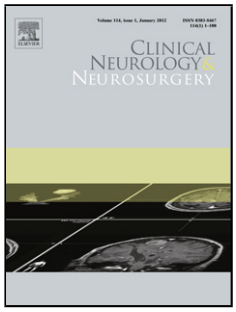

Modified Early Warning Score and Risk of Mortality after Acute Stroke

Charles Knoery (Formal analysis) (Writing - original draft) (Writing - review and editing), Raphae S. Barlas (Methodology) (Writing - review and editing), Priya Vart (Writing - review and editing), Allan B. Clark (Investigation), Stanley D. Musgrave (Investigation), Anthony K. Metcalf (Investigation), Diana J. Day (Investigation) (Writing - review and editing), Max O. Bachmann (Investigation), Elizabeth A. Warburton (Investigation), John F. Potter (Investigation), Phyo Kyaw Myint (Conceptualization) (Investigation) (Data curation) (Supervision)

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Title page:

Title: Modified Early Warning Score and Risk of Mortality after Acute Stroke

Running title: MEWS and risk of mortality after stroke

Cover title: Modified early warning score and stroke prognosis

Charles Knoery (MBChB)[a], Raphae S Barlas (MPH)[a], Priya Vart (PhD)[a], Allan B Clark (PhD)[b], Stanley D Musgrave (MD)[b], Anthony K Metcalf (MBChB)[c], Diana J Day (MSc)[d], Max O Bachmann(PhD)[b], Elizabeth A Warburton (FRCP)[d], John F Potter(DM)[b,c], Phyo Kyaw Myint (MD)[a]

[a]Institute of Applied Health Sciences, University of Aberdeen, AB25 2ZD, UK

[b]Norwich Medical School, University of East Anglia, Norwich, UK

[c]Stroke Research Group, Norfolk & Norwich University Hospital, Norwich, UK

[d]Lewin Stroke & Rehabilitation Unit, Addenbrooke's Hospital, Cambridge, UK

Correspondence to:

Professor Phyo Kyaw Myint

Room 4:013, Polwarth Building,

School of Medicine and Dentistry

University of Aberdeen

Foresterhill

AB25 2ZD

Aberdeen, Scotland, UK

Tel: +44 (0) 1224 437974

Fax: +44(0) 1224 437971

Mail to: phyo.myint@abdn.ac.uk

Highlight

- Stroke is a common cause of mortality especially in the acute phase of stroke onset
- A raised modified early warning score is an accurate indicator of in-patient mortality.
- Raised modified early warning score is also accurate predictor of mortality at 7 days, 30 days and 1 year.
- There is a linear relationship between increased modified early warning score and increased mortality.

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Abstract

Objective

An accurate prediction tool may facilitate optimal management of patients with acute stroke from an early stage. We evaluated the association between admission modified early warning score (MEWS) and mortality in patients with acute stroke.

Method

Data from the Anglia Stroke Clinical Network Evaluation Study (ASCNES) were analysed. We evaluated the association between admission MEWS and four outcomes; in-patient, 7-day, 30-day and 1-year mortality. Logistic regression models were used to calculate the odds of all mortality timeframes, whereas Cox proportional hazards models were used to calculate mortality at 1 year. Five univariate and multivariate models were constructed, adjusting for confounders. Patients with a moderate (2-3) or high (≥4) scores were compared to patients with a low score (0-1).

Results

The study population consisted of 2,006 patients. A total of 1196 patients had low MEWS, 666 had moderate MEWS and 144 had a high MEWS. A high MEWS was associated with increased mortality as an in-patient (OR 4.93, 95% CI: 2.88–8.42), at 7 days (OR 7.53, 95% CI: 4.24 – 13.38), at 30 days (OR 5.74, 95% CI: 3.38 – 9.76) and 1-year (HR 2.52, 95% CI 1.88 – 3.39). At 1 year, model 5 had a 1.02 OR (95% CI 0.83 – 1.24) with moderate MEWS and 2.52 (95% CI 1.88 – 3.39) with high MEWS.

Conclusion

Elevated MEWS on admission is a potential marker for acute-stroke mortality and may therefore be a useful risk prediction tool, able to guide clinicians attempting to prognosticate outcomes for patients with acute-stroke.

Key words: Stroke, mortality, MEWS,

1.1 Introduction

Stroke remains one of the commonest causes of mortality globally accounting for 11% of deaths[1], with the majority of fatalities occurring in the acute phase as in-hospital death[2]. The Sentinel Stroke National Audit programme in the UK demonstrated the variability in survival following an acute stroke at a regional, national and international level[3]. It is therefore important to identify factors that help prognosticate at stroke onset. A prediction rule for the identification of individuals at high risk of death may enable clinicians to accurately identify which patients should be prioritised for acute stroke unit beds. This may in turn improve acute-stroke outcomes[4].

The early warning score was designed to identify deteriorating patients with a composite score of physiological parameters to aid decisions to escalate patient care[5]. The early warning score was further refined to a modified early warning score (MEWS) including urine output, normalised blood pressure and reduced impact of minor temperature changes[5]. An elevated MEWS had a higher sensitivity and specificity for transfer of patients to high-dependency or intensive care[6].

Previous studies have assessed the predictive ability of numerous prognostic scores for acute stroke patients including iSCORE, PLAN and SOAR[7,8]. Furthermore, a recent study has identified an association between admission Shock Index and stroke mortality[9]. This suggests that a combination of acute physiological parameters can be used to prognosticate in

acute stroke. We therefore aimed to assess if admission MEWS was associated with increased acute-stroke mortality.

1.2 Methodology

Data from this study were drawn from the Anglia Stroke Clinical Network Evaluation Study (ACNES)[10]. This was a multi-centre prospective cohort study conducted in eight acute NHS trusts within the East of England between October 2009 and September 2011. Data were collected in 3 monthly cohorts and stroke was confirmed by clinical status, medical history and examination with neuroimaging (Computed Tomography or Magnetic Resonance Imaging). Ethical approval was granted by the Norfolk Ethics Committee and followed the ethical guidelines stipulated in the declaration of Helsinki[11]. Study funding was obtained from the UK National Institute of Health Research, Research for Patient Benefit Programme.

1.2.1 Modified Early Warning Score

The predictor variable was MEWS at admission. MEWS (Table 1) is a composite marker of several vital signs (respiratory rate, oxygen saturations, heart rate, blood pressure, temperature and AVPU), which help indicate if the patient has systemic disturbance from a disease process or a medical intervention[5]. The MEWS is usually monitored at regular intervals by nursing, medical or auxiliary staff who tally the score, as calculated by physiological markers that are beyond normal reference ranges. If the calculated value is raised, this is relayed onto healthcare staff who are prompted to investigate. This prompt can help instigate earlier treatment and escalation of patient-care to a high-dependency or intensive care unit. MEWS is typically recorded upon presentation to hospital and then

subsequently recorded at regular intervals, with the frequency dictated by the patient's condition.

In the current study, the variables that were used to calculate MEWS were recorded at the time of arrival to hospital by the trained clinical staff at participating sites using validated equipment e.g. blood pressure was measured using the appropriate sized cuff. These data were collected as part of the Anglia Stroke Clinical network and a clinical team in the ACNES retrieved case records to collect any unrecorded data. MEWS was divided into three categories; low (0 to 1), moderate (2 to 3) and high (>=4), with a higher score indicating worsening physiological parameters. This categorisation is based on our previous work on frail older people with regard to relationship between MEWS and mortality outcome[12]. In addition, the relationship between MEWS and mortality was analysed in a linear trend with MEWS categories 5, 6 and 7 combined into one category (due to the reduced frequency of higher scores among study participants).

1.2.2 Mortality

The primary outcomes of the study were inpatient mortality and mortality at multiple time-points; 7-days, 30-days and 1-year post-stroke. Data on mortality were recorded by the clinical teams who retrieved the case notes and conducted a questionnaire survey on patient outcomes. As the data were a partial historical cohort, this helped reduce selection bias for mortality, with further cases complying to current UK ethical guidance. The mortality occurring within inpatient stay, 7 days, 30-days and 1 year of hospital admission were examined separately.

1.2.3 Covariates

Covariates selected in the study included age, sex, pre-morbid modified Rankin scale, stroke type (ischaemic, haemorrhagic, ischaemic stroke with haemorrhagic transformation), Oxfordshire Community Stroke Project (OCSP) classification and Charlson score, which served as a surrogate maker for pre-morbid conditions (Ischaemic Heart Disease (IHD), Chronic Obstructive Pulmonary Disease (COPD), Diabetes Mellitus (DM), Peripheral Vascular Disease (PVD), Hypertension, Dementia). In addition, Pre-morbid modified Rankin classification represents a surrogate marker for pre-morbid frailty.

1.2.4 Statistical analysis

Descriptive statistical analysis (ANOVA for continuous and Chi square for categorical variables) were performed to identify differences in sample characteristics across MEWS categories. Binary logistic regression analysis was performed to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for the association between MEWS and mortality as inpatient, at 7-days and at 30-days. Cox proportional hazards models were used to calculate the hazard ratio for 1-year mortality. Multiple models were constructed to adjust for potential confounders; Model 1 was unadjusted, Model 2 adjusted for age, sex and Charlson score (incorporating pre-morbid co-morbidities as defined in patient characteristics[13]), Model 3 adjusted for the variables in Model 2 plus stroke type, Model 4 adjusted for factors in Model 3 plus OCSP and Model 5 adjusted for all the factors in Model 4 plus pre-morbid modified Rankin scale. In order to assess for possible bias, a secondary analysis was performed. This involved re-running the models using a complete case analysis (any patients with missing data were not included). The data were analysed using statistical software SPSS version 24.0 (IBM, Chicago, Illinois, USA). A p-value of <0.05 was considered statistically significant.

1.3 Results

1.3.1 Study Numbers

From a total of 2,383 patients included in the ASCNES, 373 patients were excluded due to missing data on MEWS and 4 due to missing data on age. This left a total of 2,006 patients in the final study population for Models 1 and 2. Data were missing from 65 patients on stroke type leaving 1,941 patients for Model 3 and 179 patient data missing on OSCP leaving 1,762 patients in Model 4. Another 199 patient data were missing on pre-morbid modified Rankin leaving a total of 1,563 patients for Model 5 (Figure 1).

1.3.2 Sample characteristics

Sample characteristics are described according to MEWS categories in Table 2**.** The mean age of the study population was 77.3 years and 47.6% were male. Older Patients tend to have higher MEWS and there were similar proportions of males and females in each MEWS category. Compared to low MEWS, pre-stroke modified Rankin score was higher in patients with intermediate and high MEWS. A greater proportion of patients with ischemic stroke had a low MEWS compared to haemorrhagic stroke. A significant association was observed between MEWS and OCSP classification, whereby severe stroke (TACS) was more common in the higher MEWS categories. Statistically there was no difference in prevalence of comorbidities including (IHD, COPD, Diabetes mellitus, PVD, hypertension, dementia) by levels of MEWS. Similarly, there was no difference in length of hospital stay among MEWS categories.

1.3.3 Association between MEWS and mortality

A total of 402 (20.0%) patients died as an inpatient, 224 (11.2%) died within 7 days, 383 (19.1%) died within 30 days and 662 (33%) died within 1 year. High MEWS at hospital admission was associated with increased likelihood of inpatient mortality (OR 4.93, 95% CI 2.88 – 8.42) (Table 3) and similarly within 7-days (OR 7.53, 95% CI 4.24 – 13.38). The same trend was found with high MEWS and mortality at 30-days (OR 5.74, 95% CI 3.38 – 9.76) in the multivariable adjusted model.

Table 4 depicts an increase in the hazard for 1-year for mortality with MEWS categories 4 – 7 (HR 2.52, 95% CI 1.88 – 3.39) after adjusting for confounders. However, this was not the case for categories 2 – 3 (HR 1.02, 95% CI 0.83 – 1.24). Furthermore, when analysing the trend across all MEWS categories in all mortality subgroups, there was a significant relationship ($p < 0.001$).

When analysing MEWS in a linear relationship with mortality (Figure 2) there was a significant increase in the odds of mortality at MEWS category 4 as in-patients (OR 4.92, 95% CI 2.50 – 9.69), 7-day mortality (OR 10.41, 95% CI 4.49 – 24.12) and 30-day mortality (HR 4.87, 95% CI 2.47 – 9.60). There was also a significant increase in mortality in MEWS category 5-7 with inpatients (OR 7.88, 95% CI 3.22 – 19.32), 7-day (OR 30.18, 95% CI 11.25 – 80.96) and 30-day mortality (OR 12.89, 95% CI 5.26 – 31.58). Using Cox proportional hazards models for 1-year mortality, there was also a significant increase in mortality over time with MEWS categories 4 (HR 2.57, CI 95% 1.74 – 3.78) and 5-7 (HR

3.32, 95% CI 2.11 – 5.24). Finally, the secondary analysis yielded results very similar to those in Tables 2 and 3 (Supplementary Material).

1.4 Discussion

We observed a significant increase in the odds of mortality in patients with higher MEWS on admission at various time points including; inpatient, 7-days, 30-days and 1-year. This relationship persisted subsequent to adjustment for various confounders including age, sex, Charlson score, stroke type, OCSP Classification and pre-morbid Rankin scale. These findings therefore suggest that higher MEWS on admission increase the odds of mortality in acute stroke.

Two previous studies evaluating the association between admission MEWS and mortality, found that a higher MEWS score was associated with increased mortality. However, these studies were conducted in the general population and the elderly, as opposed to stroke patients[14,15] Liljehult et al have previously assessed the association between admission MEWS and stroke mortality[16]. However, the current study builds upon the findings of Liljehult et al by adjusting for several additional variables including; pre-morbid modified Rankin, stroke type, OCSP classification and Charlson score. Furthermore, this study has a larger sample population and therefore greater statistical power, giving an increasingly accurate prediction of stroke mortality in comparison to previous studies. Finally, our follow-up was extended to 1-year whereas previous studies were limited to 30 days[16].

The findings of the current study indicate that MEWS may be a useful prognostic marker in patients with acute stroke. Due to the high prevalence of cardiac and pulmonary disease in

the acute stroke population[17], MEWS may be a useful adjunct to neurological markers such as NIH stroke scale as it includes cardiac and pulmonary parameters such as heart rate, blood pressure, respiratory rate and oxygen saturations. These parameters may detect signs of infection or cardiac and respiratory stress at an earlier point and help guide important interventions to the benefit of the patient. Overall, this could help identify patients that are at higher risk earlier and individualise our treatment and prognosis.

This study has a number of strengths. Firstly, by utilising a large sample size of 2006 patients, we attained a high level of statistical power. Secondly, by including patients recruited from 8 separate centres across the UK, we conducted our analysis using a study population that was representative of the wider UK stroke population. Furthermore, our study adjusted for numerous relevant covariates including; pre-morbid Rankin, Charlson score, stroke type and OCSP classification. Finally, no patients were lost to follow-up on mortality outcomes allowing us to analyse a complete data-set.

1.4.1 Limitations

This study also has a number of limitations. Firstly, as an observational study, we were unable to exclude the possibility of residual confounding. We cannot therefore confirm causation between stroke mortality and admission MEWS. Secondly, a number of patients were excluded from analysis due to missing data. However, due to the nature of the missing data (missing at random) and the magnitude of the observed association, this is unlikely to have a profound impact on our findings. Thirdly, NIHSS data were only recorded for thrombolysis patients, who constituted a small sub-set of the study population. We were therefore unable to adjust for this confounder. Finally, the study population was pre-

dominantly Caucasian (>95%) making this data mostly applicable to western populations, especially in the UK. However, it is likely that the physiological response would be similar amongst all ethnic groups in response to acute stroke.

1.5 Conclusion

In conclusion, our study demonstrates a strong link between MEWS at admission and stroke mortality. Clinicians may be able to identify acute stroke patients at risk of mortality with increased accuracy by using a clinical risk prediction, which includes admission MEWS. Further research should explore the association between MEWS and functional outcome and examine the usefulness of incorporating MEWS in risk prediction models to identify patients at an increased risk of death following an acute stroke.

Authors' contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Charles Knoery and Raphae Barlas. The first draft of the manuscript was written by Charles Knoery and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Ethics

Ethical approval was granted by the Norfolk Ethics Committee and followed the ethical guidelines stipulated in the declaration of Helsinki.

Conflicts of Interest/Competing interests

The authors declare that they have no conflict of interest.

CRediT authorship contribution statement

Charles Knoery (MBChB): Formal analysis, writing - original draft, review & editing.

Raphae S Barlas (MPH): Methodology, writing - review & editing.

Priya Vart (PhD): Writing - review & editing.

Allan B Clark (PhD): Investigation.

Stanley D Musgrave (MD): Investigation.

Anthony K Metcalf (MBChB): Investigation.

Diana J Day (MSc): Investigation, writing - review & editing.

Max O Bachmann (PhD): Investigation.

Elizabeth A Warburton (FRCP): Investigation.

John F Potter(DM): Investigation.

Phyo Kyaw Myint (MD): Conceptualization, investigation, data curation & supervision

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Table 1: Components of the modified early warning score

Score	**3**	**2**	**1**	**0**	**1**	**2**	**3**
Respiratory rate (min^{-1})		≤ 8		9–14	15–20	21–29	≥30
Heart rate (min^{-1})		≤ 40	41–50	51–100	101–110	111–129	≥130
Systolic BP (mmHg)	≤ 70	71–80	81–100	101–199		≥ 200	
Temperature (°C)		≤ 35	35.1–36	36.1–38	38.1–38.5	≥ 38.6	
Neurological				Alert	Reacting to voice	Reacting to pain	Unresponsive

Table 2: Sample characteristics by MEWS categories of patients presenting with acute stroke.

	Low MEWS (0 -1)	Moderate MEWS (2-3)	High MEWS (4-7)	p-value
N (2,006)	1196	666	144	
Age	76.40 ± 12.7	78.44 ± 11.8	78.85 ± 11.7	0.001
Gender: Male (%)	588 (49.2)	309 (46.4)	57 (39.6)	0.20
Pre-morbid modified Rankin (%)*				<0.001
0	560 (54.5)	258 (45.9)	46 (41.4)	
1	180 (17.5)	106 (18.9)	18 (16.2)	
2	113 (11.0)	51 (9.1)	13 (11.7)	
3	101 (9.8)	70 (12.5)	14 (12.6)	
4	48 (4.7)	57 (10.1)	11 (9.9)	
5	25 (2.4)	20 (3.6)	9 (8.1)	
Stroke type (%)*				<0.001
Ischaemic	1041 (89.2)	550 (85.3)	103 (79.8)	
Haemorrhage	123 (10.5)	86 (13.3)	26 (20.2)	
Ischaemic with haemorrhagic transformation	3 (0.3)	9 (1.4)	0 (0.0)	
OCSP Classification (%)*				<0.001
TACS	192 (17.6)	149 (25.5)	54 (44.3)	
PACS	456 (41.7)	219 (37.5)	29 (23.8)	

POCS	153 (14.0)	81 (13.9)	21 (17.2)	
LACS	292 (26.7)	135 (23.1)	18 (14.8)	
Pre-morbid conditions (%)				
MI/IHD*†	322 (27.2)	163 (24.7)	31 (21.8)	0.245
COPD*†	74 (6.2)	44 (6.6)	4 (2.8)	0.291
Diabetes Mellitus*	201 (16.9)	126 (19.0)	21 (14.8)	0.360
Peripheral Vascular Disease*	52 (4.4)	22 (3.3)	6 (4.2)	0.539
Hypertension*	701 (59.0)	403 (60.7)	87 (61.3)	0.708
Dementia*	104 (8.7)	73 (11.0)	16 (11.3)	0.228
Length of Stay median (range)	8 (0 - 191)	9 (0 - 108)	5.5 (0 - 150)	0.138
Outcomes % (n)				
In-patient mortality	175 (14.6)	150 (22.5)	77 (53.5)	<0.001
7-day mortality	81 (6.8)	86 (12.9)	57 (39.4)	<0.001
30-days mortality	166 (13.9)	142 (21.3)	75 (52.1)	<0.001
1-year mortality	335 (28.0)	238 (35.7)	89 (61.8)	<0.001

† Missing data; Pre-modified Rankin score – 306, Stroke type – 65, OCSP Classification – 207, MI/IHD – 20, COPD – 14, Diabetes Mellitus – 13, Peripheral Vascular Disease – 16, Hypertension – 11, Dementia – 11, Length of Stay = 1. ‡ MI/IHD = Myocardial Infarction / Ischemic Heart Disease, COPD = Chronic Obstructive Pulmonary Disease.

Table 3: Binary logistic regression models evaluating the association between admission MEWS categories and mortality at various time-points in acute stroke (Odds Ratios with 95% Confidence Intervals)

	Low MEWS (0 -1)	Moderate MEWS (2-3)	High MEWS (4-7)	p-value
Inpatient Mortality				
Model 1	1.00	1.70 (1.33 – 2.61)	6.70 (4.66 - 9.66)	<0.001
Model 2	1.00	1.58 (1.23-2.03)	7.14 (4.84 – 10.52)	<0.001
Model 3	1.00	1.44 (1.11 – 1.87)	5.91 (3.91- 8.92)	<0.001
Model 4	1.00	1.22 (0.90 – 1.65)	5.00 (3.06 - 8.16)	<0.001
Model 5	1.00	1.18 (0.85 - 1.65)	4.93 (2.88 - 8.42)	<0.001
7-Day Mortality				
Model 1	1.00	2.04 (1.48 – 2.81)	9.02 (6.03 – 13.50)	<0.001
Model 2	1.00	1.94 (1.40 – 2.68)	9.01 (5.96 – 13.63)	<0.001
Model 3	1.00	1.75 (1.24 – 2.46)	7.35 (4.68 – 11.52)	<0.001
Model 4	1.00	1.60 (1.08 – 2.36)	7.16 (4.26 - 12.01)	<0.001
Model 5	1.00	1.71 (1.11 - 2.62)	7.53 (4.24 - 13.38)	<0.001
30-Day mortality				
Model 1	1.00	1.68 (1.31 – 2.15)	6.74 (4.68 - 9.72)	<0.001
Model 2	1.00	1.57 (1.22 – 2.03)	7.09 (4.81 - 10.44)	<0.001
Model 3	1.00	1.41 (1.08 – 1.85)	5.89 (3.89 – 8.90)	< 0.001
Model 4	1.00	1.30 (0.95 –1.77)	5.67 (3.48 – 9.23)	<0.001
Model 5	1.00	1.26 (0.90 – 1.78)	5.74 (3.38 – 9.76)	<0.001

† Model 1: Unadjusted. Model 2: Age, Sex and Charlson score. Model 3: Model 2 + Stroke type. Model 4: Model 3 + Oxfordshire Community Stroke Project classification. Model 5: Model 4 + Pre-morbid modified Rankin scale

Table 4: Cox proportional hazards models evaluating the association between admission MEWS categories and mortality at 1-year mortality in acute stroke (Hazard Ratios with 95% Confidence Intervals)

	Low MEWS (0 -1)	**Moderate MEWS (2-3)**	**High MEWS (4-7)**	**p-value**
Model 1	1.00	1.37 (1.16-1.62)	3.45 (2.73-4.36)	<0.001
Model 2	1.00	1.23 (1.04–1.46)	3.16 (2.50–4.00)	<0.001
Model 3	1.00	1.15 (0.97–1.36)	2.80 (2.18– 3.60)	<0.001
Model 4	1.00	1.11 (0.93–1.34)	2.49 (1.90 – 3.26)	<0.001
Model 5	1.00	1.02 (0.83–1.24)	2.52 (1.88 – 3.39)	<0.001

† Model 1: Unadjusted. Model 2: Age, Sex and Charlson score. Model 3: Model 2 + Stroke type. Model 4: Model 3 + Oxfordshire Community Stroke Project classification. Model 5: Model 4 + Pre-morbid modified Rankin scale.

Figure 1: Study Inclusion Chart

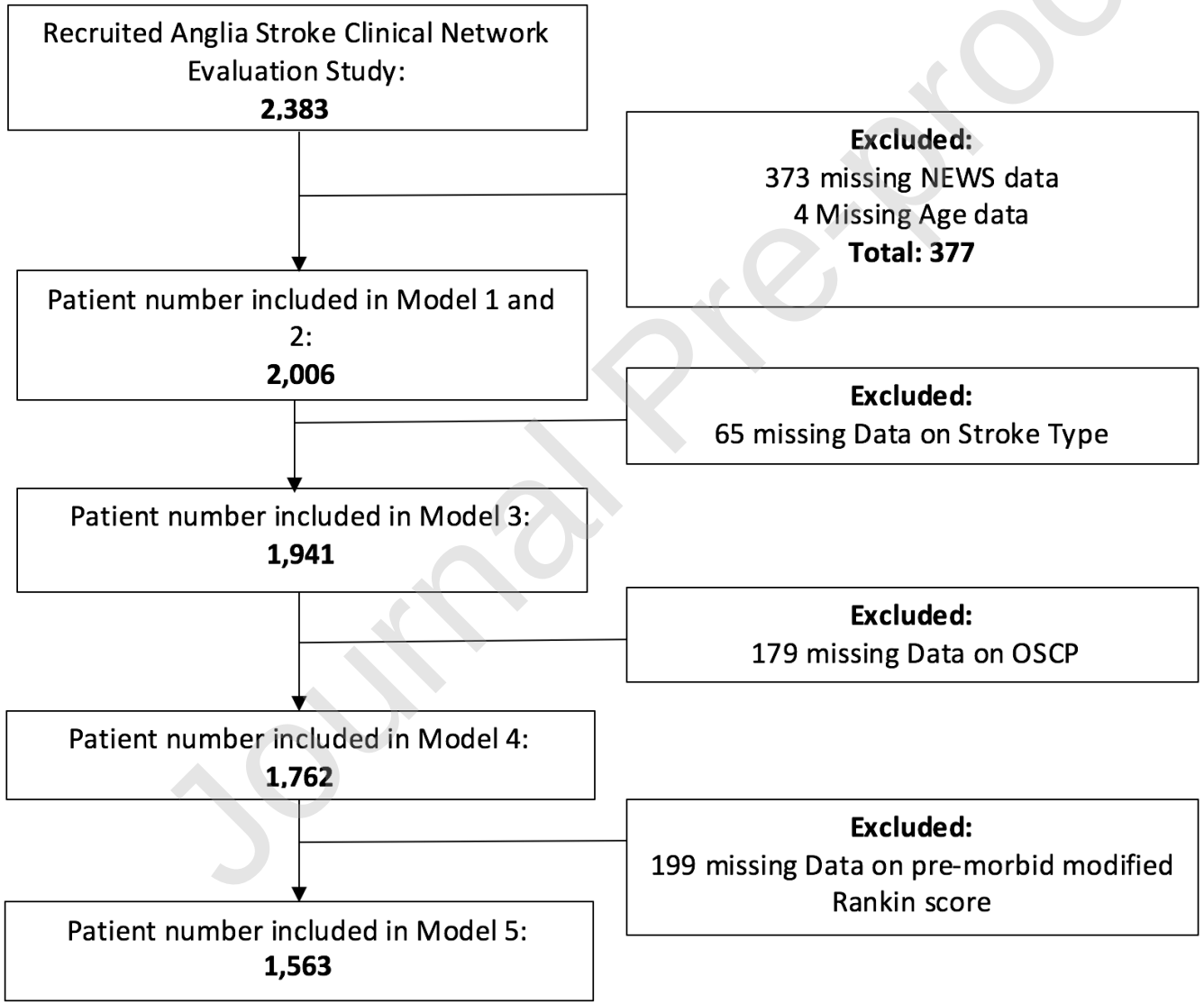

Figure 2: Cox proportional hazards models evaluating the association between admission MEWS category and mortality at 1 year in patients with acute stroke (fully adjusted).