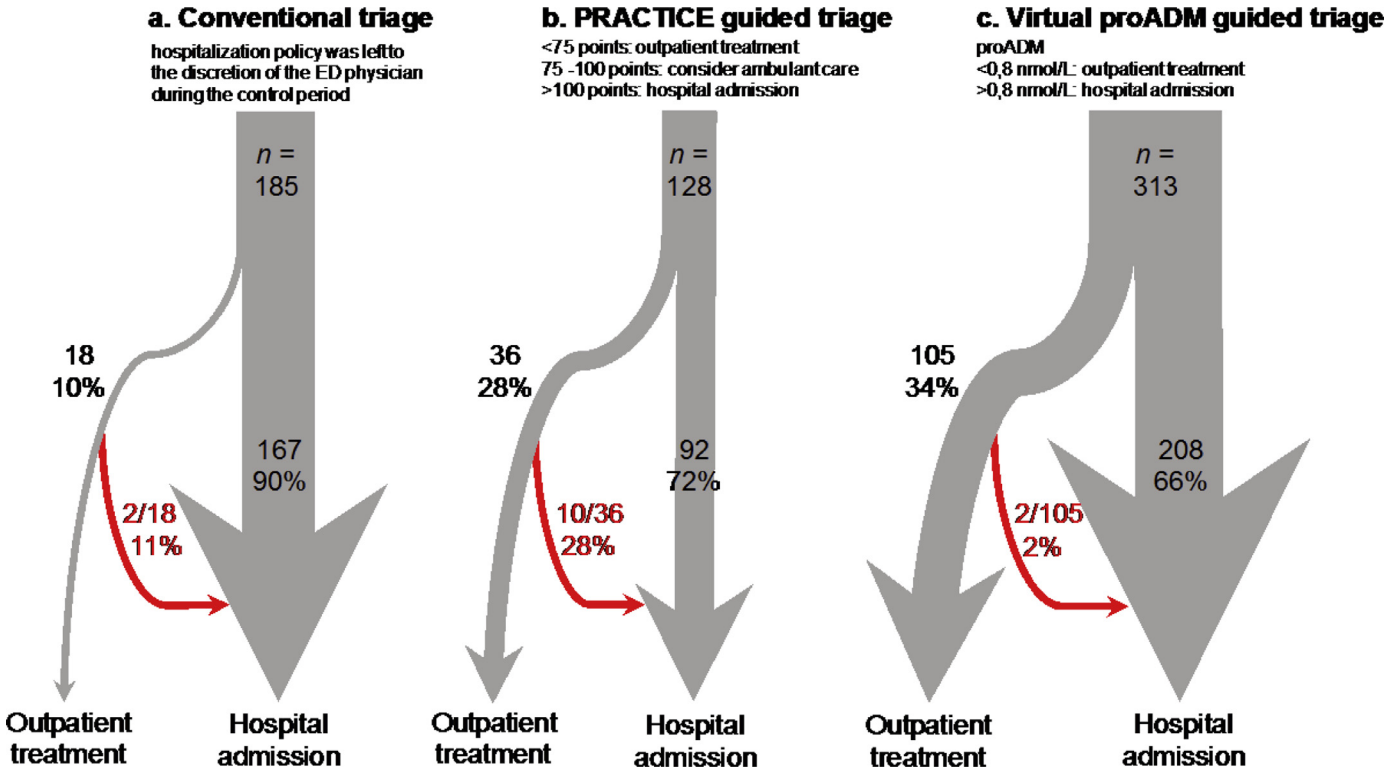


**Fig. 4.** Comparisons of hospital admission and outpatient admission in different triage models.
(a) Conventional triage in control period. (b) PRACTICE guided triage. (c) Virtual triage algorithm based on an MR-proADM with cut off 0.8 nmol/L. *ED*: emergency department. *proADM*: mid-regional proadrenomedullin.

without assigning outpatient treatment to patients with actual ICU admission or mortality within 30 days.

In comparison to the conventional hospital triage and interventional PRACTICE guided triage arms of the original study, MR-proADM guided triage at a cut-off of 0.80 nmol/L could decrease initial hospital admissions from 90% and 72%, respectively, to 66% (Fig. 4). Furthermore, outpatient readmissions could also be decreased from 11% in the conventional triage and 28% in the PRACTICE guided triage, to 2% in the virtual MR-proADM guided triage.

## Discussion

This study highlights the ability of MR-proADM in accurately predicting a severe course of febrile urinary tract infection (fUTI) in patients presenting to the emergency department (ED), and in turn, demonstrates its potential use in safely decreasing emergency department admissions, increasing outpatient numbers, and lowering subsequent outpatient hospitalization.

Urinary tract infections are the second most frequent infection diagnosed within the ED,[14] and many patients with low disease severities are hospitalized due to concerns regarding infectious progression towards sepsis, septic shock and multiple organ failure. Indeed, 20–30% of all sepsis cases originate in the urogenital tract,[15] and despite relatively low mortality rates compared to other origins of septic shock, deaths due to urosepsis can still reach up to 60% in specific patient groups.[16] Conversely, the unnecessary hospitalization of low disease severity patients can result in potential overcrowding and overtreatment issues, subsequently leading to an increase in associated clinical costs. An accurate assessment of initial disease severity and likelihood of disease progression, therefore, are crucial in order to facilitate a more personalized patient treatment strategy at the most appropriate setting.

This study therefore compared the use of commonly used biomarkers, such as procalcitonin (PCT) and C-reactive protein (CRP), and a pre-established clinical score (PRACTICE),[6] with that of mid-regional proadrenomedullin (MR-proADM) in order to predict a severe course of fUTI, and provide an appropriate model of triage. MR-proADM was found to be the most accurate parameter in identifying patients at risk of a severe course, which was significantly greater than that of either PCT or CRP. Similar results in a previous study of fUTI patients[10] found that MR-proADM performance was also greater than that of either PCT or CRP in predicting 30 day mortality, and indeed, confirm the lack of prognostic ability of CRP found within this study.

Whilst only a limited number of studies have investigated MR-proADM performance in urinary tract infections, numerous studies have been conducted in patients with lower respiratory tract infections (LRTI). In accordance with the findings of our study, the use of MR-proADM as a stand-alone parameter in LRTI patients has been shown to have either a greater or comparable accuracy in predicting mortality or the development of adverse events compared to established clinical scores, such as CURB-65 or PSI.[17–27] Numerous clinical scores have now been developed for assessing severity in several infectious diseases, with the recent addition of qSOFA in sepsis patients.[28] The use of a single biomarker to provide a simple and rapid assessment of disease severity across all infectious disease subsets, independently on the etiology of the infectious source, may therefore be of significant clinical value.

This study also found that MR-proADM may play a significant role in the triage of fUTI patients. Using a cut-off of 0.80 nmol/L, MR-proADM guided triage could decrease ED admissions and allow a higher proportion of patients to be safely treated as outpatients. Indeed, an additional 80 (25.6%) patients could have been treated on an outpatient basis as opposed to being hospitalized. Furthermore, the use of such a cut-off resulted in only 2% of outpatient re-presentations to the ED, as well as no mortalities within 30 days and no requirement for ICU admission. Despite decreases in initial hospitalization numbers, results in the original study using the PRACTICE score[6] found an unacceptably high admission rate in patients who were initially deemed suitable for outpatient treatment. This failure of the PRACTICE guided triage was also partially due to 4 “misdiagnosed” patients with primary bacteremia from another source other than the urinary tract. These subjects were initially treated as outpatients, but later re-presented to the ED and were hospitalized. All of these patients with primary bacteremia would have been admitted if the MR-proADM cut-off was set at 0.80 nmol/L. We therefore consider MR-proADM to be the optimal biomarker for UTI triage, and 0.80 nmol/L the optimal cut-off concerning patient safety, which should be further explored in any future clinical interventional trial.

To our knowledge, only one previous study addressed the use of MR-proADM for triage decisions in urinary tract infections. Litke et al. described a virtual treatment algorithm combining a MR-proADM level of 1.5 nmol/L with clinical criteria in UTI patients, and found a non-significant 7% decrease in hospitalization without a corresponding increase in adverse events.[1] The primary admission rate of 78% in this cohort of 123 patients was high, although 33% of these patients were diagnosed with cystitis, possibly due to a higher age and comorbidities as compared to our cohort. Application of their cut off on our population could have further decreased the hospitalization rate. In our cohort, 4 out of 9 patients in need for ICU admission and 7 out of 12 patients who were readmitted after being send home from the ED had an MR-proADM level below 1.5 nmol/L. It is unknown whether these patients would have met their clinical criteria for hospitalization.

It should be noted that in a Dutch clinical setting most patients with acute febrile UTI consult their general practitioner first, and are subsequently referred to the ED if required. Based on the early kinetic profile of MR-proADM in infectious patients,[29,30] MR-proADM may also be of use in the general practitioner’s office in order to provide guidance concerning hospital referrals. This in turn could lead to the more efficient use of hospital resources and a considerable reduction in costs. Indeed, Dutch general practitioners are familiar with point-of-care CRP testing since its introduction in primary care, in order to reduce antibiotic administration in respiratory tract infections.[31] In this study, we show that CRP is not a reliable marker in patients with febrile UTI concerning severity, thus, point-of-care testing in a primary setting should be expanded to MR-proADM.

The strength of this study lies within its prospective design, in which both men and women presenting with presumptive community acquired fUTI were included, thus reflecting the full spectrum of invasive UTI found at the emergency department. Detailed clinical and microbiological information was recorded in each patient, allowing for the adjustment of final diagnosis. A retrospective analysis found that some patients meeting the inclusion criteria of presumptive fUTI were in fact diagnosed with infections other than UTI, but were nevertheless included in our analysis, since such diagnostic errors are reflective of real-life patient care. Indeed, the use of clinical judgment only can often be deceptive in patients with unspecific symptoms such as fever and back pain. If these patients could be identified by the use of MR-proADM as being bacteremic and separate from the remainder of patients that could be safely managed as outpatients, the biomarker could be of great use in clinical guidance.

Our study also has a number of limitations. We included the PRACTICE score in the analysis for the prediction of hospitalization, but acknowledge the fact that this endpoint is influenced by the use of the PRACTICE score in the interventional patient group of the original study. Implementation of the PRACTICE score, on the other hand, will not have affected the prediction of a severe course of fUTI. A composite endpoint was subsequently created due to the low number of mortality and ICU admission events within this study, therefore making direct comparisons with end points from other studies difficult. Finally, biomarker guided triage can only be considered as hypothesis generating, and potential adverse events that would have led to outpatient hospitalization might have been prevented by inpatient care.

We did not include any clinical parameters in our virtual triage, because reasons for (re)admission were diverse and addition of manageable number of parameters criteria did not improve our virtual triage. Optimally, a tool to guide triage designed for the ED should be easy to use. Furthermore, any decision based on a triage algorithm should be critically appraised for the use in an individual patient. Clinical conditions such as comorbidity, patients’ preference, compliance, lack of family support cannot easily all be incorporated in a practicable decision tool. For example, in the current era of rising antimicrobial resistance, the likelihood of a causative resistant uropathogen will also influence where and how to manage fUTI.[32]

In conclusion, we show that the use of MR-proADM can accurately predict the development of severe febrile urinary tract infections compared to either PCT or CRP. Consequently, MR-proADM guided triage can identify patients who may benefit from a period of hospitalization from those with a low severity infection who can be managed as outpatients. Accordingly, resources can be focused towards patients with the greatest clinical requirements.

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## Conflict of interest

Darius Wilson is employed by Thermo Fisher Scientific/Brahms, Hennigsdorf, Germany.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2018.05.007.

## References

1. Litke A., Bossart R., Regez K., Schild U., Guglielmetti M., Conca A., Schafer P., Reutlinger B., Mueller B., Albrich W.C. The potential impact of biomarker-guided triage decisions for patients with urinary tract infections. *Infection* 2013;**41**(4):799–809.
2. Brown P., Ki M., Foxman B. Acute pyelonephritis among adults: cost of illness and considerations for the economic evaluation of therapy. *Pharmacoeconomics* 2005;**23**(11):1123–42.
3. Colgan R., Williams M., Johnson J.R. Diagnosis and treatment of acute pyelonephritis in women. *Am Fam Physician* 2011;**84**(5):519–26.
4. van Nieuwkoop C., van't Wout J.W., Spelt I.C., Becker M., Kuijper E.J., Blom J.W., Assendelft W.J., van Dissel J.T. Prospective cohort study of acute pyelonephritis in adults: safety of triage towards home based oral antimicrobial treatment. *J Infect* 2010;**60**(2):114–21.
5. Fine M.J., Auble T.E., Yealy D.M., Hanusa B.H., Weissfeld L.A., Singer D.E., Coley C.M., Marrie T.J., Kapoor W.N. A prediction rule to identify low-risk patients with community-acquired pneumonia. *New Engl J Med* 1997;**336**(4):243–50.
6. Stalenhoef J.E., van der Starre W.E., Vollaard A.M., Steyerberg E.W., Delfos N.M., Leyten E.M.S., Koster T., Ablij H.C., Van't Wout J.W., van Dissel J.T., van Nieuwkoop C. Hospitalization for community-acquired febrile urinary tract infection: validation and impact assessment of a clinical prediction rule. *BMC Infect Dis* 2017;**17**(1):400.
7. van Nieuwkoop C., Bonten T.N., van't Wout J.W., Kuijper E.J., Groeneveld G.H., Becker M.J., Koster T., Wattel-Louis G.H., Delfos N.M., Ablij H.C., Leyten E.M.S., van Dissel J.T. Procalcitonin reflects bacteremia and bacterial load in urosepsis syndrome: a prospective observational study. *Crit Care* 2010;**14**(6):R206.
8. Park J.H., Wee J.H., Choi S.P., Park K.N. Serum procalcitonin level for the prediction of severity in women with acute pyelonephritis in the ED: value of procalcitonin in acute pyelonephritis. *Am J Emerg Med* 2013;**31**(7):1092–7.
9. Ha Y.E., Kang C.I., Wi Y.M., Chung D.R., Kang E.S., Lee N.Y., Song J.H., Peck K.R. Diagnostic usefulness of procalcitonin as a marker of bacteremia in patients with acute pyelonephritis. *Scand J Clin Lab Invest* 2013;**73**(5):444–8.
10. van der Starre W.E., Zunder S.M., Vollaard A.M., van N.C., Stalenhoef J.E., Delfos N.M., van't Wout J.W., Spelt I.C., Blom J.W., Leyten E.M., Koster T., Ablij H.C., van Dissel J.T. Prognostic value of pro-adrenomedullin, procalcitonin and C-reactive protein in predicting outcome of febrile urinary tract infection. *Clin Microbiol Infect* 2014;**20**(10):1048–54.
11. Andaluz-Ojeda D., Nguyen H.B., Meunier-Beillard N., Cicuendez R., Quenot J.P., Calvo D., Dargent A., Zarca E., Andres C., Nogales L., Eiros J.M., Tamayo E., Gandía F., Bermejo-Martín J.F., Charles P.E. Superior accuracy of mid-regional proadrenomedullin for mortality prediction in sepsis with varying levels of illness severity. *Ann Intensive Care* 2017;**7**(1):15.
12. DeLong E.R., Vernon W.B., Bollinger R.R. Sensitivity and specificity of a monitoring test. *Biometrics* 1985;**41**(4):947–58.
13. Caruhel P., Mazier C., Kunde J., Morgenthaler N.G., Darbouret B. Homogeneous time-resolved fluoroimmunoassay for the measurement of midregional proadrenomedullin in plasma on the fully automated system B.R.A.H.M.S KRYPTOR. *Clin Biochem* 2009;**42**(7–8):725–8.
14. Curns A.T., Holman R.C., Sejvar J.J., Owings M.F., Schonberger L.B. Infectious disease hospitalizations among older adults in the United States from 1990 through 2002. *Arch Intern Med* 2005;**165**(21):2514–20.
15. Brun-Buisson C. The epidemiology of the systemic inflammatory response. *Intensive Care Med* 2000;**26**(Suppl 1):S64–74.
16. Rosser C.J., Bare R.L., Meredith J.W. Urinary tract infections in the critically ill patient with a urinary catheter. *Am J Surg* 1999;**177**(4):287–90.
17. Courtais C., Kuster N., Dupuy A.M., Folschveiller M., Jreige R., Bargnoux A.S., Guiot J., Lefebvre S., Cristol J.P., Sebbane M. Proadrenomedullin, a useful tool for risk stratification in high pneumonia severity index score community acquired pneumonia. *Am J Emerg Med* 2013;**31**(1):215–21.
18. Christ-Crain M., Morgenthaler N.G., Stolz D., Muller C., Bingisser R., Harbarth S., Tamm M., Struck J., Bergmann A., Muller B. Pro-adrenomedullin to predict severity and outcome in community-acquired pneumonia [ISRCTN04176397]. *Crit Care* 2006;**10**(3):R96.
19. Huang D.T., Angus D.C., Kellum J.A., Pugh N.A., Weissfeld L.A., Struck J., Delude R.L., Rosengart M.R., Yealy D.M. Midregional proadrenomedullin as a prognostic tool in community-acquired pneumonia. *Chest* 2009;**136**(3):823–31.
20. Schuetz P., Wolbers M., Christ-Crain M., Thomann R., Falconnier C., Widmer I., Neidert S., Fricker T., Blum C., Schild U., Morgenthaler N.G., Schoenenberger R., Henzen C., Bregenzer T., Hoess C., Krause M., Bucher H.C., Zimmerli W., Mueller B. Prohormones for prediction of adverse medical outcome in community-acquired pneumonia and lower respiratory tract infections. *Crit Care* 2010;**14**(3):R106.
21. Bello S., Lasierra A.B., Minchole E., Fandos S., Ruiz M.A., Vera E., de Pablo F., Ferrer M., Menendez R., Torres A. Prognostic power of proadrenomedullin in community-acquired pneumonia is independent of aetiology. *Eur Respir J* 2012;**39**(5):1144–55.
22. Cavallazzi R., El-Kersh K., Abu-Atherah E., Singh S., Loke Y.K., Wiemken T., Ramirez J. Midregional proadrenomedullin for prognosis in community-acquired pneumonia: a systematic review. *Respir Med* 2014;**108**(11):1569–80.
23. Kruger S., Ewig S., Giersdorf S., Hartmann O., Suttorp N., Welte T. Cardiovascular and inflammatory biomarkers to predict short- and long-term survival in community-acquired pneumonia: results from the German Competence Network, CAPNETZ. *Am J Respir Crit Care Med* 2010;**182**(11):1426–34.
24. Sarda Sanchez M., Hernandez J.C., Hernandez-Bou S., Teruel G.C., Rodriguez J.V., Cubells C.L. Pro-adrenomedullin usefulness in the management of children with community-acquired pneumonia, a preliminar prospective observational study. *BMC Res Notes* 2012;**5**:363.
25. Renaud B., Schuetz P., Claessens Y.E., Labarere J., Albrich W., Mueller B. Proadrenomedullin improves risk of early admission to ICU score for predicting early severe community-acquired pneumonia. *Chest* 2012;**142**(6):1447–54.
26. Espana P.P., Capelastegui A., Mar C., Bilbao A., Quintana J.M., Diez R., Esteban C., Bereciartua E., Unanue U., Uranga A. Performance of pro-adrenomedullin for identifying adverse outcomes in community-acquired pneumonia. *J Infect* 2015;**70**(5):457–66.
27. Bello S., Fandos S., Lasierra A.B., Minchole E., Panadero C., Simon A.L., Gavin O., De Pablo F., Menendez R., Torres A. Red blood cell distribution width [RDW] and long-term mortality after community-acquired pneumonia. A comparison with proadrenomedullin. *Respir Med* 2015;**109**(9):1193–206.
28. Singer M., Deutschman C.S., Seymour C.W., Shankar-Hari M., Annane D., Bauer M., Bellomo R., Bernard G.R., Chiche J.D., Coopersmith C.M., Hotchkiss R.S., Levy M.M., Marshall J.C., Martin G.S., Opal S.M., Rubenfeld G.D., van der Poll T., Vincent J.L., Angus D.C. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;**315**(8):801–10.
29. Decker S.O., Sigl A., Grumaz C., Stevens P., Vainshtein Y., Zimmermann S., Weigand M.A., Hofer S., Sohn K., Brenner T. Immune-response patterns and next generation sequencing diagnostics for the detection of mycoses in patients with septic shock-results of a combined clinical and experimental investigation. *Int J Mol Sci* 2017;**18**(8):1796.
30. Gille J., Ostermann H., Dragu A., Sablotzki A. MR-proADM: a new biomarker for early diagnosis of sepsis in burned patients. *J Burn Care Res* 2017;**38**(5):290–8.
31. Verlee L., Verheij T.J., Hopstaken R.M., Prins J.M., Salome P.L., Bindels P.J. [Summary of NHG practice guideline 'Acute cough']. *Ned Tijdschr Geneeskd* 2012;**156**(0):A4188.
32. van der Starre W.E., van N.C., Paltansing S., van't Wout J.W., Groeneveld G.H., Becker M.J., Koster T., Wattel-Louis G.H., Delfos N.M., Ablij H.C., Leyten E.M., Blom J.W., van Dissel J.T. Risk factors for fluoroquinolone-resistant Escherichia coli in adults with community-onset febrile urinary tract infection. *J Antimicrob Chemother* 2011;**66**(3):650–6.