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## Can mid-regional pro-adrenomedullin (MR-proADM) increase the prognostic accuracy of NEWS in predicting deterioration in patients admitted to hospital with mild to moderately severe illness? A prospective single-centre observational study.

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## Prognostic accuracy of MR-proADM in emergency departments

**Title:** Can mid-regional pro-adrenomedullin (MR-proADM) increase the prognostic accuracy of NEWS in predicting deterioration in patients admitted to hospital with mild to moderately severe illness? A prospective single-centre observational study.

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## Prognostic accuracy of MR-proADM in emergency departments

21 **Abstract**

22 **Objective** To assess the accuracy of a statistical model based on admission NEWS score  
23 and MR-proADM blood level in predicting deterioration in mild to moderately ill people.

24 **Design** Prospective observational study

25 **Setting** The Medical Admissions Suite of the Royal Victoria Infirmary, Newcastle.

26 **Participants** 300 adults with NEWS score between 2 and 5 on admission. Exclusion  
27 criteria included receiving palliative care, or admitted for social reasons or self-  
28 harming. Patients were enrolled between September and December 2015, and  
29 followed-up for 30 days after discharge.

30 **Outcome measure** The primary outcome measure was the proportion of patients who,  
31 within 72 hours, had an *Acuity Increase*, defined as any combination of: an increase of at  
32 least 3 in the NEWS score; transferred to a higher-dependency bed or monitored area;  
33 and, for those discharged from hospital, re-admission for medical reasons; or death.

34 **Results** NEWS predicted *Acuity Increase* poorly: the area under the curve (AUC) was  
35 0.55 (95% CI 0.48, 0.62) with univariate analysis. NEWS and MR-proADM together  
36 predicted *Acuity Increase* more accurately, increasing AUC to 0.61 (95% CI 0.54, 0.69).  
37 When the presence of chronic obstructive pulmonary disease or heart failure and  
38 interaction with MR-proADM were added to the model, the predictive accuracy further  
39 increased the AUC to 0.69 (95% CI 0.63, 0.76).

40 **Conclusions** MR-proADM improves the accuracy of prediction by NEWS of  
41 deterioration in patients admitted to hospital with a mild to moderately severe acute  
42 illness. As a growing number of NHS hospitals are implementing the NEWS score on  
43 their clinical information systems, further research should assess the practicalities and  
44 utility of developing a decision aid based on admission NEWS score, MR-proADM level,  
45 and possibly other clinical data and other biomarkers that could further improve  
46 prediction accuracy.

47 **Keywords**

48 Biochemistry, diagnosis, health services research

49

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**Strengths and limitations of this study**

- This is the first study to use rigorous statistical methods to assess the value added by MR-proADM to the admission NEWS score for predicting clinically important deterioration in mild to moderately ill patients
- Prediction accuracy might have been greater had more severely ill patients been included, but these people are already known to be severely ill.
- This was an observational study, and thus could not directly assess the utility of more accurate prediction of deterioration

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## Prognostic accuracy of MR-proADM in emergency departments

**51 Introduction**

52 The National Early Warning Score (NEWS) is recommended for assessing severity of  
53 illness in patients presenting in primary or secondary NHS care and for surveillance of  
54 patients in hospital <sup>1 2</sup>. Six physiological parameters (which can be measured at the  
55 bedside) are scored: respiratory rate, oxygen saturation, temperature, systolic blood  
56 pressure, pulse rate, and level of consciousness. The scores are aggregated, and, if the  
57 patient requires oxygen, the total is increased. NEWS predicts death, cardiac arrest, and  
58 unplanned intensive care unit (ICU) admission within 24 hours <sup>3-5</sup>. However, NEWS  
59 does not identify all patients who turn out to be seriously ill <sup>6-8</sup>, and there are also  
60 patients whose NEWS score is usually elevated and who do not require the level of  
61 observation that the NEWS tool would suggest. For example, people with chronic  
62 obstructive pulmonary disease (COPD) or chronic heart failure (HF) have higher  
63 baseline NEWS scores than those without these comorbidities. The useful predictive  
64 accuracy of NEWS for patients presenting to the Emergency Department (ED) has been  
65 confirmed in a wide range of severity of illness <sup>9 10</sup>, as has its reduced accuracy in people  
66 with COPD <sup>11</sup>. But, no previous studies of the predictive accuracy of NEWS in the  
67 ED/Medical Admissions Unit (MAU) have focussed on patients admitted with mild to  
68 moderately severe illness. Since a clinically important proportion of these patients do  
69 deteriorate unexpectedly, improved risk stratification would be useful.

70 Mid-regional pro-adrenomedullin (MR-proADM) is one of several promising biomarkers  
71 for severe illness and deterioration <sup>12-16</sup>.

72 MR-proADM is a precursor of adrenomedullin (ADM), a member of the calcitonin  
73 peptide family. ADM is widely expressed and has roles in vasodilation, immune  
74 modulation, and metabolic regulation. It is up-regulated in severe infections,  
75 inflammation, vasodilation, stimulation of diuresis, increased cardiac output, and stroke  
76 <sup>17-19</sup>. ADM has a short half-life, but MR-proADM is more stable and directly reflects ADM  
77 concentrations in blood. Both ADM and MR-proADM levels are strongly associated with  
78 risk of mortality, regardless of aetiology <sup>20-26</sup>. In people presenting with acute chest  
79 pain, MR-proADM has been reported to improve the Global Registry of Acute Coronary  
80 Events risk classification by 41% <sup>27</sup>. As with the NEWS score, people with COPD or  
81 chronic heart failure have higher baseline levels of MR-proADM.

## Prognostic accuracy of MR-proADM in emergency departments

82 The aim of this study was to assess whether the MR-proADM level used alongside the  
83 NEWS score would improve prediction of deterioration over NEWS score alone in  
84 patients admitted to the MAU with mild to moderately severe illness.

## 85 **Methods**

### 86 **Study participants and study design**

87 This was a prospective observational cohort study. Patients were enrolled between  
88 September and December 2015 at the Royal Victoria Infirmary, Newcastle, and  
89 followed-up for 30 days after discharge. If the patient died within the 30 days of follow  
90 up, this and cause of death were recorded. Adults admitted to the MAU were recruited  
91 for the study between 9am and 4pm on weekdays.

92 Sample size was determined as a pragmatic recruitment target for a three-month  
93 observational study. A recent unpublished audit conducted in the MAU at the Royal  
94 Victoria Infirmary found a deterioration rate of 20%. With 300 patients and complete  
95 data collection, 60 events would be anticipated. With this number of events, a  
96 multivariable prediction model could reliably include up to six independent predictors:  
97 models with fewer than ten events per predictor tend to be over-fitted<sup>28</sup>.

98 Patients were considered eligible for inclusion in the study if their NEWS score on  
99 admission was at least 2 and not greater than 5, and all NEWS parameters were  
100 recorded. Patients were excluded from the study if they were receiving palliative care,  
101 were admitted for social reasons only, or were self-harming, or overdosing with drugs  
102 or other substances.

103 All participants provided written informed consent, and the study was approved by the  
104 Newcastle & North Tyneside Research Ethics Committee (15/NE/0120).

### 105 **Recorded data**

106 Demographic and admission data included: gender, year of birth, reason for admissions,  
107 diagnosis on discharge, and the presence of comorbidities in which baseline MR-  
108 proADM levels are chronically raised: COPD with hypoxia ( $\text{PaO}_2 < 10 \text{ kPa}$ )<sup>7</sup>; HF<sup>29</sup>; acute  
109 brain injury<sup>6</sup>; acute coronary syndrome<sup>27</sup>; acute venous thromboembolism<sup>21</sup>; high  
110 International Normalized Ratio ( $\text{INR} > 2$ ); acute kidney injury; electrolyte disturbances

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(Na<sup>+</sup> <130 or >150 mmol/L; K<sup>+</sup> <3.0 or >5.5 mmol/L); hyperglycaemia in type 1 diabetes (random glucose >10 mmol/L).

The NEWS score was assessed at baseline and over the next 72 hours, and the scores and assessment times recorded. The 7 clinical parameters used to determine the NEWS score were recorded for the baseline assessment only.

Blood samples were taken at hospital admission for assessment of MR-proADM, C-Reactive Protein (CRP) and white blood count (WBC).

### Laboratory tests

Plasma was obtained from blood samples (collected in ethylenediaminetetraacetic acid, EDTA) that were no longer clinically required. Plasma was stored in aliquots at -80° C

MR-proADM was assayed in the on-site Blood Sciences Laboratory using the BRAHMS Kryptor system according to the manufacturer's instructions.

Blood samples were analysed in batches by personnel blinded with regard to the condition and NEWS score of the patient. Nurses who assessed the NEWS score and healthcare professionals managing patients in the MAU were blinded to MR-proADM results.

### Outcomes of interest

**Outcome 1: Acuity Increase (i.e. deterioration).** A patient was classified as having an *Acuity Increase* if one or more of the following occurred within 72 hours from admission:

1. transfer to a higher level of care (ICU or high dependency unit)
2. readmission to hospital for reasons related to the initial admission
3. death for reasons related to the initial admission
4. NEWS score increased by at least two compared to the admission score

**Outcome 2: Deterioration Event.** For most of the observed *Acuity Increase* cases the reason for classification was an increase in the NEWS score (Table 1). Because an increase in NEWS score reflects both measurement variation and physiological variation, additional exploratory analyses were carried out to assess the performance of MR-proADM in predicting deterioration. *Deterioration Events* were classified as the occurrence of one or more of the following:



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- 141 1. transfer to higher level of care within 72 hours from admission;
- 142 2. death for related reason to admission within 30 days;
- 143 3. re-admission to hospital (for the same reason as the previous admission) within
- 144 30 days from first admission.

145 Classification based on this definition is unlikely to be subject to clinically important  
146 measurement variation. This analysis, therefore, should optimise the accuracy of  
147 prediction accuracy for events which are both clinically and economically important.

148 **Outcome 3: Length of Stay.** *Length of Stay* was defined as the duration (in days) from  
149 admission to discharge or death.

### 150 Statistical analysis

151 All data analyses were performed using the R language version 3.2.0<sup>30</sup>, with the support  
152 of RStudio, version 0.99.896 (RStudio, Inc). The following R packages were used:  
153 ggplot2, pROC, psych, PredictABEL, Hmisc. For the ROC curve analyses, data were  
154 exported to SPSS version 22 (SPSS, Inc., Chicago IL) and analyses were re-run for quality  
155 assurance of results.

156 Logistic regression models were compared for their accuracy in predicting  
157 deterioration outcome measures as pre-specified in the analysis plan. Analyses are  
158 presented as unadjusted parameter estimates of risk (odds ratio (OR), with confidence  
159 intervals) and estimates adjusted for identified clinical confounding factors. The aims of  
160 the multivariable analyses were twofold: first, estimate the effect size and significance  
161 adjusted for other identified influential predictors and interactions; second, to  
162 investigate whether the addition of other predictors improved the goodness of fit and  
163 accuracy of prediction.

164 Only complete cases were analysed since missingness was minimal (see Table 1).

165 For each outcome of deterioration, logistic regression models were compared for the  
166 following sets of predictor variables:

- 167 *Predictor set a.* Comparator (base case): NEWS score on admission  
168 *Predictor set b.* Primary analysis: NEWS score, MR-proADM  
169 *Predictor set c.* Secondary analyses: NEWS score and MR-proADM always  
170 included. Age, gender, CRP, WBC, presence of COPD or HF,

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171 presence of other comorbidities, and interactions between  
172 predictors when appropriate.

173 Predictors (and the underlying assumption of linearity of their relationship with the  
174 outcome of interest) were initially investigated through univariate analyses based on  
175 simple log and quadratic functions. We have assessed interactions through visual data  
176 exploration. Transformations were applied if they improved the goodness of fit as  
177 assessed by the Akaike information criterion (AIC), and were retained in the  
178 multivariable setting. Subsequently, for the multivariate regression the set of predictors  
179 was reduced through backward elimination, again based on changes in AIC.

180 Secondary outcome of *Length of Stay* followed a similar analysis plan using multiple  
181 regressions based on a transformed outcome to address non-normality. To evaluate  
182 whether MR-proADM was a predictor of the length of stay in the hospital, linear  
183 regression was used since the outcome variable (*Length of Stay*) is a continuous  
184 variable. Variables were log-transformed if not normally distributed. Normality was  
185 assessed by visualizing the data. The regression model included *Length of Stay* as  
186 outcome variable, and NEWS and MR-proADM as predictors. More details of the  
187 methods used are reported in the Supplemental Data.

188 Predictive accuracy of the models was assessed with the area under the ROC curve  
189 (AUC) and is presented for all models with 95% confidence intervals (CI). To assess the  
190 value added by including the MR-proADM level with the NEWS score in predicting  
191 deterioration, continuous net reclassification improvement (NRI) and integrated  
192 discrimination improvement (IDI) were calculated<sup>31 32</sup>.

193 Internal validation of models was performed through bootstrapping with 10,000  
194 resamples.

## 195 Results

### 196 Study enrolment

197 The process of recruitment and enrolment of patients for the study is shown in Figure 1.  
198 The study recruited 300 patients, and the 292 were included in the analysis. Five  
199 patients were excluded because the blood samples for MR-proADM were taken more

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200 than 12 hours from baseline NEWS assessment; 3 patients were excluded from the  
201 primary outcome due to missing follow up NEWS scores.

**202 Patient characteristics**

203 Patient demographics and mean biomarker levels for each covariate are reported in  
204 Table 1. The cohort was evenly divided in gender and had a mean age of 63 years and  
205 mean NEWS on admission of 3, with the majority of patients having NEWS score of 2.  
206 COPD or HF were present in 28%, and 25% had other comorbidities.

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**Table 1.** Characteristics of the study population, classified by Outcome 1 (*Acuity Increase*), Outcome 2 (*Deterioration Event*) and All patients. Data are presented as number (no) and percentages (%) for counts, or mean and (standard deviation, SD) for continuous normally distributed data, or [25th; 50th; 75th percentile] for continuous non-normally distributed data.

	Outcome 1: <i>Acuity Increase</i>		Outcome 2: <i>Deterioration Event</i>		All patients (n = 292)
	Present (e = 84)	Absent	Present (e2 = 32)	Absent	
Age (mean years, SD)	65 (17)	62 (21)	63 (14)	63 (20)	63 (20)
Gender (no. females, %)	41 (49%)	107 (51%)	15 (47%)	133 (51%)	148 (51%)
NEWS = 2 (no., %)	34 (40%)	82 (40%)	12 (38%)	104 (40%)	116 (40%)
NEWS = 3 (no., %)	26 (31%)	59 (28%)	9 (28%)	76 (29%)	85 (29%)
NEWS = 4 (no., %)	11 (13%)	43 (21%)	4 (13%)	50 (19%)	54 (18%)
NEWS = 5 (no., %)	13 (15%)	24 (12%)	7 (22%)	30 (12%)	37 (13%)
MR-proADM (mean nmol/l, SD)	1.50 (1.4) [0.72, 1.12, 1.79]	1.19 (0.9) [0.68, 0.93, 1.28]	1.89 (2.0) [0.93, 1.13, 1.95]	1.20 (0.9) [0.68, 0.93, 1.39]	1.28 (1.1) [0.68, 0.97, 1.48]
CRP (mg/l)	59 (79) [5, 22, 80]	42 (70) [4, 13, 41]	61 (90) [7, 23, 67]	45 (71) [4, 16, 51]	47 (73) [4, 17, 54]
WBC (x10 <sup>9</sup> /l)	12 (5) [9, 10, 14]	11 (5) [8, 10, 14]	12 (4) [9, 12, 15]	11 (5) [8, 10, 14]	11 (5) [8, 10, 14]
COPD/HF (no, %)*	33 (39%)	46 (22%)	12 (38%)	67 (26%)	79 (28%)
Other comorbidities (no., %)	17 (20%)	55 (26%)	15 (47%)	57 (22%)	72 (25%)
Length of stay (hrs)	168 (196) [63, 110, 194]	137 (176) [26, 68, 176]	173 (172) [59, 106, 259]	143 (172) [33, 72, 176]	146 (182) [35, 77, 182]
Length of stay in MAU (hrs)	31 (19) [17, 25, 43]	24 (16) [13, 21, 30]	27 (17) [18, 23, 35]	26 (17) [15, 22, 31]	26 (17) [15, 22, 31]
Monitored beds (no, %)	31 (37%)	58 (27%)	11 (34%)	78 (30%)	89 (30%)

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	<b>Outcome 1: <i>Acuity Increase</i></b>		<b>Outcome 2: <i>Deterioration Event</i></b>		<b>All patients (n = 292)</b>
	<b>Present (e = 84)</b>	<b>Absent</b>	<b>Present (e2 = 32)</b>	<b>Absent</b>	
Deterioration time (hrs)	15 (13) [5, 9, 21]	N/A	170 (226) [19, 33, 301]	N/A	
* for COPD: e = number with <i>Acuity Increase</i> = 82; e2 = number with <i>Deterioration Event</i> = 29; n = total number of patients = 282					

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213 **Table 2.** Criteria met by patients classified with an *Acuity Event* or *Deterioration Event*.

Criterion for deterioration	<i>Acuity Increase</i> (e = 84)	<i>Deterioration Event</i> (e2 = 32)
NEWS (no, %)	81 (96.4%)	N/A
ICU transfer (no, %)	1 (1.2%)	4 (12.5%)
Death (no, %)	0 (0%)	6 (18.8%)
Readmission (no, %)	2 (2.4%)	22 (68.7%)

214

215 The study population was homogenous across *Acuity Increase* and No *Acuity Increase*  
 216 outcomes in terms of gender, age, and NEWS on admission. Patients who experienced  
 217 *Acuity Increase* had higher MR-proADM and CRP levels at admission, and longer length  
 218 of stay in the hospital and in the MAU.

219 The prevalence of *Acuity Increase* was 29% (somewhat higher than the anticipated  
 220 20%). The prevalence of *Deterioration Events* was 11%. The numbers of events  
 221 provided sufficient statistical power to assess statistical significance for the primary  
 222 outcome, *Acuity Increase*, but not for the secondary outcome, *Deterioration Event*, and  
 223 those results should be regarded as exploratory.

224 **Accuracy of MR-proADM for predicting *Acuity Increase***

225 In the univariate analyses (Table 3) of predictors of *Acuity Increase*, the variables were  
 226 transformed in a preliminary analysis assessing for non-linear relationships with the  
 227 outcome variable. The final analysis used untransformed variables for all predictors  
 228 except *Age*, for which a quadratic transformation,  $Age^2$ , was used. Potentially useful  
 229 predictors of *Acuity Increase* were MR-proADM (OR = 1.27, 95% CI 1.02, 1.62; p =  
 230 0.037),  $Age^2$  (OR = 1.00, 95% CI 0.99, 1.00; p = 0.023) and the presence of COPD or HF  
 231 (OR = 2.25, 95% CI 1.30, 3.91; p = 0.004). The prediction accuracy of CRP and WBC did  
 232 not reach the threshold of significance (p = 0.88 and p = 0.090).

233

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234 **Table 3.** Univariate regression analyses for predicting the three outcomes of interest:  
 235 *Acuity Increase, Deterioration Event, and Length of Stay.* The analyses for the NEWS  
 236 score as a predictor are shown in Table 4.

	Beta	CI	Odds Ratio (CI)	p-value
<b>Acuity Increase: univariate logistic regressions (n = 292, e = 84)</b>				
MR-proADM	0.24	-0.02, 0.48	1.27 (1.02, 1.62)	0.037
CRP	0.003	-0.0005, 0.0063	1.00 (1.00, 1.01)	0.088
WBC	0.04	-0.008, 0.094	1.05 (1.00, 1.10)	0.09
Gender	0.14	-0.38, 0.65	1.15 (0.69, 1.92)	0.684
Age	0.1	0.019, 0.1925	1.11 (1.02, 1.21)	0.023
Age <sup>2</sup>	-0.0008	-0.0016, -0.0001	1.00 (0.99, 1.00)	
Other Comorbidities	-0.32	-0.96, 0.28	0.72 (0.38, 1.32)	0.267
COPD/HF*	0.81	0.26, 1.36	2.25 (1.30, 3.91)	0.004
<b>Deterioration Event: univariate logistic regressions (n = 292, e2 = 32)</b>				
MR-proADM	0.37	0.11, 0.64	1.44 (1.12, 1.90)	0.006
CRP	0.003	-0.002, 0.01	1.00 (1.00, 1.01)	0.255
WBC	0.02	-0.05, 0.09	1.02 (0.95, 1.10)	0.506
Gender	0.17	-0.57, 0.92	1.19 (0.57, 2.50)	0.648
Age	0.21	0.06, 0.40	1.23 (1.06, 1.49)	0.013
Age <sup>2</sup>	-0.002	-0.003, -0.001	1.00 (1.00, 1.00)	
Other Comorbidities	1.14	0.38, 1.90	3.14 (1.47, 6.69)	0.003
COPD/HF*	0.67	-0.14, 1.46	1.96 (0.87, 4.29)	0.095
<b>Length of stay: simple linear regressions (n = 292, e = 84, e2 = 32)</b>				
MR-proADM	0.7	0.49, 0.92	N/A	<0.0001
CRP	0.05	-0.05, 0.15	N/A	0.368
WBC	-0.06	-0.38, 0.27	N/A	0.73
Gender	0.08	-0.04, 0.20	N/A	0.18
Age	0.007	0.004, 0.010	N/A	<0.0001
Other Comorbidities	0.18	0.05, 0.32	N/A	0.009
COPD/HF*	0.07	-0.07, 0.21	N/A	0.318
<b>Key:</b> n = total number of cases; e = number of <i>Acuity Increases</i> ; e <sub>2</sub> = number of <i>Deterioration Events</i> ; CI = 95% confidence interval * n = 282, e = 82, e <sub>2</sub> = 29				

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238 **Table 4.** Multivariable regression analyses for the outcomes of interest: Acuity Increase,  
 239 *Deterioration Event, Length of Stay* (Outcomes 1, 2, and 3 respectively) with NEWS  
 240 comparator group. Predictor set *a.* includes only the NEWS score as a predictor;  
 241 Predictor set *b.* includes MR-proADM and NEWS scores; Predictor set *c.* includes MR-  
 242 proADM, NEWS scores, and other significant predictors and interactions.

		Beta	CI	Odds Ratio (CI)	p-value	
<b>Acuity Increase: multivariate logistic regressions</b>						
<b>Predictor set a</b> n = 292 e = 84 e2 = 32	NEWS 3	0.06	-0.55, 0.67	1.06 (0.57, 1.95)	0.416	
	NEWS 4	-0.48	-1.29, 0.27	0.62 (0.27, 1.31)		
	NEWS 5	0.27	-0.54, 1.04	1.31 (0.58, 2.84)		
<b>Predictor set b</b> n = 292 e = 84 e2 = 32	NEWS 3	0.03	-0.59, 0.65	1.03 (0.56, 1.91)	0.247	
	NEWS 4	-0.53	-1.35, 0.23	0.59 (0.26, 1.26)		
	NEWS 5	0.18	-0.63, 0.97	1.20 (0.53, 2.64)		
	MR-proADM	0.24	0.02, 0.49	1.28 (1.02, 1.63)	0.039	
<b>Predictor set c</b> n = 282 e = 82 e2 = 29	NEWS 3	-0.11	-0.76, 0.54	0.90 (0.47, 1.71)	0.221	
	NEWS 4	-0.89	-1.77, -0.08	0.41 (0.17, 0.93)		
	NEWS 5	0.09	-0.77, 0.91	1.09 (0.46, 2.50)		
	MR-proADM	0.41	0.13, 0.76	1.51 (1.14, 2.14)		0.01
	COPD/HF	1.81	0.80, 2.85	6.08 (2.23, 17.35)		0.001
MR-proADM*COPD/HF	-0.71	-1.40, -0.10	0.49 (0.25, 0.91)	0.03		
<b>Deterioration Event: multivariate logistic regressions</b>						
<b>Predictor set a</b> n = 292 e = 84 e2 = 32	NEWS 3	0.03	-0.92, 0.94	1.03 (0.40, 2.55)	0.512	
	NEWS 4	-0.37	-1.68, 0.74	0.69 (0.19, 2.10)		
	NEWS 5	0.7	-0.36, 1.70	2.02 (0.70, 5.50)		
<b>Predictor set b</b> n = 292 e = 84 e2 = 32	NEWS 3	-0.01	-0.97, 0.92	0.99 (0.38, 2.51)	0.564	
	NEWS 4	-0.43	-1.76, 0.70	0.65 (0.17, 2.02)		
	NEWS 5	0.6	-0.49, 1.62	1.81 (0.61, 5.05)		
	MR-proADM	0.36	0.10, 0.64	1.43 (1.11, 1.89)		0.007
<b>Predictor set c</b> n = 282 e = 82 e2 = 29	NEWS 3	0.16	-0.83, 1.12	1.17 (0.44, 3.07)	0.389	
	NEWS 4	-0.49	-1.86, 0.69	0.62 (0.16, 2.00)		
	NEWS 5	0.69	-0.44, 1.76	1.99 (0.64, 5.81)		
	MR-proADM	0.32	0.02, 0.64	1.37 (1.02, 1.89)		0.044



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		Beta	CI	Odds Ratio (CI)	p-value	
	Other comorbidities	0.94	0.10, 1.77	2.56 (1.10, 5.85)	0.026	
	Age	0.21	0.06, 0.41	1.23 (1.06, 1.50)	0.011	
	Age <sup>2</sup>	-0.002	-0.003, -0.001	1.00 (1.00, 1.00)		
<b>Length of stay: multiple linear regressions</b>						
<b>Predictor set a</b> n = 292 e = 84 e <sup>2</sup> = 32	NEWS 3	-0.07	-0.21, 0.08	N/A	0.052	
	NEWS 4	0.07	-0.10, 0.24	N/A		
	NEWS 5	0.21	0.01, 0.40	N/A		
<b>Predictor set b</b> n = 292 e = 84 e <sup>2</sup> = 32	NEWS 3	-0.1	-0.24, 0.04	N/A	0.033	
	NEWS 4	0.05	-0.11, 0.21	N/A		
	NEWS 5	0.14	-0.04, 0.32	N/A		
	MR-proADM	0.69	0.48, 0.91	N/A		<0.0001
<b>Predictor set c</b> n = 282 e = 82 e <sup>2</sup> = 29	NEWS 3	-0.12	-0.25, 0.02	N/A	0.031	
	NEWS 4	0.04	-0.11, 0.20	N/A		
	NEWS 5	0.14	-0.04, 0.32	N/A		
	MR-proADM	0.55	0.31, 0.80	N/A		<0.0001
	Age	0.004	0, 0.007	N/A		0.027

243

244 The predictive accuracy for *Acuity Increase* of NEWS on its own was limited (AUC 0.55,  
 245 95% CI 0.48, 0.62), but when MR-proADM was included as an additional predictor, the  
 246 accuracy of the model increased substantially (AUC 0.61, 95% CI 0.54, 0.69; OR = 1.28,  
 247 95% CI 1.02, 1.63; p = 0.007) (Tables 4 and 5, Figure 2A), and was statistically  
 248 significant (p = 0.033 for likelihood ratio, Table 5). When including MR-proADM with  
 249 NEWS, the reclassification of patients was also significant, especially in the NRI score  
 250 (NRI = 0.3, SE 0.1, p = 0.007; IDI = 0.017, Table 4).

251 The prediction accuracy of MR-proADM and the additional value it provides to the  
 252 NEWS score was confirmed for *Deterioration Events* and *Length of Stay* (Figure 2C,  
 253 Tables 4 and 5).

254

## Prognostic accuracy of MR-proADM in emergency departments

**Table 5.** Model comparisons. Outcomes 1, 2, and 3 refer to Acuity Increase, *Deterioration Event*, and *Length of Stay* respectively. The predictors are: *Set a* NEWS score alone; *Set b* NEWS score and MR-proADM; *Set c* NEWS score, MR-proADM, and other significant predictors and interactions detailed in Table 3.

	AIC	Deviance	AUC (CI) or R <sup>2</sup> for linear regression	LR, (df) p-value	NRI (se), p-value	IDI (se), p-value
<i>Acuity Increase: logistic regressions</i>						
Outcome 1 - predictor set <i>a</i> .	348	356	0.55 (0.48, 0.62)			
Outcome 1 - predictor set <i>b</i> .	343	353	0.61 (0.54, 0.69)	5 (1), 0.033	0.3 (0.1), 0.007	0.017 (0.009), 0.058
Outcome 1 - predictor set <i>c</i> .	317	331	0.69 (0.63, 0.76)	14 (2), 0.001*	0.4 (0.1), 0.0004*	0.05 (0.01), 0.0009*
<i>Deterioration Event: logistic regressions</i>						
Outcome 2 - predictor set <i>a</i> .	199	207	0.57 (0.47, 0.68)			
Outcome 2 - predictor set <i>b</i> .	192	202	0.65 (0.54, 0.76)	7 (1), 0.007	0.4 (0.2), 0.003	0.04 (0.02), 0.10
Outcome 2 - predictor set <i>c</i> .	177	193	0.73 (0.63, 0.84)	15 (3), 0.0019*	0.5 (0.2), 0.012*	0.06 (0.02), 0.0004*
<i>Length of Stay: linear regressions (LR)</i>						
Outcome 3 - predictor set <i>a</i> .	77	-381	0.03			
Outcome 3 - predictor set <i>b</i> .	68	-417	0.14	9 (1), <0.001		
Outcome 3 - predictor set <i>c</i> .	67	-420	0.16	1 (1), 0.026		
<b>Note:</b> AIC = Akaike information criterion; AUC = area under the receiver operating characteristic curve; CI = 95% confidence interval; LR = likelihood ratio; df = degrees of freedom; NRI = net reclassification index; se = standard error; IDI = integrated discrimination improvement. * Comparison is between predictor set <i>b</i> . and <i>c</i> . Since there was a mismatch between the cases for predictor set <i>a</i> . and <i>b</i> . (10 missing values in COPD/HF), in the model with predictors set <i>b</i> . the 10 cases missing in predictor set <i>c</i> . were dropped to allow the comparison.						

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258 **Effect on prediction accuracy when clinical information is added to**  
259 **the set of predictors**

260 Ten additional patients with incomplete data were excluded from this analysis.

261 Multivariable modelling evaluated the predictive accuracy of MR-proADM when  
262 adjusted for the clinical factors in predictive set *c*: age, gender, CRP, WBC, presence of  
263 COPD or HF, presence of other comorbidities,

264 For *Acuity Increase*, COPD or HF comorbidity status and its interaction with MR-proADM  
265 level significantly improved the predictive accuracy of the model: AUC increased from  
266 0.61 (95% CI 0.54, 0.69) to 0.69 (95% CI 0.63, 0.76). The increased risk of *Acuity*  
267 *Increase* with a unit increase in MR-proADM was 0.41 (95% CI 0.13, 0.76) with OR of  
268 1.51 (95% CI 1.14, 2.14;  $p = 0.010$ ). The net reclassification index was significant (NRI =  
269 0.4 (SE 0.1,  $p = 0.0004$ ).

270 For *Deterioration Events*, the presence of other comorbidities (excluding COPD and HF)  
271 and  $Age^2$  increased the prediction accuracy of MR-proADM, (Table 4 and 5). The  
272 prediction accuracy of *Length of Stay* (Outcome 3) of MR-proADM is also increased  
273 including *Age* in the model (Table 4 and 5).

274 Because the means and standard errors of the coefficients estimated in the non-  
275 parametric bootstrapping analysis were all within 10-20% of the values evaluated by  
276 the models, the models' beta coefficients were not adjusted.

277 **Potential confounding effects**

278 **Shorter term outcomes:** NEWS and MR-proADM had lower accuracy in predicting  
279 *Acuity Increase* within 24 and 12 hours from admission than in predicting *Acuity*  
280 *Increase* within 72 hours (Supplementary material, Tables 1 and 2).

281 **Interval between admission NEWS scoring and blood collection:** Because ward  
282 processes did not allow the times of scoring NEWS and collecting blood to be specified  
283 for research, we assessed for a confounding effect from variation in the timings, but  
284 found no evidence for it (Supplementary material, Table 3).

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## 285 Discussion

### 286 Accuracy of prediction of deterioration by MR-proADM

287 This study shows that MR-proADM may be a clinically useful biomarker for predicting  
288 deterioration (i.e. *Acuity Increase*) within 72 hours from admission to hospital in  
289 patients with an admission NEWS score of 2 to 5. This contrasts with the performance  
290 of the NEWS score, assessed on admission, which did not predict deterioration within  
291 72 hours, as might have been expected from previous evaluations<sup>3-5 33</sup>. This discrepancy  
292 with previous studies might be explained by differences in selection criteria for  
293 patients. Previous research included all patients admitted to ED, but our study selected  
294 patients with NEWS between 2 and 5, because a tool to predict deterioration would be  
295 most useful in this group.

296 For most of the observed *Acuity Increase* events, the reason for classification was an  
297 increase in the NEWS score. Because an increase in NEWS score reflects both  
298 measurement variation and physiological variation, additional exploratory analyses  
299 were carried out to assess the performance of MR-proADM with an operational  
300 definition of deterioration, *Deterioration Event*, designed to minimize measurement  
301 variation. NEWS on its own had low predictive accuracy for *Deterioration Events*.  
302 However, MR-proADM level, and NEWS score together predicted *Deterioration Events*  
303 with an AUC of 0.65. Adding baseline patient characteristics (that were statistically  
304 selected) further increased the accuracy of the model (AUC = 0.73).

### 305 Comorbidities and interactions with MR-proADM levels

306 MR-proADM levels in people with COPD and/or heart failure are chronically raised and  
307 are not predictive of deterioration. However, in other people whose MR-proADM levels  
308 are not chronically raised, high levels are predictive of *Acuity Increase* (Supplementary  
309 material, Figure 1). Including these comorbidities and their interaction with MR-  
310 proADM level increased the predictive accuracy of the logistic regression model.

## 311 Limitations

312 This study included only patients who were admitted with a NEWS score between 2 and  
313 5. The predictive accuracy of the MR-proADM would perhaps have been greater if more  
314 extreme cases had been included. However, patients with NEWS scores more than 5 are

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315 known to be severely ill and to require close monitoring and/or management at higher  
316 levels of care.

### 317 **Interpretations and implications**

318 The significant increase in predictive accuracy of the models when basic clinical  
319 information is added to the models suggests that value could be added to the NEWS  
320 score by using a clinical decision aid (CDA) that would have the NEWS score, MR-  
321 proADM level, age, and the presence of comorbidities as its inputs, and as its outputs, a  
322 risk score and advice on management decisions about the level of care and intensity of  
323 monitoring.

### 324 **Future research and development**

325 As a growing number of NHS hospitals are implementing the NEWS score on their  
326 clinical information systems, it should be practical to develop a decision aid based on  
327 admission NEWS score, MR-proADM level, and possibly other clinical data. Other  
328 biomarkers may further improve prediction accuracy for deterioration, for example:  
329 lactate<sup>3</sup>; peroxiredoxin-4 (Prx4) and copeptin<sup>22 34 35</sup>; and soluble urokinase  
330 plasminogen activator receptor (suPAR)<sup>36</sup>. Developing CDAs with multiple biomarkers  
331 should increase the accuracy of prediction in ED and MAU where patients have many  
332 different conditions. The feasibility, cost-effectiveness, and acceptability of such a  
333 decision aid needs to be evaluated in further research.

334 A rapid point of care test could facilitate the assessment process and reduce delays in  
335 arranging optimal levels of care and intensity of monitoring.

### 336 **Footnotes**

337 **Contributors:** JS, AJS, MP, and DS devised the study; RO, SG, and AJA managed the  
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339 contributed to the final manuscript.

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352 **Data sharing statement** No additional data are available

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481

482 **Figure legends**483 **Figure 1.** Patient recruitment process.

484 **Figure 2. Panel A.** Predictive accuracy for Acuity Increase; predictor set *a*: NEWS;  
485 predictors set *b*: NEWS, MR-proADM; predictor set *c*: NEWS, MR-proADM, COPD/HF,  
486 interaction between MR-proADM and COPD/HF. **Panel B.** Comparisons as for panel **A**  
487 but for predicting a *Deterioration Event*; predictor set *c*: NEWS score, MR-proADM level,  
488 Age<sup>2</sup>, other comorbidities. **Panel C.** *Length of Stay* predicted by MR-proADM level.

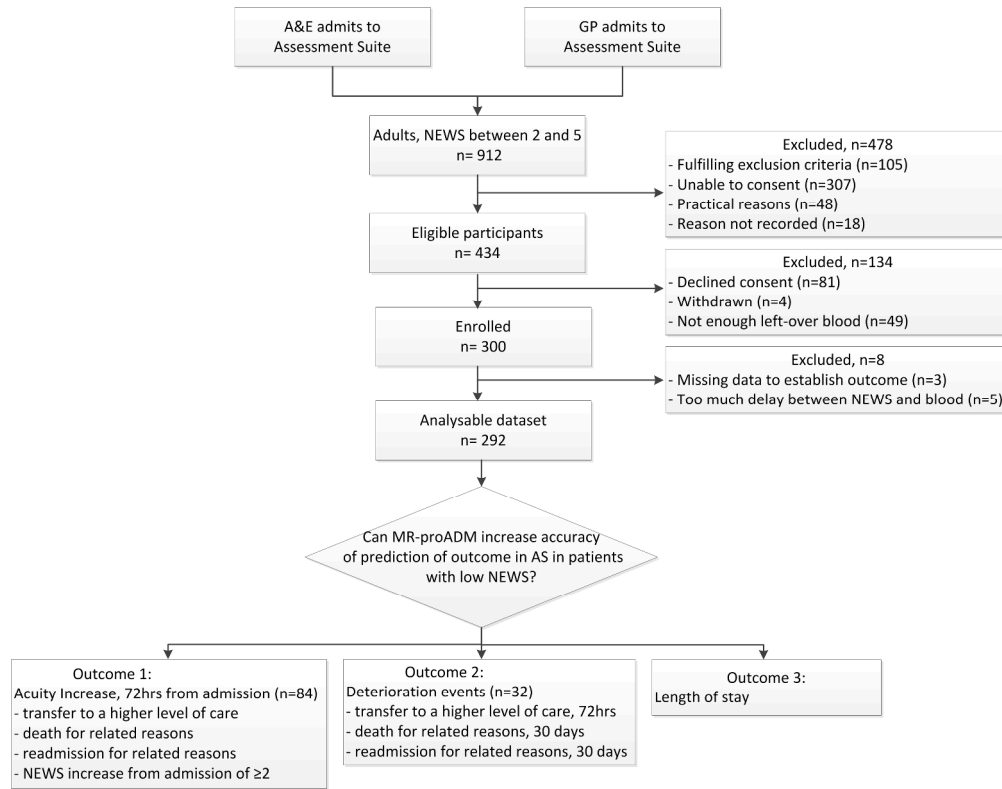


Figure 1. Patient recruitment process.

255x200mm (300 x 300 DPI)

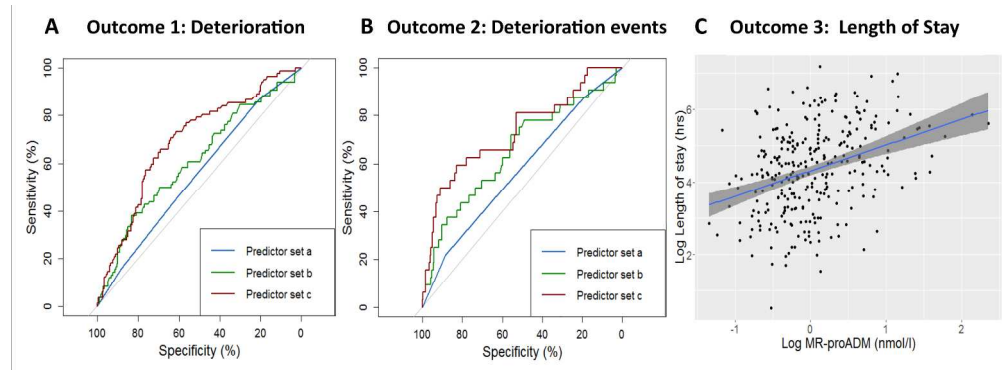


Figure 2. Panel A. Predictive accuracy for Acuity Increase; predictor set a: NEWS; predictors set b: NEWS, MR-proADM; predictor set c: NEWS, MR-proADM, COPD/HF, interaction between MR-proADM and COPD/HF. Panel B. Comparisons as for panel A but for predicting a Deterioration Event; predictor set c: NEWS score, MR-proADM level, Age2, other comorbidities. Panel C. Length of Stay predicted by MR-proADM level.

291x107mm (300 x 300 DPI)

Supplementary material for Graziadio et al, 2017

Supplementary material for *Can mid-regional pro-adrenomedullin (MR-proADM) increase the prognostic accuracy of NEWS in predicting deterioration in patients admitted to hospital with mild to moderately severe illness? A prospective single-centre observational study.*  
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Supplementary material for Graziadio et al, 2017

## Additional information on Methods

### Visual data exploration and interaction between MR-proADM and COPD/HF

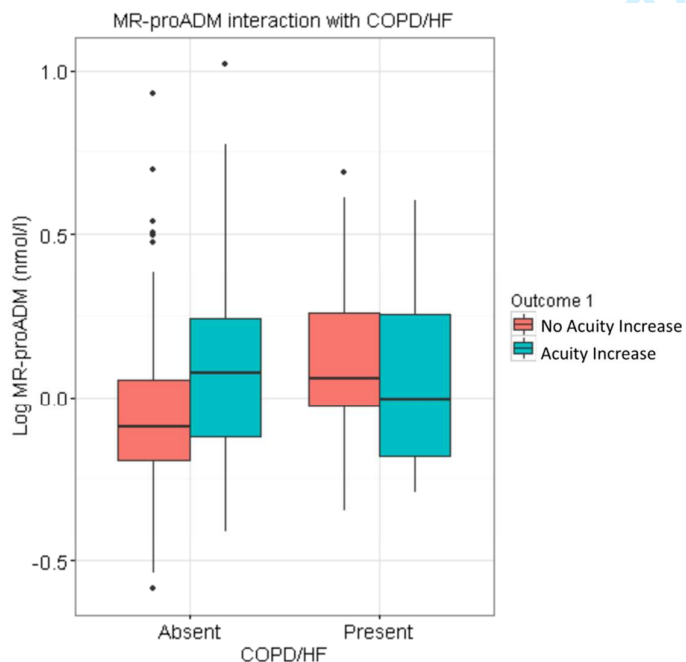
After formatting the datasets, all variables were graphed (bar-charts for categorical variables, and scatterplots/histograms for continuous variables) and visually checked for outliers and distributions that seemed potentially erroneous.

If outliers were identified, the cause(s) were investigated to understand whether they were due to human error or they were genuine data. Outliers were kept in the primary analysis. In a secondary sensitivity analysis, outliers were removed and the same analyses repeated to assess the impact on the results. If the coefficients of the predictors changed substantially, both models would be described. There was one genuine outlier patient with a very high level of MR-proADM compared to the population mean, but its exclusion made no difference to the results, and the subject was included in the final analysis.

The influence of potentially important factors on the ability of the MR-proADM to predict deterioration was explored graphically.

A significant interaction between MR-proADM and the presence of COPD/HF was discovered, and therefore included in the logistic regression (Outcome 1, predictor set c). The plot is shown in Supplementary Figure 1. This interaction showed that the MR-proADM level was increased in patients who deteriorated, but only if they did not have COPD or HF.

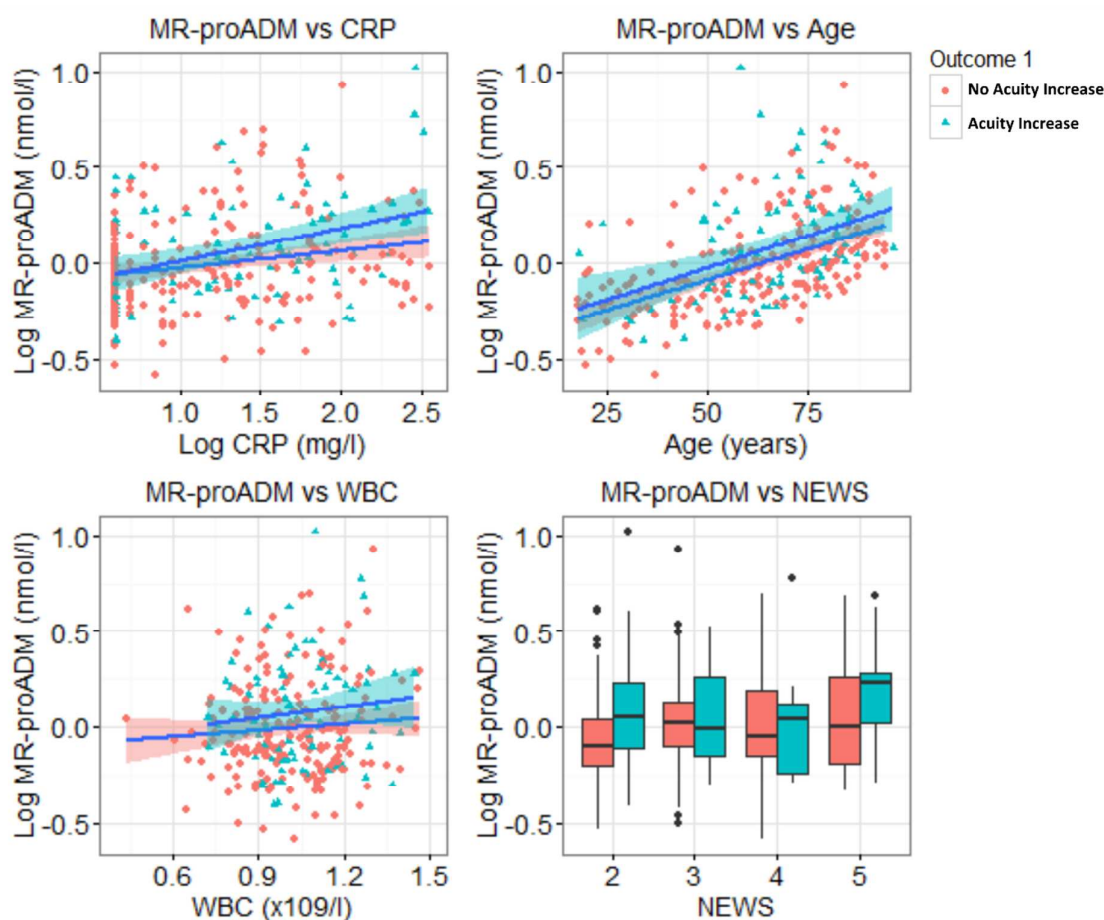
There was no suggestion that age; comorbidities: COPH and HF; other comorbidities; CRP; or WBC would improve the accuracy of prediction.



Supplemental Figure 1. Interaction between MR-proADM and COPD/HF.

Supplementary material for Graziadio et al, 2017

Correlations among biomarkers were also investigated through plotting to evaluate multicollinearity and added value of MR-proADM versus other biomarkers. Plots are shown in Supplemental Figure 2.



**Supplemental Figure 2.** Associations between MR-proADM and CRP, age, WBC, and NEWS.

### Analytical data exploration

Univariate logistic regressions were used to investigate whether the relationship between outcome variables (i.e. deterioration measures) and the input variables (NEWS and MR-proADM, age, comorbidities, gender, CRP, and WBC) were linear. If they were not linear, log transformation and squared transformation were applied. If the transformation substantially lowered the AIC, then the transformed variable was used in statistical analyses.

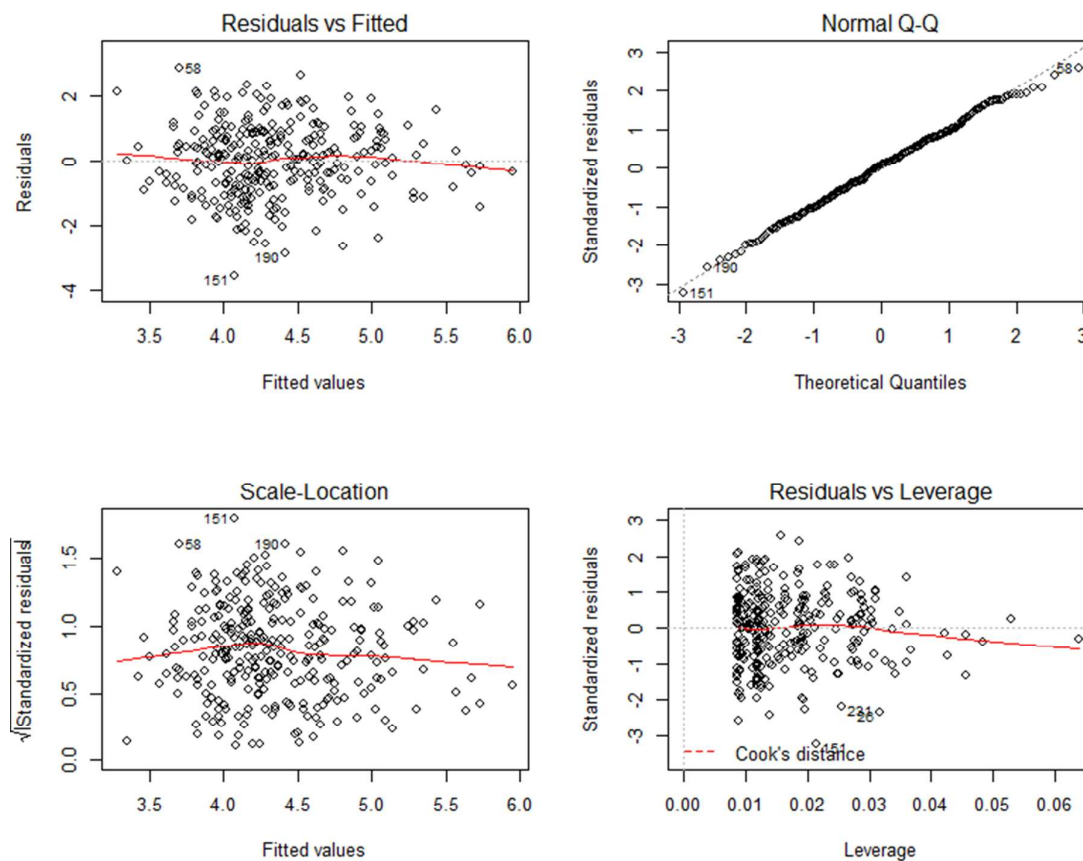
For categorical variables with multiple ordinal levels (i.e. NEWS score), the univariate analysis informed if it was appropriate to include the variable in the model as a continuous or categorical factor. If the coefficients in the univariate models increased linearly, then a linear relationship with the outcome could be assumed, and the variable was included in the model as continuous, otherwise the variable was treated as a categorical factor.

Supplementary material for Graziadio et al, 2017

Univariate analyses were also used to identify the variables that affected the outcome significantly. The variables that showed a probable relationship with the outcome variable ( $p < 0.1$ ) were included in the full model logistic regression.

## Additional information on Results

### Diagnostic plots for length of stay analysis



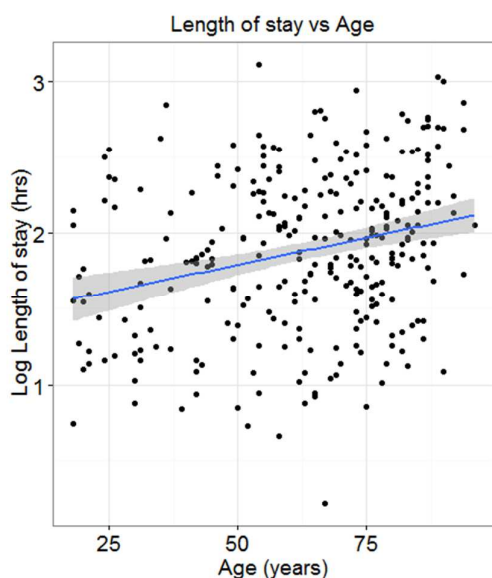
**Supplemental Figure 3.** Diagnostic plots for linear regression evaluating the prediction accuracy of MR-proADM for *Length of Stay*.

The diagnostics of the model showed no multicollinearity in the data since all the correlation coefficients among the independent variables were smaller than 0.5. No autocorrelation was found in the data, thus residuals are independent from each other: the Durbin-Watson test estimated  $d = 2.02$  ( $p = 0.56$ ). Evidence for homoscedasticity was provided graphically by the randomly scattered points and almost horizontal fitted lines in Supplemental Figure 3, (Residuals vs fitted plot). Analysis of Cook's distance showed that there were no influential points ( $d < 4/51$ , Supplemental Figure 3).

In Supplemental Figure 4 the relationship between Length of Stay and Age is shown.



## Supplementary material for Graziadio et al, 2017



**Supplemental Figure 4.** Relationship between *Length of Stay* and *Age*.

### Analyses of shorter term outcomes

The analyses found that NEWS and MR-proADM had much lower accuracy in predicting *Acuity Increase* at 24 and 12 hours from admission than in predicting *Acuity Increase* at 72 hours as apparent in Supplemental Tables 1 and 2.

**Supplemental Table 1.** Logistic regression for NEWS and MR-proADM predicting *Acuity Increase* within 24 hours. AIC = 326; AUC = 0.59.

Covariate	Beta	CI	Odds ratio(CI)	P-value
Intercept	-1.42	-1.70, -0.64	0.42 (0.27, 0.64)	NA
NEWS 3	-0.006	-0.64, 0.71	1.04 (0.53, 2.04)	0.985
NEWS 4	-0.37	-1.58, 0.20	0.52 (0.21, 1.22)	0.368
NEWS 5	0.21	-0.66, 1.01	1.25 (0.52, 2.91)	0.6244
MR-proADM	0.22	-0.06, 0.44	1.20 (0.95, 1.55)	0.0547



Supplementary material for Graziadio et al, 2017

**Supplemental Table 2.** Logistic regression for NEWS and MR-proADM predicting *Acuity Increase* within 12 hours. AIC = 266; AUC = 0.57.

Covariate	Beta	CI	Odds ratio(CI)	P-value
<b>Intercept</b>	-1.83	-2.47, -1.24	0.16 (0.08, 0.29)	NA
<b>NEWS 3</b>	0.29	-0.46, 1.04	1.34 (0.63, 2.85)	0.442
<b>NEWS 4</b>	-0.15	-1.57, 0.76	0.86 (0.31, 2.14)	0.756
<b>NEWS 5</b>	0.29	-0.74, 1.23	1.33 (0.48, 3.42)	0.564
<b>MR-proADM</b>	0.06	-0.24, 0.31	1.06 (0.79, 1.36)	0.656

### Analyses of time-lag effect between news assessment and blood collection for assessment of MR-proADM levels

Given the practicalities involved, it was not possible to stipulate the timings of taking the NEWS on admission and collecting the blood sample for MR-proADM testing. It was expected that difference in times would normally be less than 6 hours, but in 44 subjects the time difference was more than 6 hours.

To investigate the impact of time differences being greater than expected, another analysis was carried out excluding subjects for whom the difference was more than 6 hours (time-lag compliant dataset). The hypothesis was that, if the time difference was an important parameter for the predictive accuracy of MR-proADM level, model coefficients would be greater and confidence intervals narrower for the compliant model. This was not the case; results were similar in the full dataset with 292 subjects and in the compliant dataset with 248 subjects (Supplemental Table 3).

**Supplemental Table 3.** Logistic regression for NEWS and MR-proADM predicting *Acuity Increase* for the time-lag compliant dataset. AIC = 295; AUC = 0.60.

Covariate	Beta	CI	Odds ratio(CI)	P-value
<b>Intercept</b>	-1.15	-1.70, -0.64	0.42 (0.27, 0.64)	NA
<b>NEWS 3</b>	-0.04	-0.64, 0.71	1.04 (0.53, 2.04)	0.909
<b>NEWS 4</b>	-0.65	-1.58, 0.20	0.52 (0.21, 1.22)	0.152
<b>NEWS 5</b>	0.22	-0.66, 1.01	1.25 (0.52, 2.91)	0.613
<b>MR-proADM</b>	0.19	-0.06, 0.44	1.20 (0.95, 1.55)	0.135



## TRIPOD Checklist: Prediction Model Development

Section/Topic	Item	Checklist Item	Page
<b>Title and abstract</b>			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	P1 L1-3
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	P2 L22-46
<b>Introduction</b>			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	P4-5 L52-84
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	P5 L82-84
<b>Methods</b>			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	P5 L87
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	P5 L87-91
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	P5 L87-97
	5b	Describe eligibility criteria for participants.	P5 L98-102
	5c	Give details of treatments received, if relevant.	N/A
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	P6-7 L128-149
	6b	Report any actions to blind assessment of the outcome to be predicted.	P6 L123-126
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	P4 L54-57 P4-5 L70-84 P5-6 L106-117
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	P6 L123-126
Sample size	8	Explain how the study size was arrived at.	P5 L92-97
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	P8-9 L197-201
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	P7-8 L151-194
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	P7-8 L151-194 P7 L153-155
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	P7-8 L156-194
Risk groups	11	Provide details on how risk groups were created, if done.	N/A
<b>Results</b>			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	P10-11 Table 1.
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	P10-11 Table 1.
Model development	14a	Specify the number of participants and outcome events in each analysis.	P10-11 Table 1.
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	P13-15 Table3&4
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	P13-15 Table3&4
	15b	Explain how to use the prediction model.	P15 L244-253
Model performance	16	Report performance measures (with CIs) for the prediction model.	P13-15 Table3&4 P15 L244-253
<b>Discussion</b>			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	P18-19 L306-316
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	P17-19 L278-323
Implications	20	Discuss the potential clinical use of the model and implications for future research.	P19 L325-335
<b>Other information</b>			
Supplementary	21	Provide information about the availability of supplementary resources, such as study	See Comments

## TRIPOD Checklist: Prediction Model Development

information		protocol, Web calculator, and data sets.	
Funding	22	Give the source of funding and the role of the funders for the present study.	P20 L346

Comments:

- Item 21: Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.**

Supplementary material - with additional information on methods and results - is attached as separate document. Study protocol and data sets will be available in due course, new project website currently under construction.

For peer review only

# BMJ Open

## Can mid-regional pro-adrenomedullin (MR-proADM) increase the prognostic accuracy of NEWS in predicting deterioration in patients admitted to hospital with mild to moderately severe illness? A prospective single-centre observational study.

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<b>Primary Subject Heading</b>:	Diagnostics
Secondary Subject Heading:	Evidence based practice
Keywords:	INTERNAL MEDICINE, ACCIDENT & EMERGENCY MEDICINE, Adult intensive & critical care < INTENSIVE & CRITICAL CARE

SCHOLARONE™  
Manuscripts

## Prognostic accuracy of MR-proADM in emergency departments

**Title:** Can mid-regional pro-adrenomedullin (MR-proADM) increase the prognostic accuracy of NEWS in predicting deterioration in patients admitted to hospital with mild to moderately severe illness? A prospective single-centre observational study.

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Word counts

Abstract: 276

Paper (including tables, figures, legends, and references): 5950

## Prognostic accuracy of MR-proADM in emergency departments

20 **Abstract**

21 **Objective** To assess the accuracy of NEWS score and MR-proADM blood level in  
22 predicting deterioration in mild to moderately ill people.

23 **Design** Prospective observational study

24 **Setting** The Medical Admissions Suite of the Royal Victoria Infirmary, Newcastle.

25 **Participants** 300 adults with NEWS score between 2 and 5 on admission. Exclusion  
26 criteria included receiving palliative care, or admitted for social reasons or self-  
27 harming. Patients were enrolled between September and December 2015, and  
28 followed-up for 30 days after discharge.

29 **Outcome measure** The primary outcome measure was the proportion of patients who,  
30 within 72 hours, had an *Acuity Increase*, defined as any combination of: an increase of at  
31 least 2 in the NEWS score; transferred to a higher-dependency bed or monitored area;  
32 and, for those discharged from hospital, re-admission for medical reasons; or death.

33 **Results** NEWS predicted *Acuity Increase* poorly: the area under the curve (AUC) was  
34 0.55 (95% CI 0.48, 0.62) with univariate analysis. NEWS and MR-proADM together  
35 predicted *Acuity Increase* more accurately, increasing AUC to 0.61 (95% CI 0.54, 0.69).  
36 When the confounding effects of presence of chronic obstructive pulmonary disease or  
37 heart failure and interaction with MR-proADM were included, the prognostic accuracy  
38 further increased the AUC to 0.69 (95% CI 0.63, 0.76).

39 **Conclusions** MR-proADM improves the accuracy of prediction by NEWS of  
40 deterioration in patients admitted to hospital with a mild to moderately severe acute  
41 illness. As a growing number of NHS hospitals are implementing the NEWS score on  
42 their clinical information systems, further research should assess the practicalities and  
43 utility of developing a decision aid based on admission NEWS score, MR-proADM level,  
44 and possibly other clinical data and other biomarkers that could further improve  
45 prognostic accuracy.

51 **Keywords**

52  
53 Biochemistry, diagnosis, health services research  
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60

## Prognostic accuracy of MR-proADM in emergency departments

**Strengths and limitations of this study**

- This is the first study to use rigorous statistical methods to assess the value added by MR-proADM to the admission NEWS score for predicting clinically important deterioration in mild to moderately ill patients
- Prognostic accuracy might have been greater had more severely ill patients been included, but the aim of this study was to predict deterioration in less severely ill patients who could benefit from closer observation.
- This was an observational study, and thus could not directly assess the utility of more accurate prediction of deterioration
- Initial evidence for MR-proADM appears promising and requires further validation for clinical utility

49



## Prognostic accuracy of MR-proADM in emergency departments

**Introduction**

The National Early Warning Score (NEWS) is recommended for assessing severity of illness in patients presenting in primary or secondary NHS care and for surveillance of patients in hospital<sup>1,2</sup>. Six physiological parameters (which can be measured at the bedside) are scored: respiratory rate, oxygen saturation, temperature, systolic blood pressure, pulse rate, and level of consciousness. The scores are aggregated, and, if the patient requires oxygen, the total is increased. NEWS predicts death, cardiac arrest, and unplanned intensive care unit (ICU) admission within 24 hours<sup>3-5</sup>. However, NEWS does not identify all patients who turn out to be seriously ill<sup>6-8</sup>, and there are also patients whose NEWS score is usually elevated and who do not require the level of observation that the NEWS tool would suggest. For example, people with chronic obstructive pulmonary disease (COPD) or chronic heart failure (HF) have higher baseline NEWS scores than those without these comorbidities. The prognostic accuracy of NEWS for patients presenting to the Emergency Department (ED) has been confirmed in a wide range of severity of illness<sup>9,10</sup>, as has its reduced accuracy in people with COPD<sup>11</sup>. But, no previous studies of the prognostic accuracy of NEWS in the ED/Medical Admissions Unit (MAU) have focussed on patients admitted with mild to moderately severe illness. Since a clinically important proportion of these patients do deteriorate unexpectedly, improved risk stratification would be useful.

Mid-regional pro-adrenomedullin (MR-proADM) is one of several promising biomarkers for severe illness and deterioration<sup>12-16</sup>.

MR-proADM is a precursor of adrenomedullin (ADM), a member of the calcitonin peptide family. ADM is widely expressed and has roles in vasodilation, immune modulation, and metabolic regulation. It is up-regulated in severe infections, inflammation, vasodilation, stimulation of diuresis, increased cardiac output, and stroke<sup>17-19</sup>. ADM has a short half-life, but MR-proADM is more stable and directly reflects ADM concentrations in blood. Both ADM and MR-proADM levels are strongly associated with risk of mortality, regardless of aetiology<sup>20-26</sup>. In people presenting with acute chest pain, MR-proADM has been reported to improve the Global Registry of Acute Coronary Events risk classification by 41%<sup>27</sup>. As with the NEWS score, people with COPD or chronic heart failure have higher baseline levels of MR-proADM.



## Prognostic accuracy of MR-proADM in emergency departments

81 The aim of this study was to assess whether the MR-proADM level used alongside the  
82 NEWS score would improve prediction of deterioration over NEWS score alone in  
83 patients admitted to the MAU with mild to moderately severe illness.

## 84 **Methods**

### 85 **Patient and Public Involvement**

86 Patients and the public were not specifically involved in the planning and execution of  
87 this study. However, the NIHR now requires that the research it supports includes  
88 active involvement and engagement with patients and the public.

### 89 **Study participants and study design**

90 This was a prospective observational cohort study. Patients were enrolled between  
91 September and December 2015 at the Royal Victoria Infirmary, Newcastle, and  
92 followed-up for 30 days after discharge. If the patient died within the 30 days of follow  
93 up, this and cause of death were recorded. Adults admitted to the MAU were recruited  
94 for the study between 9am and 4pm on weekdays.

95 Sample size was determined as a pragmatic recruitment target for a three-month  
96 observational study. A recent unpublished audit conducted in the MAU at the Royal  
97 Victoria Infirmary found a deterioration rate of 20%. With 300 patients and complete  
98 data collection, 60 events would be anticipated. With this number of events, a  
99 multivariable prediction model could include up to six independent predictors. This is  
100 based on a widely accepted rule of thumb that models with fewer than ten events per  
101 predictor tend to be over-fitted<sup>28</sup>. However, recent research suggests that the “ten  
102 events per variable” rule of thumb may be optimistic<sup>29</sup>. Because the aim of this study  
103 was to assess if further research would be indicated, even if the rule of thumb is  
104 optimistic, 60 is considered an acceptable number of events.

105 Patients were considered eligible for inclusion in the study if their NEWS score on  
106 admission was at least 2 and not greater than 5, and all NEWS parameters were  
107 recorded. Patients were excluded from the study if they were receiving palliative care,  
108 were admitted for social reasons only, or were self-harming, or overdosing with drugs  
109 or other substances.

## Prognostic accuracy of MR-proADM in emergency departments

110 All participants provided written informed consent, and the study was approved by the  
111 Newcastle & North Tyneside Research Ethics Committee (15/NE/0120).

### 112 Recorded data

113 Demographic and admission data included: gender, year of birth, reason for admissions,  
114 diagnosis on discharge, and the presence of comorbidities in which baseline MR-  
115 proADM levels are chronically raised: COPD with hypoxia ( $\text{PaO}_2 < 10 \text{ kPa}$ )<sup>7</sup>; HF<sup>30</sup>; acute  
116 brain injury<sup>6</sup>; acute coronary syndrome<sup>27</sup>; acute venous thromboembolism<sup>21</sup>; high  
117 International Normalized Ratio ( $\text{INR} > 2$ ); acute kidney injury; electrolyte disturbances  
118 ( $\text{Na}^+ < 130$  or  $> 150 \text{ mmol/L}$ ;  $\text{K}^+ < 3.0$  or  $> 5.5 \text{ mmol/L}$ ); hyperglycaemia in type 1  
119 diabetes (random glucose  $> 10 \text{ mmol/L}$ ).

120 The NEWS score was assessed at on admission and over the next 72 hours, and the  
121 scores and assessment times recorded. The 7 clinical parameters used to determine the  
122 NEWS score were recorded for the baseline (admission) assessment only. Baseline  
123 NEWS scores were used to determine eligibility for this study. Subsequent NEWS scores  
124 were used in the analyses to identify deterioration.

125 Blood samples were taken at hospital admission for assessment of MR-proADM, C-  
126 Reactive Protein (CRP) and white blood count (WBC).

### 127 Laboratory tests

128 Plasma was obtained from blood samples (collected in ethylenediaminetetraacetic acid,  
129 EDTA) that were no longer clinically required. Plasma was stored in aliquots at  $-80^\circ \text{C}$ .

130 MR-proADM was assayed in the on-site Blood Sciences Laboratory using the B R A H M S  
131 Kryptor system according to the manufacturer's instructions.

132 Blood samples were analysed in batches by personnel blinded with regard to the  
133 condition and NEWS score of the patient. Nurses who assessed the NEWS score and  
134 healthcare professionals managing patients in the MAU were blinded to MR-proADM  
135 results.

### 136 Outcome measures

137 **Outcome measure 1: Acuity Increase.** A patient was classified as having an *Acuity*  
138 *Increase* if one or more of the following occurred within 72 hours from admission:

## Prognostic accuracy of MR-proADM in emergency departments

- 139 1. transfer to a higher level of care (ICU or high dependency unit)
- 140 2. readmission to hospital for reasons related to the initial admission
- 141 3. death for reasons related to the initial admission
- 142 4. NEWS score increased by at least two compared to the admission score

143 **Outcome measure 2: Deterioration Event.** For most of the observed *Acuity Increase*  
144 cases the reason for classification was an increase in the NEWS score (Table 1). An  
145 increase in NEWS score reflects both measurement variation and physiological  
146 variation, so additional exploratory analyses were carried out to assess the performance  
147 of MR-proADM in predicting deterioration. *Deterioration Events* were classified as the  
148 occurrence of one or more of the following:

- 149 1. transfer to higher level of care within 72 hours from admission;
- 150 2. death (for reasons related to the admission) within 30 days;
- 151 3. re-admission to hospital (for the same reason as the previous admission) within  
152 30 days from first admission.

153 Classification based on this definition is unlikely to be subject to clinically important  
154 measurement variation. This analysis, therefore, should optimise the prognostic  
155 accuracy for events which are both clinically and economically important.

156 **Outcome measure 3: Length of Stay.** *Length of Stay* was defined as the duration (in  
157 days) from admission to discharge or death.

### 158 Statistical analysis

159 All data analyses were performed using the R language version 3.2.0<sup>31</sup>, with the support  
160 of RStudio, version 0.99.896 (RStudio, Inc). The following R packages were used:  
161 ggplot2, pROC, psych, PredictABEL, Hmisc, rms.

162 Logistic regression models were compared for their accuracy in predicting  
163 deterioration outcome measures as pre-specified in an analysis plan. Analyses are  
164 presented as unadjusted parameter estimates of risk (odds ratio (OR), with confidence  
165 intervals (CI)) and estimates adjusted for identified clinical confounding factors. The  
166 aims of the multivariable analyses were twofold: first, to estimate the effect size and  
167 significance adjusted for other identified influential predictors and interactions; second,  
168 to investigate whether the addition of other predictors improved the goodness of fit and  
169 accuracy of prediction.

## Prognostic accuracy of MR-proADM in emergency departments

170 Only complete cases were analysed since missingness was minimal: 10 records without  
171 data on co-morbidities (details in footnote in Table 1).

172 For each measure of deterioration (*Acuity Increase*, *Deterioration Event*, and *Length of*  
173 *Stay*), logistic regression models were compared for the following sets of predictor  
174 variables:

175 *Predictor set a.* Comparator (base case): NEWS score on admission

176 *Predictor set b.* Primary analysis: NEWS score, MR-proADM

177 *Predictor set c.* Secondary analyses: NEWS score and MR-proADM always  
178 included. Age, gender, CRP, WBC, presence of COPD or HF,  
179 presence of other comorbidities, and interactions between  
180 predictors when appropriate.

181 Predictors (and the underlying assumption of linearity of their relationship with the  
182 outcome of interest) were initially investigated through univariate analyses based on  
183 simple log and quadratic functions. Transformations were applied if they improved the  
184 goodness of fit as assessed by the Akaike information criterion (AIC), and were retained  
185 in the multivariable setting. NEWS was treated as an ordinal variable. We have assessed  
186 interactions through visual data exploration and acknowledge this is underpowered.  
187 Subsequently, for the multivariable regression the set of predictors was assessed for  
188 independence through backward elimination, based on changes in AIC.

189 Secondary outcome of *Length of Stay* followed a similar analysis plan using multiple  
190 linear regressions based on a transformed outcome to address non-normality.  
191 Dependent and exploratory variables were log-transformed if not normally distributed.  
192 Normality was assessed by visualizing the data. More details of the methods used are  
193 reported in the Supplemental Data.

194 Goodness of fit of logistic regression models was assessed with the C-statistic (which is  
195 the area under the ROC curve and a measure of discrimination) and is presented with  
196 95% confidence intervals (CI). To assess the value added by including the MR-proADM  
197 level with the NEWS score in predicting deterioration, continuous net reclassification  
198 improvement (NRI) and integrated discrimination improvement (IDI) were calculated<sup>32</sup>  
199 <sup>33</sup>.

## Prognostic accuracy of MR-proADM in emergency departments

200 For internal validation of the statistical models the C-statistic was evaluated after  
201 correcting for optimistic predictions through bootstrapping with 10,000 resamples.

## 202 Results

### 203 Study enrolment

204 The process of recruitment and enrolment of patients for the study is shown in Figure 1.  
205 The study recruited 300 patients, and 292 were included in the analysis. Five patients  
206 were excluded because the blood samples for MR-proADM were taken more than 12  
207 hours from baseline NEWS assessment; 3 patients were excluded from the primary  
208 outcome due to missing follow up NEWS scores.

### 209 Patient characteristics

210 Patient demographics and mean biomarker levels for each covariate are reported in  
211 Table 1. The cohort was evenly divided in gender and had a mean age of 63 years and  
212 mean NEWS on admission of 3, with the majority of patients having NEWS score of 2.  
213 COPD or HF were present in 28%, and 25% had other comorbidities.

214

## Prognostic accuracy of MR-proADM in emergency departments

**Table 1.** Characteristics of the study population, classified by Outcome 1 (*Acuity Increase*), Outcome 2 (*Deterioration Event*) and All patients. Data are presented as number (no) and percentages (%) for counts, or mean and (standard deviation, SD) for continuous normally distributed data, or [25th; 50th; 75th percentile] for continuous non-normally distributed data.

	Outcome 1: <i>Acuity Increase</i>		Outcome 2: <i>Deterioration Event</i>		All patients (n = 292)
	Present (e = 84)	Absent	Present (e2 = 32)	Absent	
Age (mean years, SD)	65 (17)	62 (21)	63 (14)	63 (20)	63 (20)
Gender (no. females, %)	41 (49%)	107 (51%)	15 (47%)	133 (51%)	148 (51%)
NEWS = 2 (no., %)	34 (40%)	82 (40%)	12 (38%)	104 (40%)	116 (40%)
NEWS = 3 (no., %)	26 (31%)	59 (28%)	9 (28%)	76 (29%)	85 (29%)
NEWS = 4 (no., %)	11 (13%)	43 (21%)	4 (13%)	50 (19%)	54 (18%)
NEWS = 5 (no., %)	13 (15%)	24 (12%)	7 (22%)	30 (12%)	37 (13%)
MR-proADM (mean nmol/l, SD)	1.50 (1.4) [0.72, 1.12, 1.79]	1.19 (0.9) [0.68, 0.93, 1.28]	1.89 (2.0) [0.93, 1.13, 1.95]	1.20 (0.9) [0.68, 0.93, 1.39]	1.28 (1.1) [0.68, 0.97, 1.48]
CRP (mg/l)	59 (79) [5, 22, 80]	42 (70) [4, 13, 41]	61 (90) [7, 23, 67]	45 (71) [4, 16, 51]	47 (73) [4, 17, 54]
WBC (x10 <sup>9</sup> /l)	12 (5) [9, 10, 14]	11 (5) [8, 10, 14]	12 (4) [9, 12, 15]	11 (5) [8, 10, 14]	11 (5) [8, 10, 14]
COPD/HF (no, %)*	33 (39%)	46 (22%)	12 (38%)	67 (26%)	79 (28%)
Other comorbidities (no., %)	17 (20%)	55 (26%)	15 (47%)	57 (22%)	72 (25%)
Length of Stay (hrs)	168 (196) [63, 110, 194]	137 (176) [26, 68, 176]	173 (172) [59, 106, 259]	143 (172) [33, 72, 176]	146 (182) [35, 77, 182]
Length of Stay in MAU (hrs)	31 (19) [17, 25, 43]	24 (16) [13, 21, 30]	27 (17) [18, 23, 35]	26 (17) [15, 22, 31]	26 (17) [15, 22, 31]
Monitored beds (no, %)	31 (37%)	58 (27%)	11 (34%)	78 (30%)	89 (30%)

Prognostic accuracy of MR-proADM in emergency departments

	<b>Outcome 1: <i>Acuity Increase</i></b>		<b>Outcome 2: <i>Deterioration Event</i></b>		<b>All patients (n = 292)</b>
	<b>Present (e = 84)</b>	<b>Absent</b>	<b>Present (e2 = 32)</b>	<b>Absent</b>	
Deterioration time (hrs)	15 (13) [5, 9, 21]	N/A	170 (226) [19, 33, 301]	N/A	
* for COPD: e = number with <i>Acuity Increase</i> = 82; e2 = number with <i>Deterioration Event</i> = 29; n = total number of patients = 282					

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## Prognostic accuracy of MR-proADM in emergency departments

219

220 **Table 2.** Criteria met by patients classified with an *Acuity Increase* or *Deterioration*221 *Event.*

Criterion for deterioration	<i>Acuity Increase</i> (e = 84)	<i>Deterioration Event</i> (e2 = 32)
NEWS (no, %)	81 (96.4%)	N/A
ICU transfer (no, %)	1 (1.2%)	4 (12.5%)
Death (no, %)	0 (0%)	6 (18.8%)
Readmission (no, %)	2 (2.4%)	22 (68.7%)

222

223 The study population was homogenous across *Acuity Increase* and No *Acuity Increase*  
 224 outcomes in terms of gender, age, and NEWS on admission. Table 2 shows the  
 225 frequencies of criteria determining *Acuity Increase* and *Deterioration Event*. Notably,  
 226 around 95% of *Acuity Increases* were the result of an increase in NEWS score, while  
 227 readmission was the reason for around 70% of *Deterioration Events*.

228 Patients who experienced *Acuity Increase* had higher MR-proADM and CRP levels at  
 229 admission, and longer *Length of Stay* in the hospital and in the MAU.

230 The prevalence of *Acuity Increase* was 29% (somewhat higher than the anticipated  
 231 20%). The prevalence of *Deterioration Events* was 11%. The numbers of events  
 232 provided sufficient statistical power to assess statistical significance for the primary  
 233 outcome, *Acuity Increase*, but not for the secondary outcome, *Deterioration Event*.

234 **Accuracy of MR-proADM for predicting *Acuity Increase***

235 Potentially useful predictors with univariate analysis of *Acuity Increase* were MR-  
 236 proADM (OR = 1.27, 95% CI 1.02, 1.62; p = 0.037), Age<sup>2</sup> (OR = 1.00, 95% CI 0.99, 1.00; p  
 237 = 0.023) and the presence of COPD or HF (OR = 2.25, 95% CI 1.30, 3.91; p = 0.004;  
 238 Supplementary Figure s1). The prognostic accuracy of CRP, WBC and NEWS did not  
 239 reach the threshold of significance (p = 0.88, p = 0.090, Table 3, and p=0.416, Table 4,  
 240 respectively).

241

## Prognostic accuracy of MR-proADM in emergency departments

242 **Table 3.** Univariate regression analyses for predicting the three outcomes of interest:  
 243 *Acuity Increase, Deterioration Event, and Length of Stay.* Analyses for the NEWS score as  
 244 a predictor are shown in Table 4.

	Beta	CI	Odds Ratio (CI)	p-value
<b>Acuity Increase: univariate logistic regressions (n = 292, e = 84)</b>				
MR-proADM	0.24	-0.02, 0.48	1.27 (1.02, 1.62)	0.037
CRP	0.003	-0.0005, 0.0063	1.00 (1.00, 1.01)	0.088
WBC	0.04	-0.008, 0.094	1.05 (1.00, 1.10)	0.09
Gender	0.14	-0.38, 0.65	1.15 (0.69, 1.92)	0.684
Age	0.1	0.019, 0.1925	1.11 (1.02, 1.21)	0.023
Age <sup>2</sup>	-0.0008	-0.0016, -0.0001	1.00 (0.99, 1.00)	
Other Comorbidities	-0.32	-0.96, 0.28	0.72 (0.38, 1.32)	0.267
COPD/HF*	0.81	0.26, 1.36	2.25 (1.30, 3.91)	0.004
<b>Deterioration Event: univariate logistic regressions (n = 292, e<sub>2</sub> = 32)</b>				
MR-proADM	0.37	0.11, 0.64	1.44 (1.12, 1.90)	0.006
CRP	0.003	-0.002, 0.01	1.00 (1.00, 1.01)	0.255
WBC	0.02	-0.05, 0.09	1.02 (0.95, 1.10)	0.506
Gender	0.17	-0.57, 0.92	1.19 (0.57, 2.50)	0.648
Age	0.21	0.06, 0.40	1.23 (1.06, 1.49)	0.013
Age <sup>2</sup>	-0.002	-0.003, -0.001	1.00 (1.00, 1.00)	
Other Comorbidities	1.14	0.38, 1.90	3.14 (1.47, 6.69)	0.003
COPD/HF*	0.67	-0.14, 1.46	1.96 (0.87, 4.29)	0.095
<b>Length of Stay: simple linear regressions (n = 292, e = 84, e<sub>2</sub> = 32)</b>				
MR-proADM	0.7	0.49, 0.92	N/A	<0.0001
CRP	0.05	-0.05, 0.15	N/A	0.368
WBC	-0.06	-0.38, 0.27	N/A	0.73
Gender	0.08	-0.04, 0.20	N/A	0.18
Age	0.007	0.004, 0.010	N/A	<0.0001
Other Comorbidities	0.18	0.05, 0.32	N/A	0.009
COPD/HF*	0.07	-0.07, 0.21	N/A	0.318
<b>Key:</b> n = total number of cases; e = number of <i>Acuity Increases</i> ; e <sub>2</sub> = number of <i>Deterioration Events</i> ; CI = 95% confidence interval * n = 282, e = 82, e <sub>2</sub> = 29				

245

## Prognostic accuracy of MR-proADM in emergency departments

**Table 4.** Multivariable regression analyses for the outcomes of interest: *Acuity Increase*, *Deterioration Event*, *Length of Stay* (Outcomes 1, 2, and 3 respectively) with NEWS comparator group. Predictor set *a.* includes only the NEWS score as a predictor; Predictor set *b.* includes MR-proADM and NEWS scores; Predictor set *c.* includes MR-proADM, NEWS scores, and other significant predictors and interactions.

		Beta	CI	Odds Ratio (CI)	p-value	
<b>Acuity Increase: multivariate logistic regressions</b>						
<b>Predictor set a</b> n = 292 e = 84 e2 = 32	NEWS 3	0.06	-0.55, 0.67	1.06 (0.57, 1.95)	0.416	
	NEWS 4	-0.48	-1.29, 0.27	0.62 (0.27, 1.31)		
	NEWS 5	0.27	-0.54, 1.04	1.31 (0.58, 2.84)		
<b>Predictor set b</b> n = 292 e = 84 e2 = 32	NEWS 3	0.03	-0.59, 0.65	1.03 (0.56, 1.91)	0.247	
	NEWS 4	-0.53	-1.35, 0.23	0.59 (0.26, 1.26)		
	NEWS 5	0.18	-0.63, 0.97	1.20 (0.53, 2.64)		
	MR-proADM	0.24	0.02, 0.49	1.28 (1.02, 1.63)	0.039	
<b>Predictor set c</b> n = 282 e = 82 e2 = 29	NEWS 3	-0.11	-0.76, 0.54	0.90 (0.47, 1.71)	0.221	
	NEWS 4	-0.89	-1.77, -0.08	0.41 (0.17, 0.93)		
	NEWS 5	0.09	-0.77, 0.91	1.09 (0.46, 2.50)		
	MR-proADM	0.41	0.13, 0.76	1.51 (1.14, 2.14)		0.01
	COPD/HF	1.81	0.80, 2.85	6.08 (2.23, 17.35)		0.001
MR-proADM*COPD/HF	-0.71	-1.40, -0.10	0.49 (0.25, 0.91)	0.03		
<b>Deterioration Event: multivariate logistic regressions</b>						
<b>Predictor set a</b> n = 292 e = 84 e2 = 32	NEWS 3	0.03	-0.92, 0.94	1.03 (0.40, 2.55)	0.512	
	NEWS 4	-0.37	-1.68, 0.74	0.69 (0.19, 2.10)		
	NEWS 5	0.7	-0.36, 1.70	2.02 (0.70, 5.50)		
<b>Predictor set b</b> n = 292 e = 84 e2 = 32	NEWS 3	-0.01	-0.97, 0.92	0.99 (0.38, 2.51)	0.564	
	NEWS 4	-0.43	-1.76, 0.70	0.65 (0.17, 2.02)		
	NEWS 5	0.6	-0.49, 1.62	1.81 (0.61, 5.05)		
	MR-proADM	0.36	0.10, 0.64	1.43 (1.11, 1.89)	0.007	
<b>Predictor set c</b> n = 282 e = 82 e2 = 29	NEWS 3	0.16	-0.83, 1.12	1.17 (0.44, 3.07)	0.389	
	NEWS 4	-0.49	-1.86, 0.69	0.62 (0.16, 2.00)		
	NEWS 5	0.69	-0.44, 1.76	1.99 (0.64, 5.81)		
	MR-proADM	0.32	0.02, 0.64	1.37 (1.02, 1.89)		0.044

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		Beta	CI	Odds Ratio (CI)	p-value
	Other comorbidities	0.94	0.10, 1.77	2.56 (1.10, 5.85)	0.026
	Age	0.21	0.06, 0.41	1.23 (1.06, 1.50)	0.011
	Age <sup>2</sup>	-0.002	-0.003, -0.001	1.00 (1.00, 1.00)	
<b>Length of Stay: multiple linear regressions</b>					
<b>Predictor set a</b> n = 292 e = 84 e <sup>2</sup> = 32	NEWS 3	-0.07	-0.21, 0.08	N/A	0.052
	NEWS 4	0.07	-0.10, 0.24	N/A	
	NEWS 5	0.21	0.01, 0.40	N/A	
<b>Predictor set b</b> n = 292 e = 84 e <sup>2</sup> = 32	NEWS 3	-0.1	-0.24, 0.04	N/A	0.033
	NEWS 4	0.05	-0.11, 0.21	N/A	
	NEWS 5	0.14	-0.04, 0.32	N/A	
	MR-proADM	0.69	0.48, 0.91	N/A	<0.0001
<b>Predictor set c</b> n = 282 e = 82 e <sup>2</sup> = 29	NEWS 3	-0.12	-0.25, 0.02	N/A	0.031
	NEWS 4	0.04	-0.11, 0.20	N/A	
	NEWS 5	0.14	-0.04, 0.32	N/A	
	MR-proADM	0.55	0.31, 0.80	N/A	<0.0001
	Age	0.004	0, 0.007	N/A	0.027

251

252 The prognostic accuracy for *Acuity Increase* of NEWS on its own was not significant and  
 253 limited (AUC 0.55, 95% CI 0.48, 0.62), but when MR-proADM was included as an  
 254 additional predictor, the accuracy of the model increased (AUC 0.61, 95% CI 0.54, 0.69;  
 255 OR = 1.28, 95% CI 1.02, 1.63; p = 0.007) (Tables 4 and 5, Figure 2 panel A), and was  
 256 statistically significant (p = 0.033 for likelihood ratio, Table 5). When including MR-  
 257 proADM with NEWS, the reclassification of patients was also significant, especially for  
 258 the NRI (NRI = 0.3, SE 0.1, p = 0.007; IDI = 0.017, Table 4).

259 The prognostic accuracy of MR-proADM and the additional value it provides to the  
 260 NEWS score was confirmed for *Deterioration Events* and *Length of Stay* (Tables 4 and 5,  
 261 and Figure 2 panels B and C).

262

## Prognostic accuracy of MR-proADM in emergency departments

**Table 5.** Model comparisons. Outcomes 1, 2, and 3 refer to *Acuity Increase*, *Deterioration Event*, and *Length of Stay* respectively. The predictors are: *Set a* NEWS score alone; *Set b* NEWS score and MR-proADM; *Set c* NEWS score, MR-proADM, and other significant predictors and interactions detailed in Table 3.

	AIC	Deviance	AUC (CI) or R <sup>2</sup> for linear regression	LR, (df) p-value	NRI (se), p-value	IDI (se), p-value
<i>Acuity Increase</i> : logistic regressions						
Outcome 1 - predictor set <i>a</i> .	348	356	0.55 (0.48, 0.62)			
Outcome 1 - predictor set <i>b</i> .	343	353	0.61 (0.54, 0.69)	5 (1), 0.033	0.3 (0.1), 0.007	0.017 (0.009), 0.058
Outcome 1 - predictor set <i>c</i> .	317	331	0.69 (0.63, 0.76)	14 (2), 0.001*	0.4 (0.1), 0.0004*	0.05 (0.01), 0.0009*
<i>Deterioration Event</i> : logistic regressions						
Outcome 2 - predictor set <i>a</i> .	199	207	0.57 (0.47, 0.68)			
Outcome 2 - predictor set <i>b</i> .	192	202	0.65 (0.54, 0.76)	7 (1), 0.007	0.4 (0.2), 0.003	0.04 (0.02), 0.10
Outcome 2 - predictor set <i>c</i> .	177	193	0.73 (0.63, 0.84)	15 (3), 0.0019*	0.5 (0.2), 0.012*	0.06 (0.02), 0.0004*
<i>Length of Stay</i> : linear regressions (LR)						
Outcome 3 - predictor set <i>a</i> .	77	-381	0.03			
Outcome 3 - predictor set <i>b</i> .	68	-417	0.14	9 (1), <0.001		
Outcome 3 - predictor set <i>c</i> .	67	-420	0.16	1 (1), 0.026		
<b>Note:</b> AIC = Akaike information criterion; AUC = area under the receiver operating characteristic curve; CI = 95% confidence interval; LR = likelihood ratio; df = degrees of freedom; NRI = net reclassification index; se = standard error; IDI = integrated discrimination improvement. * Comparison is between predictor set <i>b</i> . and <i>c</i> . Since there was a mismatch between the cases for predictor set <i>a</i> . and <i>b</i> . (10 missing values in COPD/HF), in the model with predictors set <i>b</i> . the 10 cases missing in predictor set <i>c</i> . were dropped to allow the comparison.						

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## 266 **Effect on prognostic accuracy when clinical information is added to** 267 **the set of predictors**

268 Secondary multivariable modelling evaluated the prognostic accuracy of MR-proADM  
269 when adjusted for the clinical factors in predictive set *c*: age, gender, CRP, WBC,  
270 presence of COPD or HF, presence of other comorbidities,

271 For *Acuity Increase*, COPD or HF comorbidity status and its interaction with MR-proADM  
272 level significantly improved the prognostic accuracy of the model: AUC increased from  
273 0.61 (95% CI 0.54, 0.69) to 0.69 (95% CI 0.63, 0.76), likelihood ratio from 4 to 14, and  
274 net reclassification index from 0.3 to 0.4 (Table 5).

275 For *Deterioration Events*, the presence of other comorbidities (excluding COPD and HF)  
276 and *Age*<sup>2</sup> increased the prognostic accuracy of MR-proADM, (Table 4 and 5). The  
277 prognostic accuracy of *Length of Stay* (Outcome 3) of MR-proADM is also increased by  
278 including *Age* in the model (Table 4 and 5, Supplementary Figure s2).

## 279 **Potential confounding effects**

280 **Shorter term outcomes:** NEWS and MR-proADM were less accurate in predicting  
281 *Acuity Increase* within 24 and 12 hours from admission than in predicting *Acuity*  
282 *Increase* within 72 hours (Supplementary Tables s1 and s2).

283 **Interval between admission NEWS scoring and blood collection:** Because ward  
284 processes did not allow the times of scoring NEWS and collecting blood to be specified  
285 for research, we assessed for a confounding effect from variation in the timings, but  
286 found no evidence for it (Supplementary Table s3).

287 **Correlations among biomarkers.** Diagnostic plots, shown in Supplementary Figures  
288 s2 and s3, show no multicollinearity in the data, no autocorrelation, no  
289 heteroscedasticity, and no data points that stood out in terms of their influence on  
290 results.

291

## 292 **Sensitivity and specificity**

293 As overall measures of accuracy, sensitivity and specificity were calculated (where  
294 appropriate) for each model using Youden's index. The results are shown in



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295 Supplementary Table s4. In practice, the trade-off between sensitivity and specificity  
296 would depend on the type of clinical decision to be made on the result (i.e. “rule-in” or  
297 “rule out”) and this would differ from the approach in Youden’s Index, which gives equal  
298 weight to false positive and false negative results.

### 299 **Internal Validation**

300 C-statistic values after correcting for optimistic predictions were: for *Acuity Increase*:  
301 predictor set a, C-stat=0.53; predictor set b, C-stat=0.59; predictor set c, C-stat=0.66. For  
302 *Deterioration Events*: predictor set a, C-stat=0.52; predictor set b, C-stat=0.61, predictor set c,  
303 C-stat=0.68. For *Length of Stay*: predictor set a,  $R^2=0.003$ ; predictor set b,  $R^2=0.12$ ; predictor set  
304 c,  $R^2=0.13$ .

### 305 **Discussion**

#### 306 **Accuracy of prediction of deterioration by MR-proADM**

307 This study shows that MR-proADM may be a clinically useful biomarker for predicting  
308 deterioration (i.e. *Acuity Increase*) within 72 hours from admission to hospital in  
309 patients with an admission NEWS score of 2 to 5. This contrasts with the performance  
310 of the NEWS score, assessed on admission, which did not predict deterioration within  
311 72 hours, as might have been expected from previous evaluations<sup>3-5 34</sup>. This discrepancy  
312 with previous studies might be explained by differences in selection criteria for  
313 patients. Previous research included all patients admitted to ED, but our study selected  
314 patients with NEWS between 2 and 5, because a tool to predict deterioration would be  
315 most useful in this group.

316 For most of the observed *Acuity Increase* events, the reason for classification was an  
317 increase in the NEWS score. Because an increase in NEWS score reflects both  
318 measurement variation and physiological variation, additional exploratory analyses  
319 were carried out to assess the performance of MR-proADM with an operational  
320 definition of deterioration, *Deterioration Event*, designed to minimize measurement  
321 variation. NEWS on its own had low prognostic accuracy for *Deterioration Events*.  
322 However, MR-proADM level, and NEWS score together predicted *Deterioration Events*  
323 with an AUC of 0.65. Considering baseline patient characteristics further increased the  
324 accuracy of the model (AUC = 0.73).



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## 325 **Comorbidities and interactions with MR-proADM levels**

326 MR-proADM levels in people with COPD and/or heart failure are chronically raised and  
327 are not predictive of deterioration. However, in other people whose MR-proADM levels  
328 are not chronically raised, high levels are predictive of *Acuity Increase* (Supplementary  
329 Figure s1). Including these comorbidities and their interaction with MR-proADM level  
330 increased the prognostic accuracy of the logistic regression model.

## 331 **Limitations**

332 This study included only patients who were admitted with a NEWS score between 2 and  
333 5. The prognostic accuracy of the MR-proADM would perhaps have been greater if more  
334 extreme cases had been included. However, patients with NEWS scores more than 5 are  
335 already known to be severely ill and to require close monitoring and/or management at  
336 higher levels of care.

337 Internal validation found that the uncorrected C-statistics are optimistic, which implies  
338 that external validation in an independent study would be useful. However, after  
339 correction for optimistic predictions, the study's conclusions remain unchanged.

## 340 **Interpretations and implications**

341 The significance of MR-proADM in the prognostic models implies that it could provide  
342 additional prognostic information over and above NEWS score.

343 Secondary analyses suggest that a potentially useful clinical decision aid could be based  
344 on NEWS score, MR-proADM level, and clinical features.

## 345 **Future research and development**

346 As a growing number of NHS hospitals are implementing the NEWS score on their  
347 clinical information systems, it should be practical to develop a decision aid based on  
348 admission NEWS score, MR-proADM level, and clinical features. Other biomarkers may  
349 further improve prognostic accuracy for deterioration, for example: lactate<sup>3</sup>;  
350 peroxiredoxin-4 (Prx4) and copeptin<sup>22 35 36</sup>; and soluble urokinase plasminogen  
351 activator receptor (suPAR)<sup>37</sup>. The feasibility, cost-effectiveness, and acceptability of  
352 such decision aids needs to be evaluated in further research.

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353 A rapid point of care test for MR-proADM could facilitate the assessment process and  
354 reduce delays in arranging optimal levels of care and intensity of monitoring.

## 355 Footnotes

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369 Newcastle upon Tyne Hospitals NHS foundation Trust (reference number 7495).

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371 **Data sharing statement** No additional data are available

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## Prognostic accuracy of MR-proADM in emergency departments

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## Prognostic accuracy of MR-proADM in emergency departments

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56 472 mortality. *A retrospective cohort study. Emergency medicine journal : EMJ* 2016.

## Prognostic accuracy of MR-proADM in emergency departments

473

474 **Figure legends**475 **Figure 1.** Patient recruitment process.

476 **Figure 2. Panel A.** Prognostic accuracy for *Acuity Increase*; predictor set *a*: NEWS;  
477 predictors set *b*: NEWS, MR-proADM; predictor set *c*: NEWS, MR-proADM, COPD/HF,  
478 interaction between MR-proADM and COPD/HF. **Panel B.** Comparisons as for panel **A**  
479 but for predicting a *Deterioration Event*; predictor set *c*: NEWS score, MR-proADM level,  
480 Age<sup>2</sup>, other comorbidities. **Panel C.** *Length of Stay* predicted by MR-proADM level.

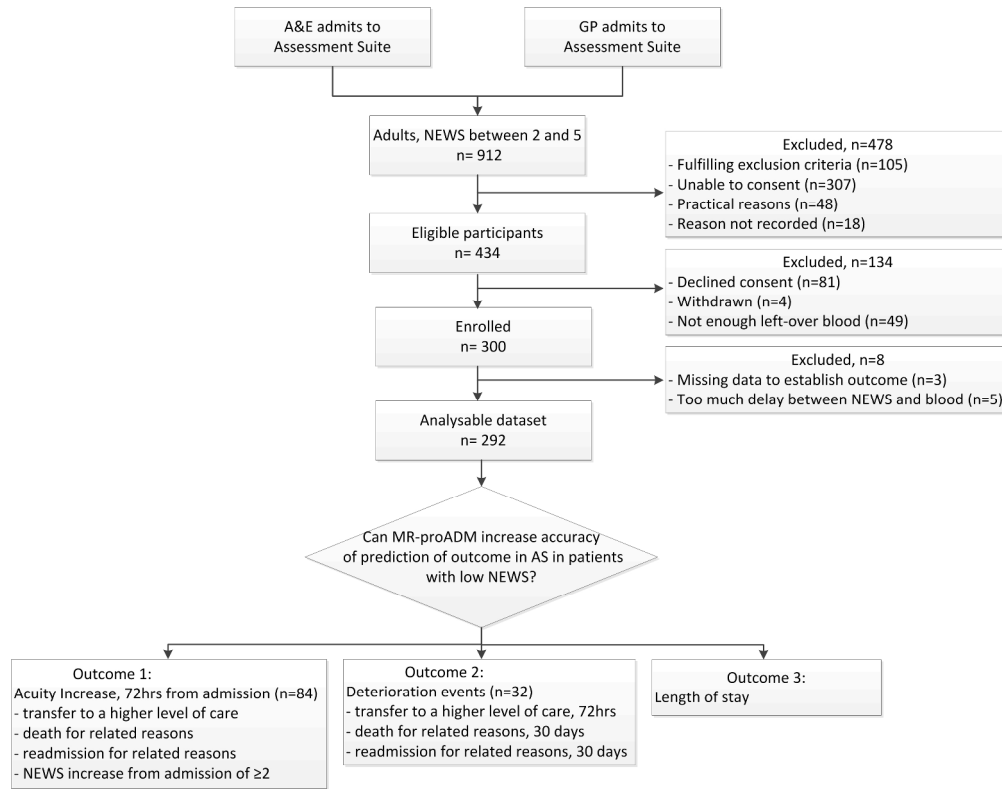


Figure 1. Patient recruitment process.

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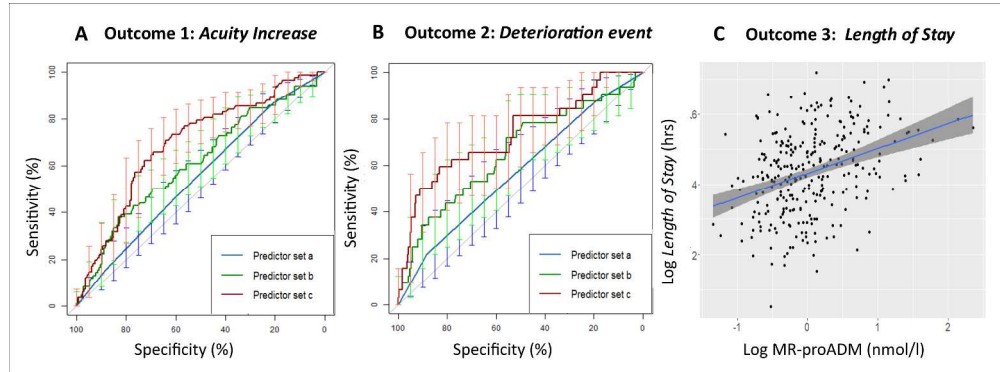


Figure 2. Panel A. Prognostic accuracy for Acuity Increase; predictor set a: NEWS; predictors set b: NEWS, MR-proADM; predictor set c: NEWS, MR-proADM, COPD/HF, interaction between MR-proADM and COPD/HF. Panel B. Comparisons as for panel A but for predicting a Deterioration Event; predictor set c: NEWS score, MR-proADM level, Age<sub>2</sub>, other comorbidities. Panel C. Length of Stay predicted by MR-proADM level.

Link text : Figure 2

320x118mm (300 x 300 DPI)



## Supplementary information for Graziadio et al, 2018

Supplementary information for *Can mid-regional pro-adrenomedullin (MR-proADM) increase the prognostic accuracy of NEWS in predicting deterioration in patients admitted to hospital with mild to moderately severe illness? A prospective single-centre observational study.*  
Graziadio et al, 2018

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2  
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## 4 Additional information on Methods

### 5 NEWS as a predictor of deterioration in patients with mild to moderately 6 severe illness 7 8

#### 9 Operational definitions of deterioration

10 In the original validation of NEWS, about 2% of the population had the combined outcome  
11 of cardiac arrest, unanticipated ICU admission, or death — each within 24 hours [Smith  
12 2013]. Furthermore, the proportions for each of the three individual outcomes and the  
13 composite outcomes increased monotonically through the range of NEWS scores.  
14  
15

16 Thus, as designed in its development, a NEWS score between 2 and 5 defines a population at  
17 low risk of cardiac arrest within 24 hours, death within 24 hours, or ICU admission within 24  
18 hours.  
19

20 However, a clinically important proportion of patients admitted to A&E or Medical Admissions  
21 Unit with mild to moderately severe illness (NEWS scores between 2 and 5) do deteriorate,  
22 and the NEWS score is, by design, not able to identify these patients.  
23  
24

25 The improvement challenge is to identify biomarkers that will increase the discrimination of  
26 low NEWS scores. And the methodological challenge was to develop convenient and effective  
27 operational definitions of deterioration from mild/moderately severe.  
28  
29

30 As NEWS is used to monitor changes in severity of illness, we decided to base our primary  
31 operational definition of deterioration on an increase of at least 2 in the NEWS score.  
32  
33

34 **Acuity Increase.** The primary outcome was the proportion of patients who, within 72 hours,  
35 had any combination of:  
36

- 37 • an increase of at least 2 in the NEWS score
- 38 • transfer to a higher-dependency bed or monitored area
- 39 • death
- 40 • for those discharged from hospital, re-admission for medical reasons.  
41  
42

43 We labelled this measure *Acuity Increase*.  
44  
45

46 Because there was concern about variations in NEWS scoring and about using NEWS to  
47 predict a change in NEWS (which it is designed not to do in this study's population), we  
48 defined two other measures of deterioration, one direct, and the other indirect:  
49  
50

51 **Deterioration Event:** the occurrence of one or more of the following:

- 52 • transfer to higher level of care within 72 hours from admission;
- 53 • death (for reasons related to admission) within 30 days;
- 54 • re-admission to hospital (for the same reason as the previous admission) within 30  
55 days from first admission  
56  
57  
58

59 **Length of Stay:** the duration in days from admission to discharge or death  
60

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## 2 3 **Predictors of deterioration for statistical modelling**

4  
5 In the analyses, we included NEWS as a possible predictor of deterioration. As expected,  
6 NEWS scores consistently do not predict deterioration, for all three of our operational  
7 definitions.  
8

9  
10 In line with the original validation of NEWS, we included NEWS as an ordinal variable [Smith  
11 2013].  
12

## 13 **Analytical data exploration**

14  
15 Univariate logistic regressions were used to investigate whether the relationship between  
16 outcome variables (i.e. deterioration measures) and the input variables (NEWS and MR-  
17 proADM, age, comorbidities, gender, CRP, and WBC) were linear. If they were not linear, log  
18 transformation and squared transformation were applied. If the transformation substantially  
19 lowered the AIC, then the transformed variable was used in statistical analyses.  
20  
21

22  
23 For categorical variables with multiple ordinal levels (i.e. NEWS score), the univariate analysis  
24 informed if it was appropriate to include the variable in the model as a continuous or  
25 categorical factor. If the coefficients in the univariate models increased linearly, then a linear  
26 relationship with the outcome could be assumed, and the variable was included in the model  
27 as continuous, otherwise the variable was treated as a categorical factor.  
28

29  
30 Univariate analyses were also used to identify the variables that affected the outcome  
31 significantly. Variables with a probable relationship with the outcome variable ( $p < 0.1$ ) were  
32 included in the full model logistic regression.  
33  
34

## 35 **Visual data exploration and interaction between MR-proADM and COPD/HF**

36  
37 After formatting the datasets, all variables were graphed (bar-charts for categorical variables,  
38 and scatterplots/histograms for continuous variables) and visually checked for outliers and  
39 distributions that seemed potentially erroneous.  
40

41  
42 If outliers were identified, the cause(s) were investigated to understand whether they were  
43 due to human error or they were genuine data. Outliers were kept in the primary analysis. In  
44 a secondary sensitivity analysis, outliers were removed and the same analyses repeated to  
45 assess the impact on the results. If the coefficients of the predictors changed substantially,  
46 both models would be described. There was one genuine outlier patient with a very high  
47 level of MR-proADM compared to the population mean, but its exclusion made no meaningful  
48 difference to the results, and the subject was included in the final analysis.  
49

50  
51 The influence of potentially important factors (such as comorbidities) on the ability of the MR-  
52 proADM to predict deterioration was explored graphically.  
53

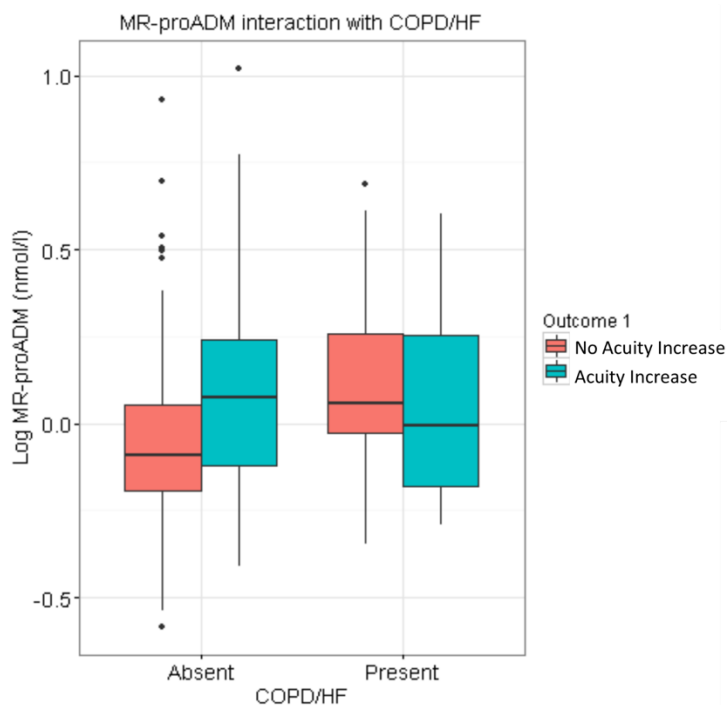
## 54 **Interaction between MR-proADM and COPD/HF**

55  
56 A significant interaction between MR-proADM and the presence of COPD/HF was discovered,  
57 and therefore included in the logistic regression (Outcome 1, predictor set c). The plot is  
58  
59  
60

## Supplementary information for Graziadio et al, 2018

shown in **Supplementary Figure s1**. This interaction showed that the MR-proADM level was increased in patients who deteriorated, but only if they did not have COPD or HF.

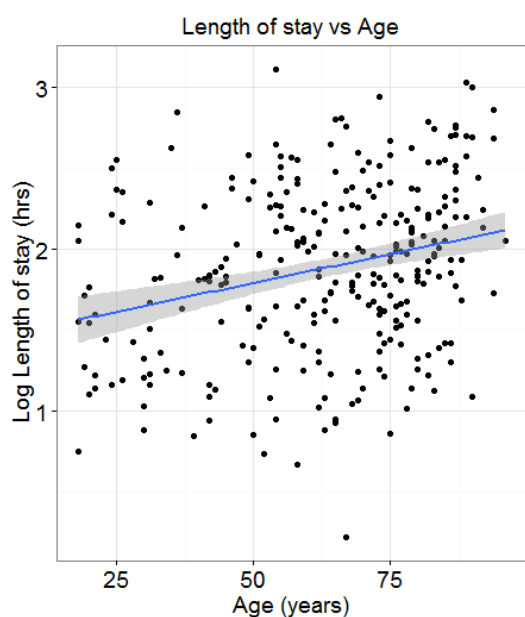
There was no suggestion that age; comorbidities: COPH and HF; other comorbidities; CRP; or WBC would improve the accuracy of prediction.



Interaction between MR-proADM and COPD/HF.

### Relationship between Length of Stay and Age

In **Supplementary Figure s1** the relationship between *Length of Stay* and *Age* is shown.

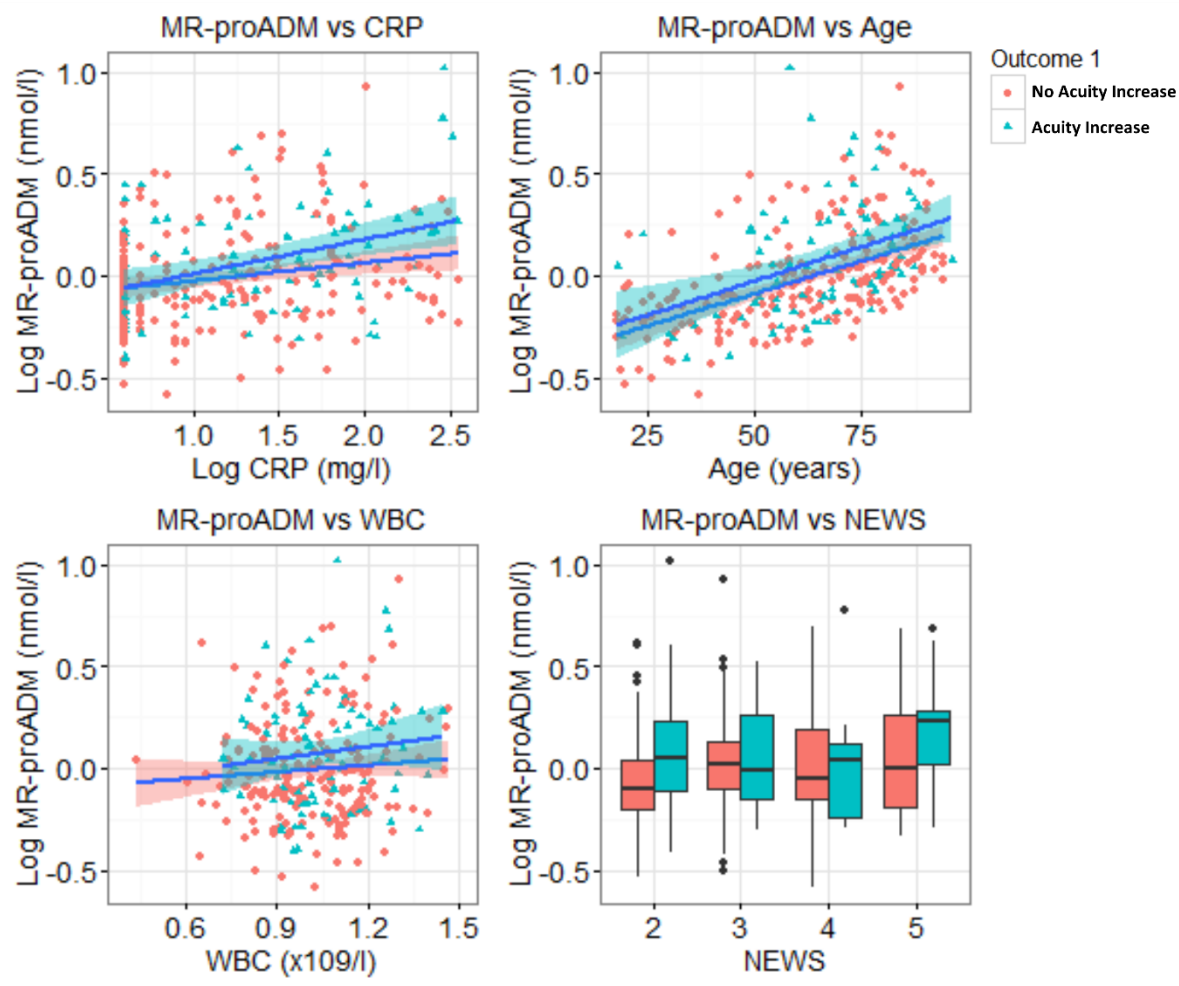


**Supplementary Figure s1.** Relationship between *Length of Stay* and *Age*.

Supplementary information for Graziadio et al, 2018

### Checking for multicollinearity and autocorrelation

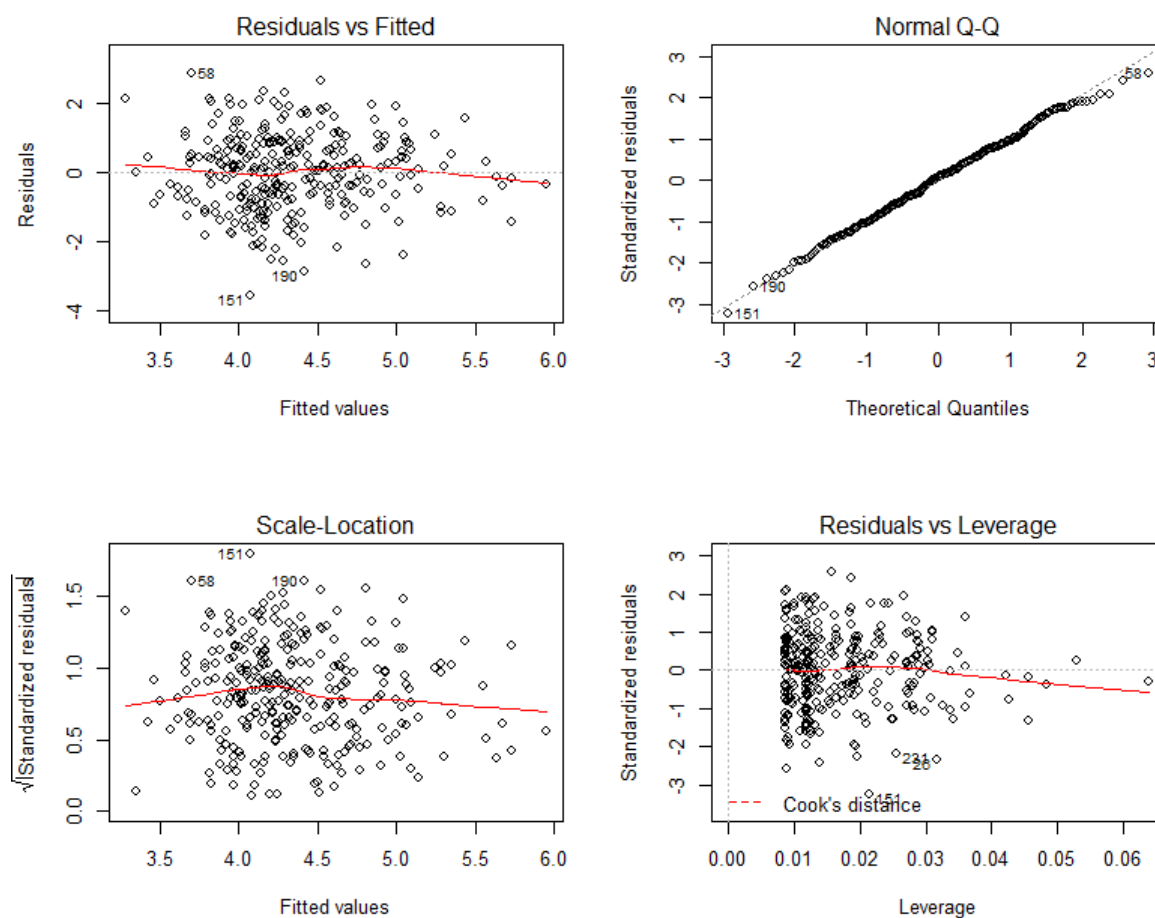
Correlations among biomarkers were also investigated through plotting to evaluate multicollinearity and added value of MR-proADM versus other biomarkers. Plots are shown in **Supplementary Figure s2**.



**Supplementary Figure s2.** Associations between MR-proADM and CRP, age, WBC, and NEWS.

Supplementary information for Graziadio et al, 2018

### Diagnostic plots for length of stay analysis



**Supplementary Figure s3.** Diagnostic plots for linear regression evaluating the prediction accuracy of MR-proADM for *Length of Stay*.

The diagnostics of the model showed no multicollinearity in the data since all the correlation coefficients among the independent variables were smaller than 0.5. No autocorrelation was found in the data, thus residuals are independent from each other: the Durbin-Watson test estimated  $d = 2.02$  ( $p = 0.56$ ). Evidence for homoscedasticity was provided graphically by the randomly scattered points and almost horizontal fitted lines in [Supplementary Figure s3](#), (Residuals vs fitted plot). Analysis of Cook's distance showed that there were no influential points ( $d < 4/51$ , [Supplementary Figure s3](#)).

### Analyses of shorter term outcomes

The analyses found that NEWS and MR-proADM had much lower accuracy in predicting *Acuity Increase* at 24 and 12 hours from admission than in predicting *Acuity Increase* at 72 hours as apparent in [Supplementary Table s1](#).

Supplementary information for Graziadio et al, 2018

**Supplementary Table s1.** Logistic regression for NEWS and MR-proADM predicting *Acuity Increase* within 24 hours. AIC = 326; AUC = 0.59.

Covariate	Beta	CI	Odds ratio(CI)	P-value
<b>Intercept</b>	-1.42	-1.70, -0.64	0.42 (0.27, 0.64)	NA
<b>NEWS 3</b>	-0.006	-0.64, 0.71	1.04 (0.53, 2.04)	0.985
<b>NEWS 4</b>	-0.37	-1.58, 0.20	0.52 (0.21, 1.22)	0.368
<b>NEWS 5</b>	0.21	-0.66, 1.01	1.25 (0.52, 2.91)	0.6244
<b>MR-proADM</b>	0.22	-0.06, 0.44	1.20 (0.95, 1.55)	0.0547

**Supplementary Table s2.** Logistic regression for NEWS and MR-proADM predicting *Acuity Increase* within 12 hours. AIC = 266; AUC = 0.57.

Covariate	Beta	CI	Odds ratio(CI)	P-value
<b>Intercept</b>	-1.83	-2.47, -1.24	0.16 (0.08, 0.29)	NA
<b>NEWS 3</b>	0.29	-0.46, 1.04	1.34 (0.63, 2.85)	0.442
<b>NEWS 4</b>	-0.15	-1.57, 0.76	0.86 (0.31, 2.14)	0.756
<b>NEWS 5</b>	0.29	-0.74, 1.23	1.33 (0.48, 3.42)	0.564
<b>MR-proADM</b>	0.06	-0.24, 0.31	1.06 (0.79, 1.36)	0.656

### Analyses of time-lag effect between news assessment and blood collection for assessment of MR-proADM levels

Given the practicalities involved, it was not possible to stipulate the timings of taking the NEWS on admission and collecting the blood sample for MR-proADM testing. It was expected that difference in times would normally be less than 6 hours, but in 44 subjects the time difference was more than 6 hours.

To investigate the impact of time differences being greater than expected, another analysis was carried out excluding subjects for whom the difference was more than 6 hours (time-lag compliant dataset). The hypothesis was that, if the time difference was an important parameter for the predictive accuracy of MR-proADM level, model coefficients would be greater and confidence intervals narrower for the compliant model. This was not the case; results were similar in the full dataset with 292 subjects and in the compliant dataset with 248 subjects ([Supplementary Table s3](#)).



## Supplementary information for Graziadio et al, 2018

**Supplementary Table s3.** Logistic regression for NEWS and MR-proADM predicting *Acuity Increase* for the time-lag compliant dataset. AIC = 295; AUC = 0.60.

Covariate	Beta	CI	Odds ratio(CI)	P-value
<b>Intercept</b>	-1.15	-1.70, -0.64	0.42 (0.27, 0.64)	NA
<b>NEWS 3</b>	-0.04	-0.64, 0.71	1.04 (0.53, 2.04)	0.909
<b>NEWS 4</b>	-0.65	-1.58, 0.20	0.52 (0.21, 1.22)	0.152
<b>NEWS 5</b>	0.22	-0.66, 1.01	1.25 (0.52, 2.91)	0.613
<b>MR-proADM</b>	0.19	-0.06, 0.44	1.20 (0.95, 1.55)	0.135

### Estimation of sensitivities and specificities

For completeness we estimated the sensitivity and specificity for each model in the article (**Supplementary Table s4**). We used the Youden's index to estimate the cut-off. In the next phase of the MR-proADM evaluation, the cut-off will be re-estimated through a decision analysis informed by the role of the test in the pathway.

**Supplementary Table s4.** Sensitivity and specificity of the logistic regression models. Predictor set a. was excluded from the table since the AUROC was too low to calculate meaningful diagnostic accuracy data.

Models	Sensitivity	Specificity
<b><i>Acuity Increase</i></b>		
<b>Predictor set b.</b>	0.38 (0.29, 0.49)	0.83 (0.78, 0.88)
<b>Predictor set c.</b>	0.66 (0.55, 0.76)	0.69 (0.63, 0.76)
<b><i>Deterioration Event</i></b>		
<b>Predictor set b.</b>	0.72 (0.56, 0.88)	0.56 (0.50, 0.62)
<b>Predictor set c.</b>	0.59 (0.44, 0.75)	0.83 (0.78, 0.87)



## TRIPOD Checklist: Prediction Model Development

Section/Topic	Item	Checklist Item	Page
<b>Title and abstract</b>			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	P1 L1-3
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	P2 L22-46
<b>Introduction</b>			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	P4-5 L52-84
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	P5 L82-84
<b>Methods</b>			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	P5 L87
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	P5 L87-91
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	P5 L87-97
	5b	Describe eligibility criteria for participants.	P5 L98-102
	5c	Give details of treatments received, if relevant.	N/A
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	P6-7 L128-149
	6b	Report any actions to blind assessment of the outcome to be predicted.	P6 L123-126
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	P4 L54-57 P4-5 L70-84 P5-6 L106-117
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	P6 L123-126
Sample size	8	Explain how the study size was arrived at.	P5 L92-97
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	P8-9 L197-201
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	P7-8 L151-194
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	P7-8 L151-194 P7 L153-155
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	P7-8 L156-194
Risk groups	11	Provide details on how risk groups were created, if done.	N/A
<b>Results</b>			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	P10-11 Table 1.
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	P10-11 Table 1.
Model development	14a	Specify the number of participants and outcome events in each analysis.	P10-11 Table 1.
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	P13-15 Table3&4
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	P13-15 Table3&4
	15b	Explain how to use the prediction model.	P15 L244-253
Model performance	16	Report performance measures (with CIs) for the prediction model.	P13-15 Table3&4 P15 L244-253
<b>Discussion</b>			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	P18-19 L306-316
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	P17-19 L278-323
Implications	20	Discuss the potential clinical use of the model and implications for future research.	P19 L325-335
<b>Other information</b>			
Supplementary	21	Provide information about the availability of supplementary resources, such as study	See Comments

## TRIPOD Checklist: Prediction Model Development

information		protocol, Web calculator, and data sets.	
Funding	22	Give the source of funding and the role of the funders for the present study.	P20 L346

Comments:

- Item 21: Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.**

Supplementary material - with additional information on methods and results - is attached as separate document. Study protocol and data sets will be available in due course, new project website currently under construction.

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# BMJ Open

## Can mid-regional pro-adrenomedullin (MR-proADM) increase the prognostic accuracy of NEWS in predicting deterioration in patients admitted to hospital with mild to moderately severe illness? A prospective single-centre observational study.

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## Prognostic accuracy of MR-proADM in emergency departments

**Title:** Can mid-regional pro-adrenomedullin (MR-proADM) increase the prognostic accuracy of NEWS in predicting deterioration in patients admitted to hospital with mild to moderately severe illness? A prospective single-centre observational study.

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## Prognostic accuracy of MR-proADM in emergency departments

24 **Abstract**

25 **Objective** To assess the value added to the NEWS score by MR-proADM blood level in  
26 predicting deterioration in mild to moderately ill people.

27 **Design** Prospective observational study

28 **Setting** The Medical Admissions Suite of the Royal Victoria Infirmary, Newcastle.

29 **Participants** 300 adults with NEWS score between 2 and 5 on admission. Exclusion  
30 criteria included receiving palliative care, or admitted for social reasons or self-  
31 harming. Patients were enrolled between September and December 2015, and  
32 followed-up for 30 days after discharge.

33 **Outcome measure** The primary outcome measure was the proportion of patients who,  
34 within 72 hours, had an *Acuity Increase*, defined as any combination of: an increase of at  
35 least 2 in the NEWS score; transfer to a higher-dependency bed or monitored area;  
36 death; or for those discharged from hospital, re-admission for medical reasons.

37 **Results** NEWS and MR-proADM together predicted *Acuity Increase* more accurately  
38 than NEWS alone, increasing the AUC to 0.61 (95% CI 0.54, 0.69) from 0.55 (95% CI  
39 0.48, 0.62). When the confounding effects of presence of chronic obstructive pulmonary  
40 disease or heart failure and interaction with MR-proADM were included, the prognostic  
41 accuracy further increased the AUC to 0.69 (95% CI 0.63, 0.76).

42 **Conclusions** MR-proADM is potentially a clinically useful biomarker for deterioration  
43 in patients admitted to hospital with a mild to moderately severe acute illness, i.e. with  
44 NEWS score between 2 and 5. As a growing number of NHS hospitals are routinely  
45 recording the NEWS score on their clinical information systems, further research should  
46 assess the practicality and utility of developing a decision aid based on admission NEWS  
47 score, MR-proADM level, and possibly other clinical data and other biomarkers that  
48 could further improve prognostic accuracy.

49 **Keywords**

50 Biochemistry, diagnosis, health services research

51

## Prognostic accuracy of MR-proADM in emergency departments

**Strengths and limitations of this study**

- This is the first study to use rigorous statistical methods to assess the value added by MR-proADM to the admission NEWS score for predicting clinically important deterioration in mild to moderately ill patients.
- Overall prognostic accuracy might have been greater had more severely ill patients been included, but the aim of this study was to predict deterioration in less severely ill patients who could benefit from closer observation.
- This was an observational study, and thus could not directly assess the utility of more accurate prediction of deterioration.
- Initial evidence for MR-proADM as a biomarker for deterioration appears promising, but requires further validation for clinical utility.

52



## Prognostic accuracy of MR-proADM in emergency departments

**Introduction**

The National Early Warning Score (NEWS) is recommended for assessing severity of illness in patients presenting in primary or secondary NHS care and for surveillance of patients in hospital<sup>1,2</sup>. Six physiological parameters (which can be measured at the bedside) are scored: respiratory rate, oxygen saturation, temperature, systolic blood pressure, pulse rate, and level of consciousness. The scores are aggregated, and, if the patient requires oxygen, the total is increased. NEWS predicts death, cardiac arrest, and unplanned intensive care unit (ICU) admission within 24 hours<sup>3-5</sup>. However, NEWS does not identify all patients who turn out to be seriously ill<sup>6-8</sup>, and there are also patients whose NEWS score is usually elevated and who do not require the level of observation that the NEWS tool would suggest. For example, people with chronic obstructive pulmonary disease (COPD) or chronic heart failure (HF) have higher baseline NEWS scores than those without these comorbidities. The prognostic accuracy of NEWS for patients presenting to the Emergency Department (ED) has been confirmed in a wide range of severity of illness<sup>9,10</sup>, as has its reduced accuracy in people with COPD<sup>11</sup>. But, no previous studies of the prognostic accuracy of NEWS in the ED/Medical Admissions Unit (MAU) have focussed on patients admitted with mild to moderately severe illness. Since a clinically important proportion of these patients do deteriorate unexpectedly, improved risk stratification would be useful.

Mid-regional pro-adrenomedullin (MR-proADM) is one of several promising biomarkers for severe illness and deterioration<sup>12-16</sup>.

MR-proADM is a precursor of adrenomedullin (ADM), a member of the calcitonin peptide family. ADM is widely expressed and has roles in vasodilation, immune modulation, and metabolic regulation. It is up-regulated in severe infections, inflammation, vasodilation, stimulation of diuresis, increased cardiac output, and stroke<sup>17-19</sup>. ADM has a short half-life, but MR-proADM is more stable and directly reflects ADM concentrations in blood. Both ADM and MR-proADM levels are strongly associated with risk of mortality, regardless of aetiology<sup>20-26</sup>. In people presenting with acute chest pain, MR-proADM has been reported to improve the Global Registry of Acute Coronary Events risk classification by 41%<sup>27</sup>. As with the NEWS score, people with COPD or chronic heart failure have higher baseline levels of MR-proADM.

## Prognostic accuracy of MR-proADM in emergency departments

84 The aim of this study was to assess whether the MR-proADM level used alongside the  
85 NEWS score would improve prediction of deterioration over NEWS score alone in  
86 patients admitted to the MAU with mild to moderately severe illness.

## 87 **Methods**

### 88 **Patient and Public Involvement**

89 Patients and the public were not specifically involved in the planning and execution of  
90 this study. However, the NIHR now requires that the research it supports includes  
91 active involvement and engagement with patients and the public.

### 92 **Study participants and study design**

93 This was a prospective observational cohort study. Patients were enrolled between  
94 September and December 2015 at the Royal Victoria Infirmary, Newcastle, and  
95 followed-up for 30 days after discharge. If the patient died within the 30 days of follow  
96 up, this and the cause of death were recorded. Adults admitted to the MAU were  
97 recruited for the study between 9 am and 4 pm on weekdays.

98 Sample size was based on a pragmatic recruitment target for a three-month  
99 observational study. A recent unpublished audit conducted in the MAU at the Royal  
100 Victoria Infirmary found a deterioration rate of 20%. With 300 patients and complete  
101 data collection, 60 events would be anticipated. With this number of events, a  
102 multivariable prediction model could include up to six independent predictors. This is  
103 based on a widely accepted rule of thumb that models with fewer than ten events per  
104 predictor tend to be over-fitted<sup>28</sup>. However, recent research suggests that the “ten  
105 events per variable” rule of thumb may be optimistic<sup>29</sup>. Because the aim of this study  
106 was to assess if further research would be indicated, 60 is considered an acceptable  
107 number of events, even if the rule of thumb is optimistic.

108 Patients were considered eligible for inclusion in the study if their NEWS score on  
109 admission was at least 2 and not greater than 5, and all NEWS parameters were  
110 recorded. Patients were excluded from the study if they were receiving palliative care,  
111 were admitted for social reasons only, or were self-harming, or overdosing with drugs  
112 or other substances.

## Prognostic accuracy of MR-proADM in emergency departments

113 All participants provided written informed consent, and the study was approved by the  
114 Newcastle & North Tyneside Research Ethics Committee (15/NE/0120).

### 115 Recorded data

116 Demographic and admission data included: gender, year of birth, reason for admissions,  
117 diagnosis on discharge, and the presence of comorbidities in which baseline MR-  
118 proADM levels are chronically raised: COPD with hypoxia ( $\text{PaO}_2 < 10 \text{ kPa}$ )<sup>7</sup>; HF<sup>30</sup>; acute  
119 brain injury<sup>6</sup>; acute coronary syndrome<sup>27</sup>; acute venous thromboembolism<sup>21</sup>; high  
120 International Normalized Ratio ( $\text{INR} > 2$ ); acute kidney injury; electrolyte disturbances  
121 ( $\text{Na}^+ < 130$  or  $> 150 \text{ mmol/L}$ ;  $\text{K}^+ < 3.0$  or  $> 5.5 \text{ mmol/L}$ ); hyperglycaemia in type 1  
122 diabetes (random glucose  $> 10 \text{ mmol/L}$ ).

123 The NEWS score was assessed at on admission and over the next 72 hours, and the  
124 scores and assessment times recorded. The 7 clinical parameters used to determine the  
125 NEWS score were recorded for the baseline (admission) assessment only. Baseline  
126 NEWS scores were used to determine eligibility for this study. Subsequent NEWS scores  
127 were used in the analyses to identify deterioration.

128 Blood samples were taken at hospital admission for assessment of MR-proADM, C-  
129 Reactive Protein (CRP) and white blood count (WBC).

### 130 Laboratory tests

131 Plasma was obtained from blood samples (collected in ethylenediaminetetraacetic acid,  
132 EDTA) that were no longer clinically required. Plasma was stored in aliquots at  $-80^\circ \text{C}$ .

133 MR-proADM was assayed in the on-site Blood Sciences Laboratory using the B R A H M S  
134 Kryptor system according to the manufacturer's instructions.

135 Blood samples were analysed in batches by personnel blinded with regard to the  
136 condition and NEWS score of the patient. Nurses who assessed the NEWS score and  
137 healthcare professionals managing patients in the MAU were blinded to MR-proADM  
138 results.

### 139 Outcome measures

140 **Outcome measure 1: Acuity Increase.** A patient was classified as having an *Acuity*  
141 *Increase* if one or more of the following occurred within 72 hours from admission:

## Prognostic accuracy of MR-proADM in emergency departments

- 142 1. transfer to a higher level of care (ICU or high dependency unit)
- 143 2. readmission to hospital for reasons related to the initial admission
- 144 3. death for reasons related to the initial admission
- 145 4. NEWS score increased by at least two compared to the admission score

146 **Outcome measure 2: Deterioration Event.** For most of the observed *Acuity Increase*  
147 cases the reason for classification was an increase in the NEWS score (Table 1). An  
148 increase in NEWS score reflects both measurement variation and physiological  
149 variation, so additional exploratory analyses were carried out to assess the performance  
150 of MR-proADM in predicting deterioration. *Deterioration Events* were classified as the  
151 occurrence of one or more of the following:

- 152 1. transfer to higher level of care within 72 hours from admission;
- 153 2. death (for reasons related to the admission) within 30 days;
- 154 3. re-admission to hospital (for the same reason as the previous admission) within  
155 30 days from first admission.

156 Classification based on this definition is unlikely to be subject to clinically important  
157 measurement variation. This analysis, therefore, should optimise the prognostic  
158 accuracy for events which are both clinically and economically important.

159 **Outcome measure 3: Length of Stay.** *Length of Stay* was defined as the duration (in  
160 days) from admission to discharge or death.

### 161 Statistical analysis

162 All data analyses were performed using the R language, version 3.2.0<sup>31</sup>, with the  
163 support of RStudio, version 0.99.896 (RStudio, Inc). The following R packages were  
164 used: ggplot2, pROC, psych, PredictABEL, Hmisc, rms.

165 Logistic regression models were compared for their accuracy in predicting  
166 deterioration outcome measures as pre-specified in an analysis plan. Analyses are  
167 presented as unadjusted parameter estimates of risk (odds ratio (OR), with confidence  
168 intervals (CI)) and estimates adjusted for identified clinical confounding factors. The  
169 aims of the multivariable analyses were twofold: first, to estimate the effect size and  
170 significance adjusted for other identified influential predictors and interactions; second,  
171 to investigate whether the addition of other predictors improved the goodness of fit and  
172 accuracy of prediction.

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173 Only complete cases were analysed since missingness was minimal: 10 records without  
174 data on co-morbidities (details in footnote in Table 1).

175 For each measure of deterioration (*Acuity Increase*, *Deterioration Event*, and *Length of*  
176 *Stay*), logistic regression models were compared for the following sets of predictor  
177 variables:

178 *Predictor set a.* Comparator (base case): NEWS score on admission

179 *Predictor set b.* Primary analysis: NEWS score, MR-proADM

180 *Predictor set c.* Secondary analyses: NEWS score and MR-proADM always  
181 included. Age, gender, CRP, WBC, presence of COPD or HF,  
182 presence of other comorbidities, and interactions between  
183 predictors when appropriate.

184 Predictors (and the underlying assumption of linearity of their relationship with the  
185 outcome of interest) were initially investigated through univariate analyses based on  
186 simple log and quadratic functions. Transformations were applied if they improved the  
187 goodness of fit as assessed by the Akaike information criterion (AIC), and were retained  
188 in the multivariable setting. NEWS was treated as an ordinal variable. We assessed  
189 interactions through visual data exploration without significance testing as the study  
190 was not powered for this. For the multivariable regression models, the set of predictors  
191 was assessed for independence through backward elimination, based on changes in AIC.

192 The analysis plan for the secondary outcome of *Length of Stay* was similar: using  
193 multiple linear regressions based on transformed outcomes to address non-normality.  
194 Dependent and exploratory variables were log-transformed if not normally distributed.  
195 Normality was assessed by visualizing the data. More details on the methods used are  
196 reported in the online Supplemental Material.

197 Goodness of fit of logistic regression models was assessed with the C-statistic (which is  
198 the area under the ROC curve, and is used as a measure of discrimination) presented  
199 with 95% confidence intervals (CI). To assess the value added by including the MR-  
200 proADM level with the NEWS score in predicting deterioration, continuous net  
201 reclassification improvement (NRI) and integrated discrimination improvement (IDI)  
202 were calculated<sup>32 33</sup>.

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203 For internal validation of the statistical models the C-statistic was evaluated after  
204 correcting for optimistic predictions through bootstrapping with 10,000 resamples.

## 205 Results

### 206 Study enrolment

207 The process of recruitment and enrolment of patients for the study is shown in Figure 1.  
208 The study recruited 300 patients, and 292 were included in the analysis. Five patients  
209 were excluded because the blood samples for MR-proADM were taken more than 12  
210 hours from baseline NEWS assessment; 3 patients were excluded from the primary  
211 outcome due to missing follow up NEWS scores.

### 212 Patient characteristics

213 Patient demographics and mean biomarker levels for each covariate are reported in  
214 Table 1. The cohort was evenly divided in gender and had a mean age of 63 years and  
215 mean NEWS on admission of 3, with the majority of patients having NEWS score of 2.  
216 COPD or HF were present in 28%, and 25% had other comorbidities.

217



## Prognostic accuracy of MR-proADM in emergency departments

**Table 1.** Characteristics of the study population, classified by Outcome 1 (*Acuity Increase*), Outcome 2 (*Deterioration Event*) and All patients. Data are presented as number (no) and percentages (%) for counts, or mean and (standard deviation, SD) for continuous normally distributed data, or [25th; 50th; 75th percentile] for continuous non-normally distributed data.

	Outcome 1: <i>Acuity Increase</i>		Outcome 2: <i>Deterioration Event</i>		All patients (n = 292)
	Present (e = 84)	Absent	Present (e2 = 32)	Absent	
Age (mean years, SD)	65 (17)	62 (21)	63 (14)	63 (20)	63 (20)
Gender (no. females, %)	41 (49%)	107 (51%)	15 (47%)	133 (51%)	148 (51%)
NEWS = 2 (no., %)	34 (40%)	82 (40%)	12 (38%)	104 (40%)	116 (40%)
NEWS = 3 (no., %)	26 (31%)	59 (28%)	9 (28%)	76 (29%)	85 (29%)
NEWS = 4 (no., %)	11 (13%)	43 (21%)	4 (13%)	50 (19%)	54 (18%)
NEWS = 5 (no., %)	13 (15%)	24 (12%)	7 (22%)	30 (12%)	37 (13%)
MR-proADM (mean nmol/l, SD)	1.50 (1.4) [0.72, 1.12, 1.79]	1.19 (0.9) [0.68, 0.93, 1.28]	1.89 (2.0) [0.93, 1.13, 1.95]	1.20 (0.9) [0.68, 0.93, 1.39]	1.28 (1.1) [0.68, 0.97, 1.48]
CRP (mg/l)	59 (79) [5, 22, 80]	42 (70) [4, 13, 41]	61 (90) [7, 23, 67]	45 (71) [4, 16, 51]	47 (73) [4, 17, 54]
WBC (x10 <sup>9</sup> /l)	12 (5) [9, 10, 14]	11 (5) [8, 10, 14]	12 (4) [9, 12, 15]	11 (5) [8, 10, 14]	11 (5) [8, 10, 14]
COPD/HF (no, %)*	33 (39%)	46 (22%)	12 (38%)	67 (26%)	79 (28%)
Other comorbidities (no., %)	17 (20%)	55 (26%)	15 (47%)	57 (22%)	72 (25%)
Length of Stay (hrs)	168 (196) [63, 110, 194]	137 (176) [26, 68, 176]	173 (172) [59, 106, 259]	143 (172) [33, 72, 176]	146 (182) [35, 77, 182]
Length of Stay in MAU (hrs)	31 (19) [17, 25, 43]	24 (16) [13, 21, 30]	27 (17) [18, 23, 35]	26 (17) [15, 22, 31]	26 (17) [15, 22, 31]
Monitored beds (no, %)	31 (37%)	58 (27%)	11 (34%)	78 (30%)	89 (30%)



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	<b>Outcome 1: <i>Acuity Increase</i></b>		<b>Outcome 2: <i>Deterioration Event</i></b>		<b>All patients (n = 292)</b>
	<b>Present (e = 84)</b>	<b>Absent</b>	<b>Present (e2 = 32)</b>	<b>Absent</b>	
Deterioration time (hrs)	15 (13) [5, 9, 21]	N/A	170 (226) [19, 33, 301]	N/A	
* for COPD: e = number with <i>Acuity Increase</i> = 82; e2 = number with <i>Deterioration Event</i> = 29; n = total number of patients = 282					

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## Prognostic accuracy of MR-proADM in emergency departments

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223 **Table 2.** Criteria met by patients classified with an *Acuity Increase* or *Deterioration*224 *Event.*

Criterion for deterioration	<i>Acuity Increase</i> (e = 84)	<i>Deterioration Event</i> (e2 = 32)
NEWS (no, %)	81 (96.4%)	N/A
ICU transfer (no, %)	1 (1.2%)	4 (12.5%)
Death (no, %)	0 (0%)	6 (18.8%)
Readmission (no, %)	2 (2.4%)	22 (68.7%)

225

226 The study population was homogenous across *Acuity Increase* and No *Acuity Increase*  
 227 outcomes in terms of gender, age, and NEWS on admission. Table 2 shows the  
 228 frequencies of criteria determining *Acuity Increase* and *Deterioration Event*. Notably,  
 229 around 95% of *Acuity Increases* were the result of an increase in NEWS score, while  
 230 readmission was the reason for around 70% of *Deterioration Events*.

231 Patients who experienced *Acuity Increase* had higher MR-proADM and CRP levels at  
 232 admission, and longer *Length of Stay* in the hospital and in the MAU.

233 The prevalence of *Acuity Increase* was 29% (somewhat higher than the anticipated  
 234 20%). The prevalence of *Deterioration Events* was 11%. The numbers of events  
 235 provided sufficient statistical power to assess statistical significance for the primary  
 236 outcome, *Acuity Increase*, but not for the secondary outcome, *Deterioration Event*.

237 **Accuracy of MR-proADM for predicting *Acuity Increase***

238 Potentially useful predictors with univariate analysis of *Acuity Increase* were MR-  
 239 proADM (OR = 1.27, 95% CI 1.02, 1.62; p = 0.037), Age<sup>2</sup> (OR = 1.00, 95% CI 0.99, 1.00; p  
 240 = 0.023) and the presence of COPD or HF (OR = 2.25, 95% CI 1.30, 3.91; p = 0.004;  
 241 Supplementary Figure s1). The prognostic accuracy of CRP, WBC and NEWS did not  
 242 reach the threshold of significance (p = 0.88, p = 0.090, Table 3, and p=0.416, Table 4,  
 243 respectively).

244

## Prognostic accuracy of MR-proADM in emergency departments

**Table 3.** Univariate regression analyses for predicting the three outcomes of interest: *Acuity Increase*, *Deterioration Event*, and *Length of Stay*. The p-values are for the statistical significance of the corresponding covariate in the related model. Analyses for the NEWS score as a predictor are shown in Table 4.

	Beta	CI	Odds Ratio (CI)	p-value
<b>Acuity Increase: univariate logistic regressions (n = 292, e = 84)</b>				
MR-proADM	0.24	-0.02, 0.48	1.27 (1.02, 1.62)	0.037
CRP	0.003	-0.0005, 0.0063	1.00 (1.00, 1.01)	0.088
WBC	0.04	-0.008, 0.094	1.05 (1.00, 1.10)	0.09
Gender	0.14	-0.38, 0.65	1.15 (0.69, 1.92)	0.684
Age	0.1	0.019, 0.1925	1.11 (1.02, 1.21)	0.023
Age <sup>2</sup>	-0.0008	-0.0016, -0.0001	1.00 (0.99, 1.00)	
Other Comorbidities	-0.32	-0.96, 0.28	0.72 (0.38, 1.32)	0.267
COPD/HF*	0.81	0.26, 1.36	2.25 (1.30, 3.91)	0.004
<b>Deterioration Event: univariate logistic regressions (n = 292, e<sub>2</sub> = 32)</b>				
MR-proADM	0.37	0.11, 0.64	1.44 (1.12, 1.90)	0.006
CRP	0.003	-0.002, 0.01	1.00 (1.00, 1.01)	0.255
WBC	0.02	-0.05, 0.09	1.02 (0.95, 1.10)	0.506
Gender	0.17	-0.57, 0.92	1.19 (0.57, 2.50)	0.648
Age	0.21	0.06, 0.40	1.23 (1.06, 1.49)	0.013
Age <sup>2</sup>	-0.002	-0.003, -0.001	1.00 (1.00, 1.00)	
Other Comorbidities	1.14	0.38, 1.90	3.14 (1.47, 6.69)	0.003
COPD/HF*	0.67	-0.14, 1.46	1.96 (0.87, 4.29)	0.095
<b>Length of Stay: simple linear regressions (n = 292, e = 84, e<sub>2</sub> = 32)</b>				
MR-proADM	0.7	0.49, 0.92	N/A	<0.0001
CRP	0.05	-0.05, 0.15	N/A	0.368
WBC	-0.06	-0.38, 0.27	N/A	0.73
Gender	0.08	-0.04, 0.20	N/A	0.18
Age	0.007	0.004, 0.010	N/A	<0.0001
Other Comorbidities	0.18	0.05, 0.32	N/A	0.009
COPD/HF*	0.07	-0.07, 0.21	N/A	0.318
<b>Key:</b> n = total number of cases; e = number of <i>Acuity Increases</i> ; e <sub>2</sub> = number of <i>Deterioration Events</i> ; CI = 95% confidence interval * n = 282, e = 82, e <sub>2</sub> = 29				

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## Prognostic accuracy of MR-proADM in emergency departments

**Table 4.** Multivariable regression analyses for the outcomes of interest: *Acuity Increase*, *Deterioration Event*, *Length of Stay* (Outcomes 1, 2, and 3 respectively) with NEWS comparator group. Predictor set *a*. includes only the NEWS score as a predictor; Predictor set *b*. includes MR-proADM and NEWS scores; Predictor set *c*. includes MR-proADM, NEWS scores, and other significant predictors and interactions. . The p-values are for the statistical significance of the corresponding covariate in the related model.

		Beta	CI	Odds Ratio (CI)	p-value	
<b>Acuity Increase: multivariate logistic regressions</b>						
<b>Predictor set a</b> n = 292 e = 84 e2 = 32	NEWS 3	0.06	-0.55, 0.67	1.06 (0.57, 1.95)	0.416	
	NEWS 4	-0.48	-1.29, 0.27	0.62 (0.27, 1.31)		
	NEWS 5	0.27	-0.54, 1.04	1.31 (0.58, 2.84)		
<b>Predictor set b</b> n = 292 e = 84 e2 = 32	NEWS 3	0.03	-0.59, 0.65	1.03 (0.56, 1.91)	0.247	
	NEWS 4	-0.53	-1.35, 0.23	0.59 (0.26, 1.26)		
	NEWS 5	0.18	-0.63, 0.97	1.20 (0.53, 2.64)		
	MR-proADM	0.24	0.02, 0.49	1.28 (1.02, 1.63)		0.039
<b>Predictor set c</b> n = 282 e = 82 e2 = 29	NEWS 3	-0.11	-0.76, 0.54	0.90 (0.47, 1.71)	0.221	
	NEWS 4	-0.89	-1.77, -0.08	0.41 (0.17, 0.93)		
	NEWS 5	0.09	-0.77, 0.91	1.09 (0.46, 2.50)		
	MR-proADM	0.41	0.13, 0.76	1.51 (1.14, 2.14)		0.01
	COPD/HF	1.81	0.80, 2.85	6.08 (2.23, 17.35)		0.001
MR-proADM*COPD/HF	-0.71	-1.40, -0.10	0.49 (0.25, 0.91)	0.03		
<b>Deterioration Event: multivariate logistic regressions</b>						
<b>Predictor set a</b> n = 292 e = 84 e2 = 32	NEWS 3	0.03	-0.92, 0.94	1.03 (0.40, 2.55)	0.512	
	NEWS 4	-0.37	-1.68, 0.74	0.69 (0.19, 2.10)		
	NEWS 5	0.7	-0.36, 1.70	2.02 (0.70, 5.50)		
<b>Predictor set b</b> n = 292 e = 84 e2 = 32	NEWS 3	-0.01	-0.97, 0.92	0.99 (0.38, 2.51)	0.564	
	NEWS 4	-0.43	-1.76, 0.70	0.65 (0.17, 2.02)		
	NEWS 5	0.6	-0.49, 1.62	1.81 (0.61, 5.05)		
	MR-proADM	0.36	0.10, 0.64	1.43 (1.11, 1.89)		0.007

## Prognostic accuracy of MR-proADM in emergency departments

		Beta	CI	Odds Ratio (CI)	p-value	
<b>Predictor set c</b> n = 282 e = 82 e <sup>2</sup> = 29	NEWS 3	0.16	-0.83, 1.12	1.17 (0.44, 3.07)	0.389	
	NEWS 4	-0.49	-1.86, 0.69	0.62 (0.16, 2.00)		
	NEWS 5	0.69	-0.44, 1.76	1.99 (0.64, 5.81)		
	MR-proADM	0.32	0.02, 0.64	1.37 (1.02, 1.89)		0.044
	Other comorbidities	0.94	0.10, 1.77	2.56 (1.10, 5.85)		0.026
	Age	0.21	0.06, 0.41	1.23 (1.06, 1.50)		0.011
	Age <sup>2</sup>	-0.002	-0.003, -0.001	1.00 (1.00, 1.00)		
<b>Length of Stay: multiple linear regressions</b>						
<b>Predictor set a</b> n = 292 e = 84 e <sup>2</sup> = 32	NEWS 3	-0.07	-0.21, 0.08	N/A	0.052	
	NEWS 4	0.07	-0.10, 0.24	N/A		
	NEWS 5	0.21	0.01, 0.40	N/A		
<b>Predictor set b</b> n = 292 e = 84 e <sup>2</sup> = 32	NEWS 3	-0.1	-0.24, 0.04	N/A	0.033	
	NEWS 4	0.05	-0.11, 0.21	N/A		
	NEWS 5	0.14	-0.04, 0.32	N/A		
	MR-proADM	0.69	0.48, 0.91	N/A		<0.0001
<b>Predictor set c</b> n = 282 e = 82 e <sup>2</sup> = 29	NEWS 3	-0.12	-0.25, 0.02	N/A	0.031	
	NEWS 4	0.04	-0.11, 0.20	N/A		
	NEWS 5	0.14	-0.04, 0.32	N/A		
	MR-proADM	0.55	0.31, 0.80	N/A		<0.0001
	Age	0.004	0, 0.007	N/A		0.027

256

257 The prognostic accuracy for *Acuity Increase* of NEWS on its own was limited and not  
 258 significant (AUC 0.55, 95% CI 0.48, 0.62), but when MR-proADM was included as an  
 259 additional predictor, the accuracy of the model increased (AUC 0.61, 95% CI 0.54, 0.69;  
 260 OR = 1.28, 95% CI 1.02, 1.63; p = 0.039) (Tables 4 and 5, Figure 2 panel A). When  
 261 including MR-proADM with NEWS, the reclassification of patients was also significant,  
 262 especially for the NRI (NRI = 0.3, SE 0.1, p = 0.007; IDI = 0.017, Table 4).

263 The prognostic accuracy of MR-proADM and the additional value it provides to the  
 264 NEWS score was confirmed for *Deterioration Events* and *Length of Stay* (Tables 4 and 5,  
 265 and Figure 2 panels B and C).

## Prognostic accuracy of MR-proADM in emergency departments

266 For MR-proADM alone, the AUCs were for: *Acuity Increase* 0.58 (0.51-0.66), and  
267 *Deterioration Event* 0.64 (0.54-0.74). For *Length of Stay* the R squared was 0.12.

268

269 **Table 5.** Model comparisons. Outcomes 1, 2, and 3 refer to *Acuity Increase*, *Deterioration*  
270 *Event*, and *Length of Stay* respectively. The predictors are: *Set a* NEWS score alone; *Set b*  
271 NEWS score and MR-proADM; *Set c* NEWS score, MR-proADM, and other significant  
272 predictors and interactions detailed in Table 3.

	AIC	Deviance	AUC (CI) or R <sup>2</sup> for linear regression	NRI (se), p-value	IDI (se), p-value
Outcome 1 - predictor set <i>a</i> .	348	356	0.55 (0.48, 0.62)		
Outcome 1 - predictor set <i>b</i> .	343	353	0.61 (0.54, 0.69)	0.3 (0.1), 0.007	0.017 (0.009), 0.058
Outcome 1 - predictor set <i>c</i> .	317	331	0.69 (0.63, 0.76)	0.4 (0.1), 0.0004*	0.05 (0.01), 0.0009*
Outcome 2 - predictor set <i>a</i> .	199	207	0.57 (0.47, 0.68)		
Outcome 2 - predictor set <i>b</i> .	192	202	0.65 (0.54, 0.76)	0.4 (0.2), 0.003	0.04 (0.02), 0.10
Outcome 2 - predictor set <i>c</i> .	177	193	0.73 (0.63, 0.84)	0.5 (0.2), 0.012*	0.06 (0.02), 0.0004*
Outcome 3 - predictor set <i>a</i> .	77	-381	0.03		
Outcome 3 - predictor set <i>b</i> .	68	-417	0.14		
Outcome 3 - predictor set <i>c</i> .	67	-420	0.16		

273

### 274 Effect on prognostic accuracy when clinical information is added to 275 the set of predictors

276 Secondary multivariable modelling evaluated the prognostic accuracy of MR-proADM  
277 when adjusted for the clinical factors in predictive set *c*: age, gender, CRP, WBC,  
278 presence of COPD or HF, presence of other comorbidities,

279 For *Acuity Increase*, COPD or HF comorbidity status and its interaction with MR-proADM  
280 level improved the prognostic accuracy of the model: AUC increased from 0.61 (95% CI  
281 0.54, 0.69) to 0.69 (95% CI 0.63, 0.76), and net reclassification index from 0.3 to 0.4  
282 (Table 5).

283 For *Deterioration Events*, the presence of other comorbidities (excluding COPD and HF)  
284 and *Age*<sup>2</sup> increased the prognostic accuracy of MR-proADM, (Table 4 and 5). The

## Prognostic accuracy of MR-proADM in emergency departments

285 prognostic accuracy of *Length of Stay* (Outcome 3) of MR-proADM is also increased by  
286 including *Age* in the model (Table 4 and 5, Supplementary Figure s2).

### 287 **Potential confounding effects**

288 **Shorter term outcomes:** NEWS and MR-proADM were less accurate in predicting  
289 *Acuity Increase* within 24 and 12 hours from admission than in predicting *Acuity*  
290 *Increase* within 72 hours (Supplementary Tables s1 and s2).

291 **Interval between admission NEWS scoring and blood collection:** Because ward  
292 processes did not allow the times of scoring NEWS and collecting blood to be specified  
293 for research, we assessed for a confounding effect from variation in the timings, but  
294 found no evidence for it (Supplementary Table s3).

295 **Correlations among biomarkers.** Diagnostic plots, shown in Supplementary Figures  
296 s2 and s3, show no multicollinearity in the data, no autocorrelation, no  
297 heteroscedasticity, and no data points that stood out in terms of their influence on  
298 results.

### 299 **Sensitivity and specificity**

300 As overall measures of accuracy, sensitivity and specificity were calculated (where  
301 appropriate) for each model using Youden's index. The results are shown in  
302 Supplementary Table s4. In practice, the trade-off between sensitivity and specificity  
303 would depend on the type of clinical decision to be made on the result (i.e. "rule-in" or  
304 "rule out") and this would differ from the approach in Youden's Index, which gives equal  
305 weight to false positive and false negative results.

### 306 **Internal Validation**

307 C-statistic values after correcting for optimistic predictions (i.e. bootstrapped average of  
308 the AUC for each model) were: for *Acuity Increase*: predictor set *a*, C-stat=0.53; predictor  
309 set *b*, C-stat=0.59; predictor set *c*, C-stat=0.66. For *Deterioration Events*: predictor set *a*, C-  
310 stat=0.52; predictor set *b*, C-stat=0.61, predictor set *c*, C-stat=0.68. For *Length of Stay*: predictor  
311 set *a*,  $R^2=0.003$ ; predictor set *b*,  $R^2=0.12$ ; predictor set *c*,  $R^2=0.13$ . AUCs decreased slightly with  
312 the bootstrapped averages, but the differences between the AUCs for Predictor sets *a*, *b*, and *c*  
313 were constant. These results are an internal validation, and further validation on an external  
314 dataset is required.



Prognostic accuracy of MR-proADM in emergency departments

## 315 Discussion

### 316 Accuracy of prediction of deterioration by MR-proADM

317 This study shows that MR-proADM may be a clinically useful biomarker for predicting  
318 deterioration (i.e. *Acuity Increase*) within 72 hours from admission to hospital in mild to  
319 moderately ill patients with admission NEWS score between 2 to 5. By design, NEWS  
320 scores in this range imply a low risk of deterioration, and our data are consistent with  
321 this. Previous evaluations of the NEWS score assessed on admission have found that it  
322 predicts deterioration<sup>3-5 34</sup>, which may seem inconsistent. But these studies included all  
323 patients admitted to ED, whatever their NEWS score.

324 For most of the observed *Acuity Increase* events, the reason for classification was an  
325 increase in the NEWS score. Because an increase in NEWS score reflects both  
326 measurement variation and physiological variation, additional exploratory analyses  
327 were carried out to assess the performance of MR-proADM, using an operational  
328 definition of deterioration, *Deterioration Event*, designed to minimize measurement  
329 variation. NEWS on its own had low prognostic accuracy for *Deterioration Events*.  
330 However, MR-proADM level, and NEWS score together predicted *Deterioration Events*  
331 with an AUC of 0.65. Considering baseline patient characteristics further increased the  
332 accuracy of the model (AUC = 0.73).

### 333 Comorbidities and interactions with MR-proADM levels

334 MR-proADM levels in people with COPD and/or heart failure are chronically raised and  
335 are not predictive of deterioration. However, in other people whose MR-proADM levels  
336 are not chronically raised, high levels are predictive of *Acuity Increase* (Supplementary  
337 Figure s1). Including these comorbidities and their interaction with MR-proADM level  
338 increased the prognostic accuracy of the logistic regression model.

### 339 Limitations

340 This study included only patients who were admitted with a NEWS score between 2 and  
341 5. The prognostic accuracy of the MR-proADM would perhaps have been greater if more  
342 extreme cases had been included. However, patients with NEWS scores more than 5 are  
343 already known to be severely ill and to require close monitoring and/or management at  
344 higher levels of care.

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Internal validation found that the uncorrected C-statistics are optimistic, which implies that external validation in an independent study would be useful. However, after correction for optimistic predictions, the study's conclusions remain unchanged.

### Interpretations and implications

The contributions of MR-proADM to the accuracy of the prognostic models suggests that it could provide additional prognostic information over and above NEWS score.

Secondary analyses suggest that a potentially useful clinical decision aid could be based on the NEWS score, MR-proADM level, and clinical features.

### Future research and development

As a growing number of NHS hospitals are implementing the NEWS score on their clinical information systems, it should be practical to develop a decision aid based on admission NEWS score, MR-proADM level, and clinical features. Other biomarkers may further improve prognostic accuracy for deterioration, for example: lactate<sup>3</sup>; peroxiredoxin-4 (Prx4) and copeptin<sup>22 35 36</sup>; and soluble urokinase plasminogen activator receptor (suPAR)<sup>37</sup>. The feasibility, cost-effectiveness, and acceptability of such decision aids needs to be evaluated in further research.

A rapid point of care test for MR-proADM could facilitate the assessment process and reduce delays in arranging optimal levels of care and intensity of monitoring. Future research could identify the threshold MR-proADM level corresponding to the optimal combination of sensitivity and specificity for a binary test (e.g. "present" or "absent") for deterioration.

### Footnotes

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## Figure legends

**Figure 1.** Patient recruitment process.

**Figure 2. Panel A.** Prognostic accuracy for *Acuity Increase*; predictor set *a*: NEWS; predictor set *b*: NEWS, MR-proADM; predictor set *c*: NEWS, MR-proADM, COPD/HF, interaction between MR-proADM and COPD/HF. **Panel B.** Comparisons as for panel **A** but for predicting a *Deterioration Event*; predictor set *c*: NEWS score, MR-proADM level, Age<sup>2</sup>, other comorbidities. **Panel C.** *Length of Stay* predicted by MR-proADM level.

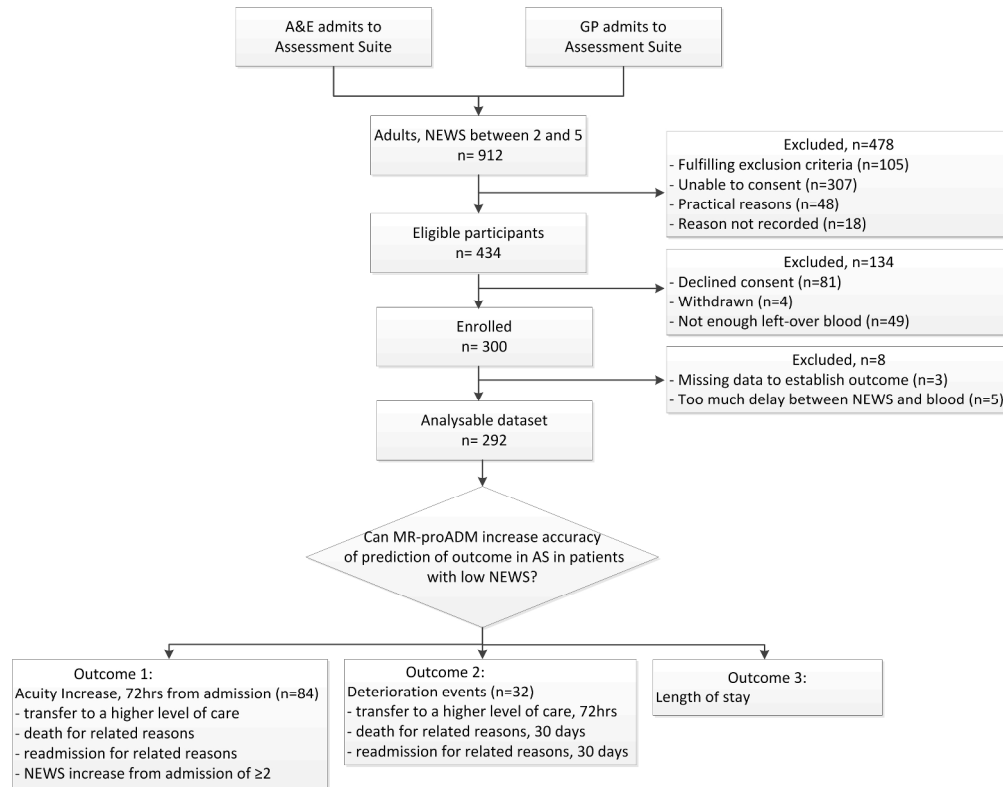


Figure 1. Patient recruitment process.

255x200mm (300 x 300 DPI)



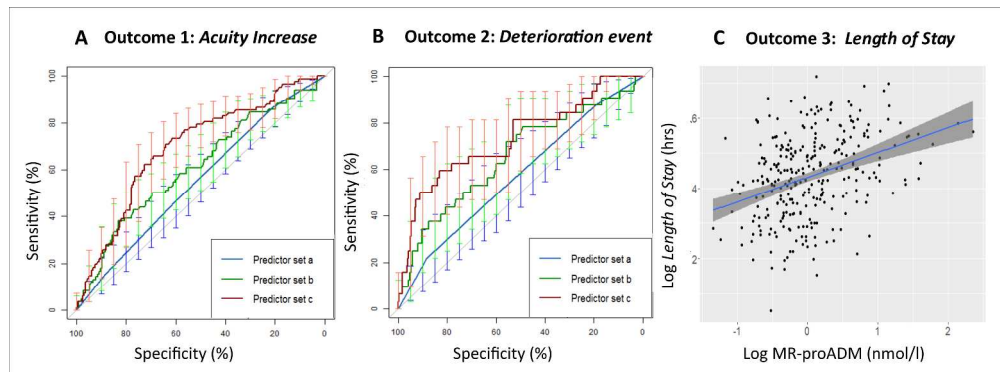


Figure 2. Panel A. Prognostic accuracy for Acuity Increase; predictor set a: NEWS; predictors set b: NEWS, MR-proADM; predictor set c: NEWS, MR-proADM, COPD/HF, interaction between MR-proADM and COPD/HF. Panel B. Comparisons as for panel A but for predicting a Deterioration Event; predictor set c: NEWS score, MR-proADM level, Age2, other comorbidities. Panel C. Length of Stay predicted by MR-proADM level.

Link text : Figure 2

320x118mm (300 x 300 DPI)



Supplementary information for Graziadio et al, 2018

Supplementary information for *Can mid-regional pro-adrenomedullin (MR-proADM) increase the prognostic accuracy of NEWS in predicting deterioration in patients admitted to hospital with mild to moderately severe illness? A prospective single-centre observational study.*  
Graziadio et al, 2018

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Supplementary information for Graziadio et al, 2018

## Additional information on Methods

### NEWS as a predictor of deterioration in patients with mild to moderately severe illness

#### Operational definitions of deterioration

In the original validation of NEWS, about 2% of the population had the combined outcome of cardiac arrest, unanticipated ICU admission, or death — each within 24 hours [Smith 2013]. Furthermore, the proportions for each of the three individual outcomes and the composite outcomes increased monotonically through the range of NEWS scores.

Thus, as designed in its development, a NEWS score between 2 and 5 defines a population at low risk of cardiac arrest within 24 hours, death within 24 hours, or ICU admission within 24 hours.

However, a clinically important proportion of patients admitted to A&E or Medical Admissions Unit with mild to moderately severe illness (NEWS scores between 2 and 5) do deteriorate, and the NEWS score is, by design, not able to identify these patients.

The improvement challenge is to identify biomarkers that will increase the discrimination of low NEWS scores. And the methodological challenge was to develop convenient and effective operational definitions of deterioration from mild/moderately severe.

As NEWS is used to monitor changes in severity of illness, we decided to base our primary operational definition of deterioration on an increase of at least 2 in the NEWS score.

**Acuity Increase.** The primary outcome was the proportion of patients who, within 72 hours, had any combination of:

- an increase of at least 2 in the NEWS score
- transfer to a higher-dependency bed or monitored area
- death
- for those discharged from hospital, re-admission for medical reasons.

We labelled this measure *Acuity Increase*.

Because there was concern about variations in NEWS scoring and about using NEWS to predict a change in NEWS (which it is designed not to do in this study's population), we defined two other measures of deterioration, one direct, and the other indirect:

**Deterioration Event:** the occurrence of one or more of the following:

- transfer to higher level of care within 72 hours from admission;
- death (for reasons related to admission) within 30 days;
- re-admission to hospital (for the same reason as the previous admission) within 30 days from first admission

**Length of Stay:** the duration in days from admission to discharge or death

Supplementary information for Graziadio et al, 2018

### Predictors of deterioration for statistical modelling

In the analyses, we included NEWS as a possible predictor of deterioration. As expected, NEWS scores consistently do not predict deterioration, for all three of our operational definitions.

In line with the original validation of NEWS, we included NEWS as an ordinal variable [Smith 2013].

### Analytical data exploration

Univariate logistic regressions were used to investigate whether the relationship between outcome variables (i.e. deterioration measures) and the input variables (NEWS and MR-proADM, age, comorbidities, gender, CRP, and WBC) were linear. If they were not linear, log transformation and squared transformation were applied. If the transformation substantially lowered the AIC, then the transformed variable was used in statistical analyses.

For categorical variables with multiple ordinal levels (i.e. NEWS score), the univariate analysis informed if it was appropriate to include the variable in the model as a continuous or categorical factor. If the coefficients in the univariate models increased linearly, then a linear relationship with the outcome could be assumed, and the variable was included in the model as continuous, otherwise the variable was treated as a categorical factor.

Univariate analyses were also used to identify the variables that affected the outcome significantly. Variables with a probable relationship with the outcome variable ( $p < 0.1$ ) were included in the full model logistic regression.

### Visual data exploration and interaction between MR-proADM and COPD/HF

After formatting the datasets, all variables were graphed (bar-charts for categorical variables, and scatterplots/histograms for continuous variables) and visually checked for outliers and distributions that seemed potentially erroneous.

If outliers were identified, the cause(s) were investigated to understand whether they were due to human error or they were genuine data. Outliers were kept in the primary analysis. In a secondary sensitivity analysis, outliers were removed and the same analyses repeated to assess the impact on the results. If the coefficients of the predictors changed substantially, both models would be described. There was one genuine outlier patient with a very high level of MR-proADM compared to the population mean, but its exclusion made no meaningful difference to the results, and the subject was included in the final analysis.

The influence of potentially important factors (such as comorbidities) on the ability of the MR-proADM to predict deterioration was explored graphically.

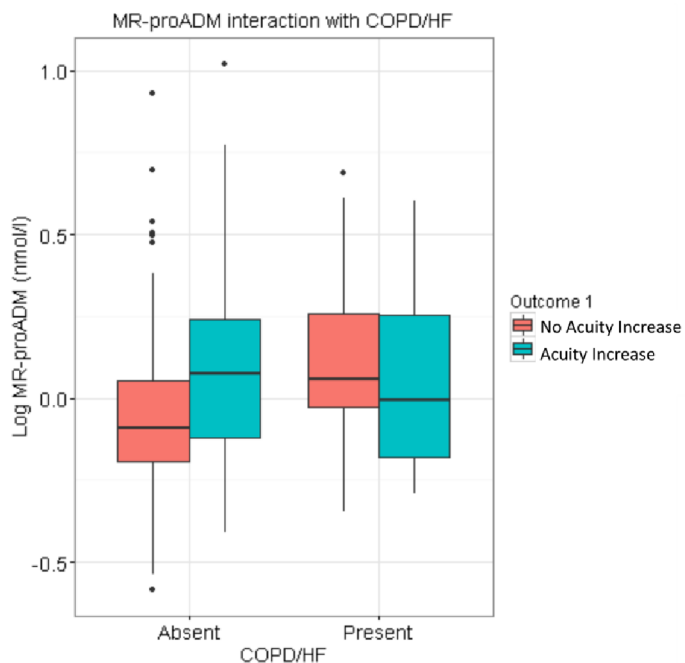
### Interaction between MR-proADM and COPD/HF

A significant interaction between MR-proADM and the presence of COPD/HF was discovered, and therefore included in the logistic regression (Outcome 1, predictor set c). The plot is

Supplementary information for Graziadio et al, 2018

shown in **Supplementary Figure s1**. This interaction showed that the MR-proADM level was increased in patients who deteriorated, but only if they did not have COPD or HF.

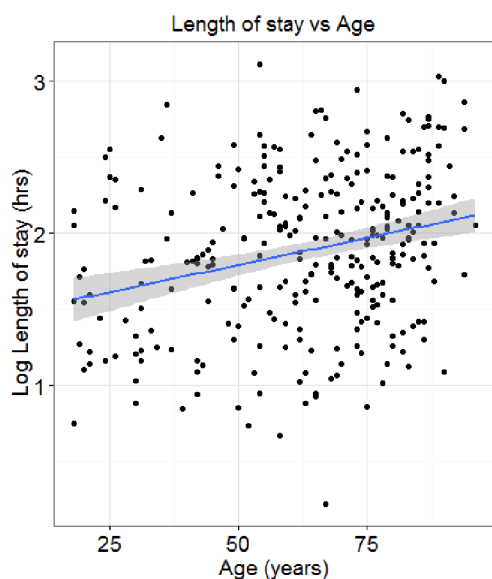
There was no suggestion that age; comorbidities: COPD and HF; other comorbidities; CRP; or WBC would improve the accuracy of prediction.



Interaction between MR-proADM and COPD/HF.

### Relationship between Length of Stay and Age

In **Supplementary Figure s1** the relationship between *Length of Stay* and *Age* is shown.

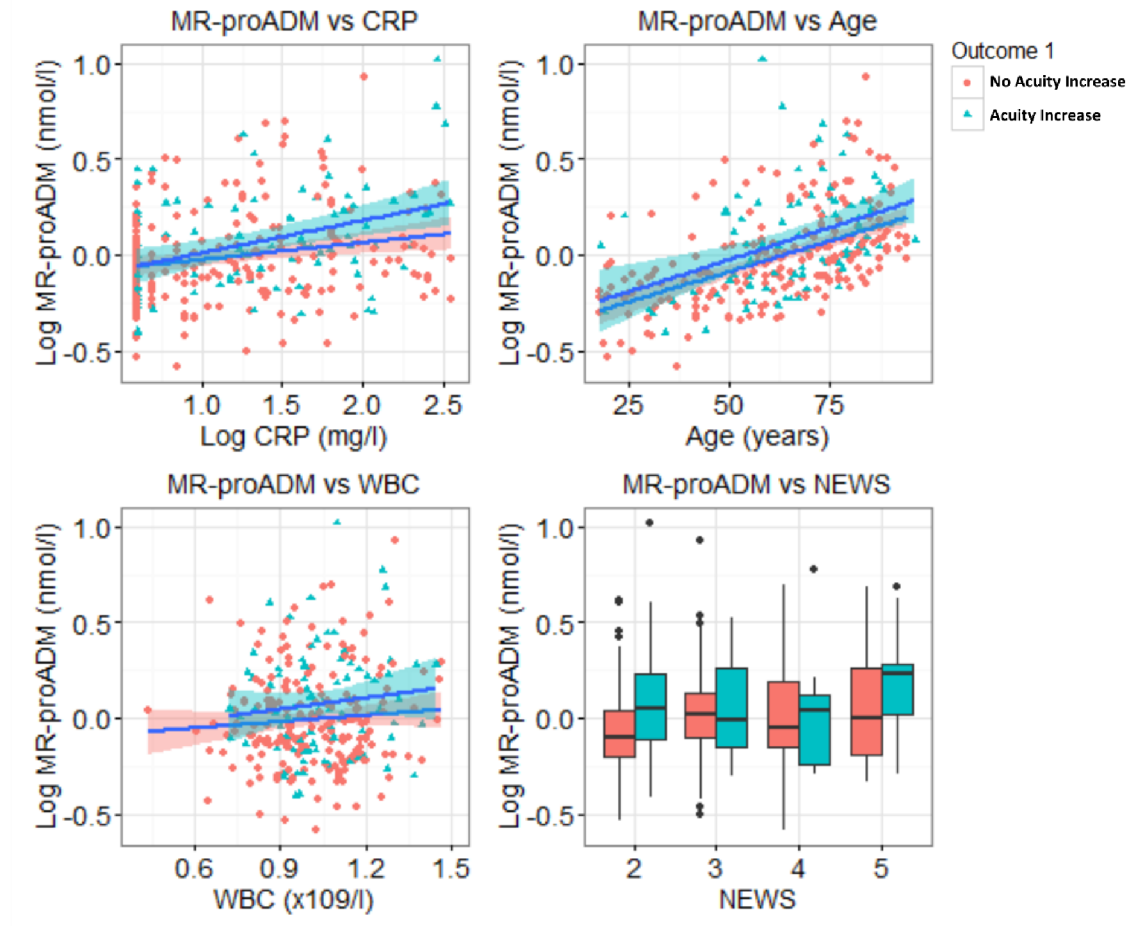


**Supplementary Figure s1**. Relationship between *Length of Stay* and *Age*.

Supplementary information for Graziadio et al, 2018

### Checking for multicollinearity and autocorrelation

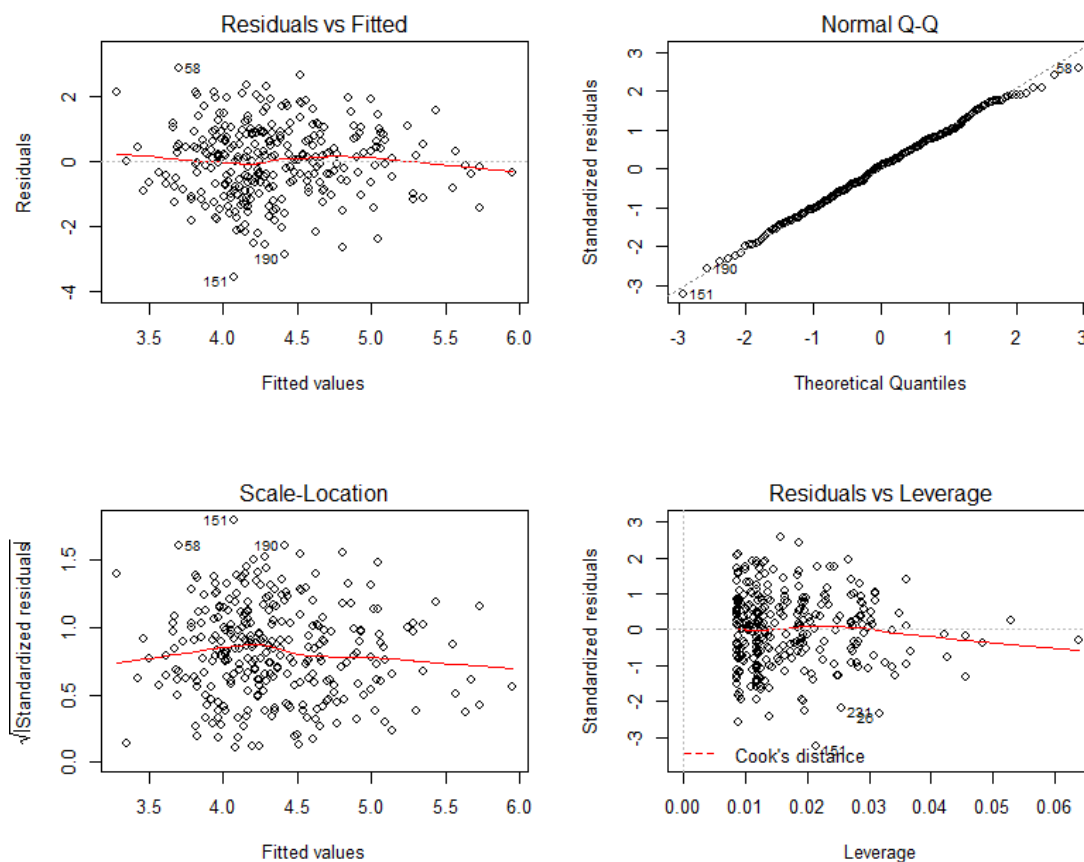
Correlations among biomarkers were also investigated through plotting to evaluate multicollinearity and added value of MR-proADM versus other biomarkers. Plots are shown in [Supplementary Figure s2](#).



**Supplementary Figure s2.** Associations between MR-proADM and CRP, age, WBC, and NEWS.

Supplementary information for Graziadio et al, 2018

### Diagnostic plots for length of stay analysis



**Supplementary Figure s3.** Diagnostic plots for linear regression evaluating the prediction accuracy of MR-proADM for *Length of Stay*.

The diagnostics of the model showed no multicollinearity in the data since all the correlation coefficients among the independent variables were smaller than 0.5. No autocorrelation was found in the data, thus residuals are independent from each other: the Durbin-Watson test estimated  $d = 2.02$  ( $p = 0.56$ ). Evidence for homoscedasticity was provided graphically by the randomly scattered points and almost horizontal fitted lines in [Supplementary Figure s3](#), (Residuals vs fitted plot). Analysis of Cook's distance showed that there were no influential points ( $d < 4/51$ , [Supplementary Figure s3](#)).

### Analyses of shorter term outcomes

The analyses found that NEWS and MR-proADM had much lower accuracy in predicting *Acuity Increase* at 24 and 12 hours from admission than in predicting *Acuity Increase* at 72 hours as apparent in [Supplementary Table s1](#).

Supplementary information for Graziadio et al, 2018

**Supplementary Table s1.** Logistic regression for NEWS and MR-proADM predicting *Acuity Increase* within 24 hours. AIC = 326; AUC = 0.59.

Covariate	Beta	CI	Odds ratio(CI)	P-value
<b>Intercept</b>	-1.42	-1.70, -0.64	0.42 (0.27, 0.64)	NA
<b>NEWS 3</b>	-0.006	-0.64, 0.71	1.04 (0.53, 2.04)	0.985
<b>NEWS 4</b>	-0.37	-1.58, 0.20	0.52 (0.21, 1.22)	0.368
<b>NEWS 5</b>	0.21	-0.66, 1.01	1.25 (0.52, 2.91)	0.6244
<b>MR-proADM</b>	0.22	-0.06, 0.44	1.20 (0.95, 1.55)	0.0547

**Supplementary Table s2.** Logistic regression for NEWS and MR-proADM predicting *Acuity Increase* within 12 hours. AIC = 266; AUC = 0.57.

Covariate	Beta	CI	Odds ratio(CI)	P-value
<b>Intercept</b>	-1.83	-2.47, -1.24	0.16 (0.08, 0.29)	NA
<b>NEWS 3</b>	0.29	-0.46, 1.04	1.34 (0.63, 2.85)	0.442
<b>NEWS 4</b>	-0.15	-1.57, 0.76	0.86 (0.31, 2.14)	0.756
<b>NEWS 5</b>	0.29	-0.74, 1.23	1.33 (0.48, 3.42)	0.564
<b>MR-proADM</b>	0.06	-0.24, 0.31	1.06 (0.79, 1.36)	0.656

### Analyses of time-lag effect between news assessment and blood collection for assessment of MR-proADM levels

Given the practicalities involved, it was not possible to stipulate the timings of taking the NEWS on admission and collecting the blood sample for MR-proADM testing. It was expected that difference in times would normally be less than 6 hours, but in 44 subjects the time difference was more than 6 hours.

To investigate the impact of time differences being greater than expected, another analysis was carried out excluding subjects for whom the difference was more than 6 hours (time-lag compliant dataset). The hypothesis was that, if the time difference was an important parameter for the predictive accuracy of MR-proADM level, model coefficients would be greater and confidence intervals narrower for the compliant model. This was not the case; results were similar in the full dataset with 292 subjects and in the compliant dataset with 248 subjects ([Supplementary Table s3](#)).



Supplementary information for Graziadio et al, 2018

**Supplementary Table s3.** Logistic regression for NEWS and MR-proADM predicting *Acuity Increase* for the time-lag compliant dataset. AIC = 295; AUC = 0.60.

Covariate	Beta	CI	Odds ratio(CI)	P-value
<b>Intercept</b>	-1.15	-1.70, -0.64	0.42 (0.27, 0.64)	NA
<b>NEWS 3</b>	-0.04	-0.64, 0.71	1.04 (0.53, 2.04)	0.909
<b>NEWS 4</b>	-0.65	-1.58, 0.20	0.52 (0.21, 1.22)	0.152
<b>NEWS 5</b>	0.22	-0.66, 1.01	1.25 (0.52, 2.91)	0.613
<b>MR-proADM</b>	0.19	-0.06, 0.44	1.20 (0.95, 1.55)	0.135

### Estimation of sensitivities and specificities for each model

For completeness we estimated the sensitivity and specificity for each model in the article (**Supplementary Table s4**). We used the Youden's index to estimate "optimal" cut-offs. In the next phase of the MR-proADM evaluation, the optimal cut-off will be re-estimated through a decision analysis informed by the role of the test in the pathway.

**Supplementary Table s4.** Sensitivity and specificity of the logistic regression models. Predictor set a. was excluded from the table since the AUROC was too low to calculate meaningful diagnostic accuracy data.

Models	Sensitivity	Specificity
<b><i>Acuity Increase</i></b>		
<b>Predictor set b.</b>	0.38 (0.29, 0.49)	0.83 (0.78, 0.88)
<b>Predictor set c.</b>	0.66 (0.55, 0.76)	0.69 (0.63, 0.76)
<b><i>Deterioration Event</i></b>		
<b>Predictor set b.</b>	0.72 (0.56, 0.88)	0.56 (0.50, 0.62)
<b>Predictor set c.</b>	0.59 (0.44, 0.75)	0.83 (0.78, 0.87)

## TRIPOD Checklist: Prediction Model Development

Section/Topic	Item	Checklist Item	Page
<b>Title and abstract</b>			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	P1 L1-3
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	P2 L22-46
<b>Introduction</b>			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	P4-5 L52-84
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	P5 L82-84
<b>Methods</b>			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	P5 L87
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	P5 L87-91
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	P5 L87-97
	5b	Describe eligibility criteria for participants.	P5 L98-102
	5c	Give details of treatments received, if relevant.	N/A
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	P6-7 L128-149
	6b	Report any actions to blind assessment of the outcome to be predicted.	P6 L123-126
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	P4 L54-57 P4-5 L70-84 P5-6 L106-117
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	P6 L123-126
Sample size	8	Explain how the study size was arrived at.	P5 L92-97
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	P8-9 L197-201
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	P7-8 L151-194
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	P7-8 L151-194 P7 L153-155
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	P7-8 L156-194
Risk groups	11	Provide details on how risk groups were created, if done.	N/A
<b>Results</b>			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	P10-11 Table 1.
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	P10-11 Table 1.
Model development	14a	Specify the number of participants and outcome events in each analysis.	P10-11 Table 1.
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	P13-15 Table3&4
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	P13-15 Table3&4
	15b	Explain how to use the prediction model.	P15 L244-253
Model performance	16	Report performance measures (with CIs) for the prediction model.	P13-15 Table3&4 P15 L244-253
<b>Discussion</b>			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	P18-19 L306-316
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	P17-19 L278-323
Implications	20	Discuss the potential clinical use of the model and implications for future research.	P19 L325-335
<b>Other information</b>			
Supplementary	21	Provide information about the availability of supplementary resources, such as study	See Comments



TRIPOD Checklist: Prediction Model Development

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information		protocol, Web calculator, and data sets.	
Funding	22	Give the source of funding and the role of the funders for the present study.	P20 L346

Comments:

- Item 21: Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.**

Supplementary material - with additional information on methods and results - is attached as separate document. Study protocol and data sets will be available in due course, new project website currently under construction.

For peer review only

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