Early Warning Scores in Pre-hospital and Emergency Care

Thesis

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Contents

Abstract IV
List of Abbreviations V
List of Tables VI
List of Figures VII
List of Accompanying Material VIII
Ethics and Information Governance VIII
Funding VIII
Published Papers IX
Published Abstracts and Conference Presentations X
Preface XI
Acknowledgements XII
Chapter 1 . National Early Warning Scores as a single marker in ED 1
Introduction 1
Background 3
Literature Review 4
Aims 5
Methods 6
Data collection 7
Definition of NEWS 8
Outcomes 10
Statistical Analysis 10
Results 10
Discussion 19
Conclusions of Part 1 21
Chapter 2 : Early Warning Scores in the pre-hospital environment 22
Introduction 22
Aims 24
Methods 24
Data Definitions 25
Results 26
Section 1. Performance of NEWS 28
Section 2. Performance of qSOFA versus NEWS 32

Discussion 40
Limitations 44
Conclusions of Part 2 45
Chapter 3 : PEWS in the pre-hospital environment 46
Introduction 46
Literature Review 46
Aims 48
Methods 48
Results 52
Discussion 58
Limitations 60
Conclusions of Part 3 62
Chapter 4 Modification of PEWS: qPEWS prediction of adverse outcome 63
Introduction 63
Literature Review 63
Aims 64
Methods 64
Results 65
Discussion 71
Limitations 74
Conclusions of Chapter 4 75
Chapter 5 Prehospital PEWS as a predictor of the need for hospital admission 76
Background 76
Literature Review 77
Aims 79
Methods 80
Results 80
Discussion 84
Limitations 86
Conclusions of Chapter 5 87
Chapter 6 Review of current literature and clinical practice 88
NEWS in the Emergency Department 88
Sepsis 89
Other condition specific use of NEWS in ED 90
All patients in ED 92

Wider in hospital setting 93
Non NEWS or enhanced NEWS scoring systems in ED 96
NEWS in the Pre-hospital setting 98
PEWS in the Pre-hospital setting 100
Chapter 7 Summary 103
Summary of theses 103
Impact of work 103
Future research 104
Reflection 105
Epilogue 105
Glossary 107
References 108

Abstract

Background: Early warning scores (EWS) are a composite, ordinal scale based on observed patient physiology values. Their original description was to be used in a hospital setting, as a method of tracking patient deterioration and triggering an appropriate response to a deteriorating patient.

The aim of this work is to describe whether an EWS taken at a single time point are useful tools to use in the pre-hospital and emergency hospital setting to identify patients at high risk of clinical deterioration.

Methods: Datasets covering national presentations to acute hospitals and single centre data were used. Datasets contained adult and paediatric data – National Early Warning Score (NEWS) was used for adults and Paediatric Early Warning Score (PEWS) was used for under 16 years of age. Models were constructed to test the utility of a single EWS, either pre-hospital or in the Emergency Department (ED), as a predictor of adverse outcome (death or ICU admission) or hospital admissions for paediatric patients.

Results: NEWS and PEWS have moderate to good predictive value for adverse outcome in a variety of settings. ED patients with sepsis AUROC 0.71 (95% CI 0.68 to 0.74), all adult ambulance patients AUROC 0.81 (95% CI 0.73-0.99), all paediatric ambulance patients AUROC 0.80 (95% CI 0.76 to 0.84). A modified qPEWS performs as well as PEWS. PEWS is not predictive of the need for hospital admission AUROC 0.62 (95% CI 0.61 - 0.63).

Conclusion: A single NEWS and PEWS in ED or the pre-hospital environment has the ability to predict patients at greater risk of deterioration and adverse outcome. A modified qPEWS may improve data collection without sacrificing predictive value. These results do not examine whether this association can be implemented to improve outcomes, and further prospective research is required in this area.

List of Abbreviations

EWS	Early Warning Score
ED	Emergency Department (hospital department)
EM	Emergency Medicine (medical specialty)
EMS	Emergency Medical Service
ICM	Intensive Care Medicine (medical specialty)
ICU	Intensive Care Unit
MET	Medical Emergency Team
NEWS	National Early Warning Score
NICE	National institute for Clinical Excellence
PEWS	Paediatric Early Warning Score
PHC	Pre Hospital Care
PPV	Positive Predictive Value
qSOFA	quick Sepsis related Organ Failure Assessment Score
RETTS	Rapid Emergency Triage and Treatment System
RRT	Rapid Response Team
SAS	Scottish Ambulance Service
SSC	Surviving Sepsis Campaign

List of Tables

Table 1-1. Participating Centres 6

Table 1-2 National Early Warning Score (NEWS) 9

Table 1-3 Median age and NEWS by gender, admission to ICU within two days, 30-day outcome and combined outcome (ICU and/or mortality)..... 12

Table 1-4 Age adjusted odds ratios for each NEWS category for (a) admission to ICU within two days (b) 30-day mortality (c) combined outcome (ICU and/or mortality). 13

Table 2-1. AUROC for mortality 28

Table 2-2 Risks of each outcome at each NEWS category. AR: Absolute risk, RR: relative risk, 95%CI: 95 % confidence interval of relative risk. 31

Table 2-3 Risks of each outcome at each NEWS category. AR: Absolute risk, RR: Relative risk, 95%: 95 % confidence interval of relative risk. 31

Table 2-4. Risk ratio of combined outcomes of ICU admission within 48 hours of presentation and or 30 day mortality, by NEWS category 33

Table 2-5. Risk ratio of combined outcomes of ICU admission within 48 hours of presentation and / or 30 day mortality, by qSOFA score 34

Table 2-6. Risk ratio admission to ICU within 48 hours, by NEWS category..... 36

Table 2-7. Risk ratio admission to ICU within 48 hours, by qSOFA score 36

Table 2-8. Risk ratio 30 day mortality, by NEWS category 38

Table 2-9. Risk ratio 30 day mortality, by qSOFA score..... 38

Table 3-1 Demographics of study population 53

Table 3-2 Multivariate analysis of primary outcome..... 56

Table 4-1 PEWS components combinations data capture rates 67

Table 4-2 Stepwise analysis of individual PEWS components 68

Table 4-4. The performance of different models for how variables recorded for 102,993 children transported by ambulance to hospital associated with subsequent admission to paediatric intensive care (48 h) or death (30 days). 71

Table 5-1 Youden's value for hospital admission by age..... 83

Table 6-1. Key recommendations from Gerry at al 2020 systematic review..... 95

List of Figures

Figure 1-1. Patient Inclusion Pathway 8

Figure 1-2 Frequency of NEWS (based on first set of observation taken in the Emergency Department) 11

Figure 1-3 NEWS and age adjusted NEWS receiver operating curve (ROC) for admission to ICU within two days. 15

Figure 1-4. NEWS and age adjusted NEWS receiver operating curve (ROC) for 30-mortality 16

Figure 1-5. NEWS and age adjusted NEWS receiver operating curve (ROC) for combined outcome (ICU and/or mortality). 17

Figure 1-6 NEWS receiver operating curve (ROC) characteristics for combined outcome (ICU and/or mortality). 18

Figure 2-1. Patient pathway into the study 27

Figure 2-2. Histogram of NEWS score 28

Figure 2-3 Receiver Operating Characteristic curves for mortality at 24, 48 hours, 7 and 30 days 29

Figure 2-4 ROC curves demonstrating prediction of 48hr mortality or ICU admission within 48hrs of presentation, both individually and as a combined outcome 30

Figure 2-5. Histogram of qSOFA scores 32

Figure 2-6. . ROC curves demonstrating prediction of combined outcomes of 30 day mortality and / or ICU admission within 48 hours of presentation 35

Figure 2-7. ROC curves demonstrating prediction of ICU admission within 48 hours of presentation 37

Figure 2-8. ROC curves demonstrating prediction of 30 day mortality 39

Figure 3-1. PEWS (Scotland) 49

Figure 3-2. Patient inclusion in the study 54

Figure 3-3 Histogram of PEWS (Scotland) 55

Figure 3-4. Area under Curve for PEWS (Scotland) total score 56

Figure 3-5. Sensitivity and Specificity of PEWS (Scotland) by PEWS value 57

Figure 4-1 . Percentage of value observed against age for all eight PEWS components 65

Figure 5-1 Proportion of patients admitted by age 81

Figure 5-2. Odds Ratio for hospital admission 81

Figure 5-3 AUROC for PEWS and PEWS Age 82

Figure 5-4 PEWS Score against total length of hospital stay 84

List of Accompanying Material

Ethics and Information Governance

No personally identifiable data is used and all data is collected as part of the routine operation of NHS services. Ethical approval was therefore not required for this research. All data was handled in accordance with the NHS Scotland Data Protection Policies. These data processes changed considerably during the time period covered by work undertaken as part of this thesis.

The data in chapter 1 were part of national audit data (Scottish Trauma Audit Group), and anonymised, aggregate use of these data was approved by the STAG Steering Group in 2012. The Caldicott Guardian for each participating Health Board was informed of the audit and the processes involved.

For data used in chapter 2 local Caldicott Guardian approval from the relevant health board (NHS Greater Glasgow & Clyde) was received in 2013.

For data used in Chapters 3, 4 and 5, ethical approval was not sought. Information Governance approval was sought through the Caldicott Guardian National Scrutiny Process for Scotland (ref 2015-23 VESPA), who approved the study design and the use of personal health data from multiple health boards in Scotland. Research & Development approval was also granted by NHS Greater Glasgow & Clyde Health Board (GN15AE477).

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Published Papers

These are the published works that form the basis for this thesis:

Corfield AR, Lees F, Zealley I et al. Early Warning Scores in Sepsis – Utility of a single EWS in the Emergency Department *Emerg Med J* 2014; **31:482**-487

Contribution – lead author, developed concept, designed study, interpreted results, drafts of manuscript, journal submission including revisions

Silcock DJ, Corfield AR, Gowens PA, Rooney KD. Validation of the National Early Warning Score in the prehospital setting. *Resuscitation* 2015; 89:31-35

Contribution – developed concept, designed study, interpreted results, drafts of manuscript, journal submission including revisions

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Corfield AR, Silcock D, Clerihew L. Paediatric early warning scores are predictors of adverse outcome in the pre-hospital setting: A national cohort study. *Resuscitation* 2018; 133; 153-159

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Corfield AR, Clerihew L, Staines H et al. The discrimination of quick Paediatric Early Warning Scores (qPEWS) in the pre-hospital setting. *Anaesthesia.* 2020 Mar; 75(3):353-358.

Contribution – lead author, developed concept, designed study, interpreted results, and drafts of manuscript

Corfield AR, Booth KL, Clerihew L, Staines H, Stewart E, Rooney KD. Association of out of hospital paediatric early warning score with need for hospital admission in a Scottish emergency ambulance population. *Eur J Emerg Med* 2020 27(6): 454-460

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Published Abstracts and Conference Presentations

Corfield AR, Fletcher G. The use of scoring systems to identify critically ill patients and potential impact on mortality of critically ill patients. *Resuscitation* 11(2) 2002; 55(1):81-2. Presented in moderated poster format at the 6th Scientific Congress of the European Resuscitation Council in Florence, October 2002.

Corfield AR et al. Early Warning Scores in Sepsis – utility of a single EWS in the Emergency Department. Presentation American College of Emergency Physicians October 2012. Published *Annals of Emergency Medicine* 2012; 60(4): S20

Corfield AR, Clerihew L, Staines H, Stewart E, Tough D, Rooney KR. A Quick Paediatric Early Warning Scores is Predictive of Adverse Outcome in an Out-of-Hospital Cohort of Unselected Ambulance Patients *Annals of Emergency Medicine* 2019; 74 (4), S53-S54

Preface

This thesis will examine the use of early warning scores (EWS) in the context of pre-hospital and emergency hospital settings. Early warning scores are a composite, ordinal scale based on observed patient physiology values. Their original description was to be used in a hospital setting, as a method of tracking patient deterioration and triggering an appropriate response to a deteriorating patient.

This thesis will aim to describe whether an EWS taken at a single time point are useful tools to use in the pre-hospital and emergency hospital setting to identify patients at high risk of clinical deterioration.

In Chapter 1, the use of NEWS will be examined in an in-hospital context, specifically in the Emergency Department. The association of a single NEWS value at presentation will be examined in relation to outcome in adult patients with sepsis.

In Chapter 2, having examined the utility of NEWS in hospital, the use of NEWS in the pre-hospital environment will be examined using the first single value of NEWS obtained. The association with adverse outcome in a more general adult population will be examined and NEWS will also be compared to qSOFA in this population.

In Chapter 3, EWS are examined in the paediatric population to examine whether PEWS is associated with adverse outcomes in the pre-hospital environment. Chapter 4 builds on this and an abbreviated PEWS (qPEWS) will be evaluated as a predictor of adverse outcome. Chapter 5 looks at a different outcome and examines the utility of PEWS for prediction of need for hospital admission. Chapter 6 summarises other current relevant literature especially that published since the publications that form the basis for this thesis.

At the conclusion of this thesis, a progression through the use of EWS in different contexts should result in clinically and operationally relevant results. This analysis should allow clinicians and NHS organisations to understand the validity of EWS in a pre-hospital and emergency hospital context, in adults and children.

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Author’s Declaration

This thesis, except where explicitly stated, is the result of my own work

This work has not been submitted previously for examination or degree at either the University of Glasgow or any other institution

Dr Alasdair R Corfield

Chapter 1 . National Early Warning Scores as a single marker in ED

Introduction

Patient deterioration often precedes in-hospital cardiac arrest. In up to 30% of in-hospital cardiac arrests, a physiological deterioration is seen in the hours prior to cardiac arrest. This pattern of physiological deterioration also is evident in the hours prior to unplanned intensive care unit admission. The two seminal publications (Hillman et al., 2002) (Kause et al., 2004) provided strong evidence of this. This realisation led to the development of a number of physiological scoring systems that attempted to quantify patient physiology using ordinal scoring systems.

There were many initial scoring systems developed, usually at a single hospital level or small group of hospitals. Almost all were based on patient physiological observations such as heart rate, blood pressure, respiration rate, oxygen saturation level and conscious level or Glasgow Coma Scale. The perceived benefit of a single scoring system was the ability to collect and codify a number of different physiological variables into a single score, allowing an easier way to define physiological abnormality. The scoring systems also gave a degree of objectivity to reporting physiological abnormality and appropriate weighting to the deviance of a single physiological parameter from normal values.

These physiological scoring systems became early warning scores, with stratified levels of risk, dependent on the cumulative score. The “early” part of early warning scores came into use as the EWS were then integrated with a structured response within hospital. The concept was that the EWS gave an objective score of the physiology of a patient becoming more unwell as a hospital in-patient. The use of the early warning score for hospital in-patients (either all in-patients or a subgroup) allowed an objective way to collectively track an individual patients physiological parameters. When an individual patients EWS reached a pre-determined level, this triggered a specific response. There was a stratified response with increasing levels of response as the EWS increases.

The top tier of the response was the use of a rapid response team (RRT) or medical emergency team (MET) to rapidly review the patient and formulate a management plan. Evidence from Bellomo et al (2004), Buist et al (2002) and Dacey et al (2007), in observational series, showed that the introduction of the system of care with a defined early warning scores and a structured response, was associated with improved clinical outcomes. These studies showed was that the impact was seen more in a reduction in unexpected cardiac arrests or unplanned intensive care admissions rather than absolute mortality. These studies were interpreted as showing that the use of EWS and RRT/MET impacts most on patients in whom resuscitation and/or organ support in a critical care environment is unlikely to give them benefit, usually due to the underlying disease process or other comorbidities. Whilst not preventing excess mortality, this is a positive development ensuring that patients are not subject to unnecessary or futile interventions, from which they will derive no benefit.

This proof of concept of EWS and a structured response had an issue in that there were still many different versions of EWS in use throughout the UK, and globally. A piece of work led by the Royal College of Physicians (2012) and the National Health Service led to the development of a unified National Early Warning Score (NEWS) which is currently implemented in acute hospitals across the UK. NEWS has been shown to be able to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death in a UK in-hospital population (Smith et al, 2013).

NEWS was implemented as an in-hospital tool, where a diagnosis had been made and a course of treatment had already been started. The evidence from NEWS supported its use as a “track and trigger” tool for hospital in-patients over a period of hours or days, to allow early identification of deteriorating patients and timely intervention for those patients.

Uncertainty exists as to the applicability of the NEWS to other settings, particularly the Emergency Department (ED) setting, where scores would be derived prior to the

institution of any treatment, or very early on in the course of treatment, and often when there is significant diagnostic dilemma. If NEWS were a valid tool in these environments, then decision about escalation of care, treatments, likely clinical course and patient destination could be made whilst the diagnostic pathway is running in parallel.

Background

Sepsis results from overwhelming reactions to microbial infections where the immune system initiates dysregulated responses that lead to remote organ dysfunction, shock and ultimately death. Sepsis remains a significant global health issue (Fleischmann et al, 2015) – as well as direct mortality, survivors suffer long term reductions in patient centered outcomes, with reduced quality of life and functional status (Shankar-Hari et al, 2016). Patients with hypotension and organ hypoperfusion as a result of sepsis have poorer outcomes with mortality of 30-40% (Singer et al, 2016). Early sepsis management is likely to contribute to improved long-term outcomes, by reducing inflammation, endothelial dysfunction, immune suppression, and organ dysfunction.

At the time of the first piece of work in this thesis in 2012, sepsis was defined in terms of a systemic inflammatory response syndrome (SIRS). Sepsis was defined as SIRS in response to a bacterial infection. The components of SIRS were:

- Body temperature less than 36 °C (96.8 °F) or greater than 38 °C (100.4 °F)
- Heart rate greater than 90 beats per minute
- Tachypnoea (high respiratory rate), with greater than 20 breaths per minute; or, an arterial partial pressure of carbon dioxide less than 4.3 kPa (32 mmHg)
- White blood cell count less than 4000 cells/mm^3 (4 x 10^9 cells/L) or greater than 12,000 cells/mm^3 (12 x 10^9 cells/L); or the presence of greater than 10% immature neutrophils (band forms). Band forms greater than 3% is called bandemia or a "left-shift."

The original consensus guidelines on the management of sepsis were published by the Surviving Sepsis Campaign in 2003. From these guidelines onwards through

multiple iterations of UK and international guidelines, an important element in improving the care of patients with sepsis is early identification and early intervention, which has been shown to improve outcomes.

Literature Review

As outlined in the previous section, EWS and then NEWS have been shown to be a useful in-hospital tool to identify deteriorating patients at an early stage and prevent unexpected cardiac arrest and admission to critical care.

Even as EWS were being developed, there was a realisation and interest in the performance of EWS at the front door of a hospital in the Emergency Department (Rees and Mann, 2004). However there remained significant controversy about the validity and clinical usefulness of EWS in the Emergency Department. Data from the Netherlands (Groake et al, 2008) showed that a single EWS on presentation to hospital had utility in predicting patients at risk of adverse outcomes. This was a small single centre study of 225 patients, but showed that the concept of using a single value at presentation, rather than serial measurement, had potential clinical usefulness.

The combination of a condition such as sepsis, which has a potential time critical element of benefit to identification and treatment along with a potential tool in EWS, led to a further study from study from the Netherlands (Vorwerk et al, 2008). This was another single centre study of 307 patients, which showed that a higher EWS was associated with a higher 28 day mortality. The EWS used however was not just based on physiology, including variables such as nursing home resident, a "terminal illness" diagnosis and platelet count.

Further data was published (Burch et al, 2008) on the use of early warning scores in the Emergency Department. This was a single centre study based on a population in Emergency Department in South Africa, with 790 patients. This showed that increasing EWS was associated with increased in-hospital mortality. In this study, the EWS used was based on five immediately available physiological parameters –

pulse rate, systolic blood pressure, respiratory rate, temperature and level of consciousness.

At the time of the publication of these data in 2012, there were no other studies looking at early warning scores in the Emergency Department adult population with sepsis.

The benefit of EWS based on physiology is that they can be calculated at the bedside immediately and are not dependent on other information such as social factors or laboratory values. The national adoption of NEWS in the UK in 2012, along with the need for better identification of patients with sepsis, led to the first study in this thesis

Aims

In this first study, the aim was to evaluate an early warning score in a national cohort of patients with sepsis presenting to EDs, to determine whether a single EWS in the ED was a useful predictor of outcome, either death or ICU admission.

Methods

Study population

Data were collected over a three month period between March and May 2009 as part of the Scottish Trauma Audit Group (STAG) Sepsis Audit. 20 of the 25 mainland district general and teaching hospital EDs in Scotland participated in audit (Table 1-0-1).

Table 1-0-1. Participating Centres

Name	Town / City	Urban / Rural
Aberdeen Royal infirmary	Aberdeen	Mixed
Ayr Hospital	Ayr	Mixed
Crosshouse Hospital	Kilmarnock	Mixed
Dumfries and Galloway Royal Infirmary	Dumfries	Rural
Glasgow Royal Infirmary	Glasgow	Urban
Hairmyres Hospital	East Kilbride	Urban
Inverclyde Royal Hospital	Greenock	Urban
Monklands Hospital	Airdrie	Urban
Ninewells Hospital	Dundee	Mixed
Perth Royal Infirmary	Perth	Mixed
Queen Margaret Hospital	Dunfermline	Mixed
Raigmore Hospital	Inverness	Rural
Royal Alexandra Hospital	Paisley	Urban
Royal Infirmary of Edinburgh	Edinburgh	Urban
Southern General Hospital	Glasgow	Urban
Stirling Royal infirmary	Stirling	Mixed
Victoria Infirmary	Glasgow	Urban
Victoria Hospital	Kirkcaldy	Mixed
Western Infirmary	Glasgow	Urban
Wishaw General Hospital	Wishaw	Mixed

Adult patients (>16 years) attending as an emergency were identified prospectively from ED or Admission Unit records. Hospital information systems were then interrogated to ascertain whether the patient had an inpatient stay of at least two days. Patients who died within the first two days, and who therefore may have been omitted from data collection, were identified retrospectively using General Register Office Scotland records. Patients who had an obviously non-infective cause for attendance such as acute cardiac ischaemia, trauma or stroke were excluded. This process identified 27,046 patients who required case note review in order to determine the presence of 'Sepsis' criteria. The definition used was the 2008 Surviving Sepsis Campaign guidelines, based on SIRS. Patients were included in the audit if they had (a) a suspicion or confirmation of infection within two days of attendance and (b) two or more of the following physiological derangements: temperature >38.3˚C or < 36˚C˚; heart rate > 90bpm; respiratory rate > 20/min; white cell count of >12000/μL or < 4000/μL or >10% immature forms; acutely altered mental status; systolic blood pressure <90mmHg; blood glucose >7.7mmol/L (in the absence of diabetes).

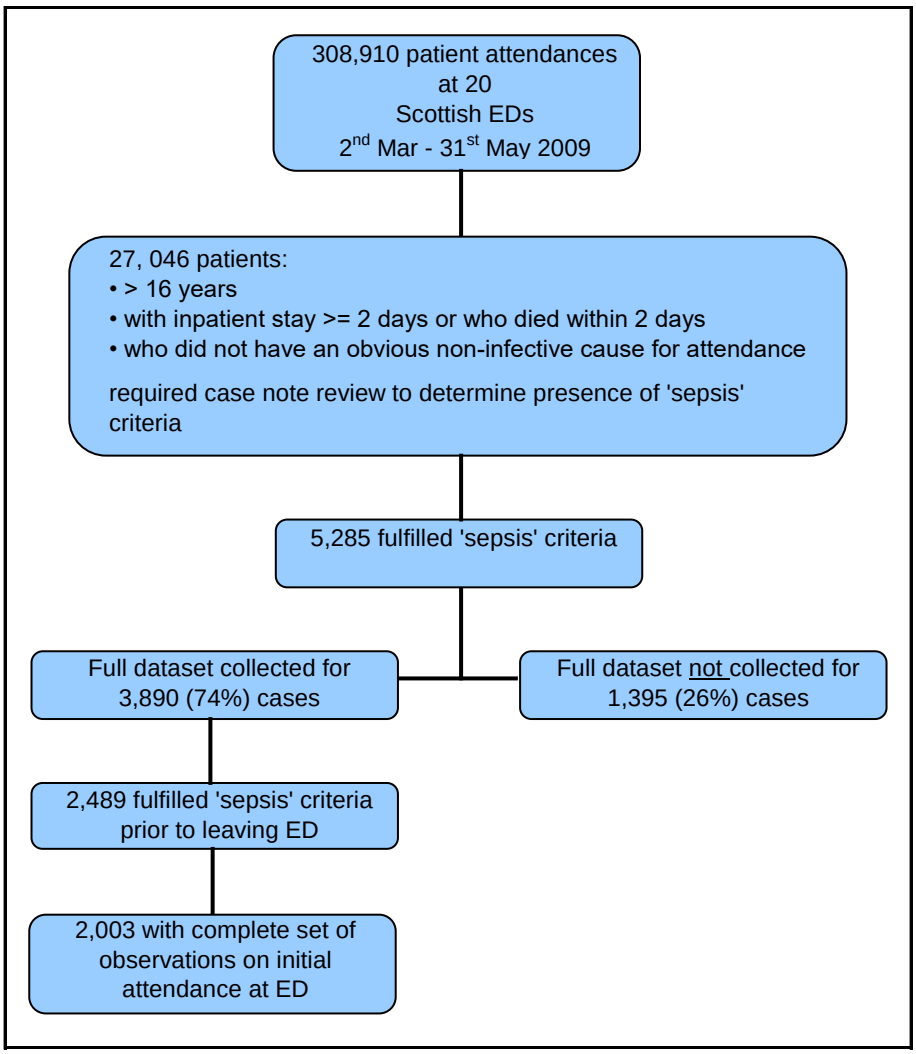
Data collection

A total of 5,285 patients fulfilled the entry criteria. Data were collected retrospectively by Local Audit Coordinators at each hospital on a variety of demographic, physiological, process and outcome variables using a standardised proforma. Where available, patient observations taken on attendance were recorded. All patients were followed to discharge or death. The difficulties encountered in obtaining and extracting data from case notes were such that a pragmatic decision was taken to stop data collection in July 2010.

Of the 5,285 patients identified, complete data were collected for 3,890 (74%). Age, gender, length of stay, critical care attendance and outcome were recorded for all patients who met the sepsis criteria (N=5,285). For each of these variables, the sample population (N=3890) was representative. For the purposes of this analysis, only patients who presented with or developed signs of sepsis prior to leaving ED were included (N=2,489). In this sample of 2489 patients, patients were

excluded if they did not have a full set of observations made as part of their first set of observations. This resulted in a final sample size of 2,003 patients (Figure 1-1)

Figure 1-1. Patient Inclusion Pathway



Definition of NEWS

The National Early Warning Score (NEWS) contains six physiological parameters (Table 1-2), each of which is assigned a value of between 0 and 3 along with an additional parameter for supplemental oxygen, which scores 0 or 2. The score for each of the seven parameters is summed to calculate the NEWS which may range between 0 and 20; the higher the score the greater the deviation from normality.

Table 1-0-2 National Early Warning Score (NEWS)

	NHS Early Warning Score						
	3	2	1	0	1	2	3
Respiration Rate	≤8		9-11	12-20		21-24	≥25
Oxygen Saturations	≤91	92-93	94-95	≥96			
Supplemental Oxygen		Yes		No			
Temperature	≤35°		35.1-36°	36.1-38°	38.1-39°	≥39.1°	
Systolic Blood Pressure	≤90	91-100	101-110	111-219			≥220
Pulse	≤40		41-50	51-90	91-110	111-130	≥131
Conscious Level				A			V,P,U

Observations taken on attendance were used to calculate the NEWS. For some analyses patients were divided into four categories based on their total score: 0-4, 5-6, 7-8, 9-20. This analysis grouping was based on the distribution of NEWS scores to give 4 approximately equal sized groups for comparison.

In order to assess the effect of age on all outcomes an age adjusted NEWS was also calculated (+0 points for < 50 years, +2 points for 50-70 years, +3 points for > 70 years).

The NEWS uses an AVPU (Alert, Voice, Pain, Unresponsive) score to define the patient's level of consciousness. Where an AVPU score was unavailable, GCS was considered to be an acceptable alternative (GCS 15 = A, GCS < 15 = V,P,U).

Outcomes

Primary outcomes were Intensive Care Unit (ICU) admission within two days of attendance and 30-day mortality (in hospital). A combined outcome of ICU admission and/or mortality was also assessed.

Statistical Analysis

All analyses were carried out using SPSS 17.0 for MS Windows.

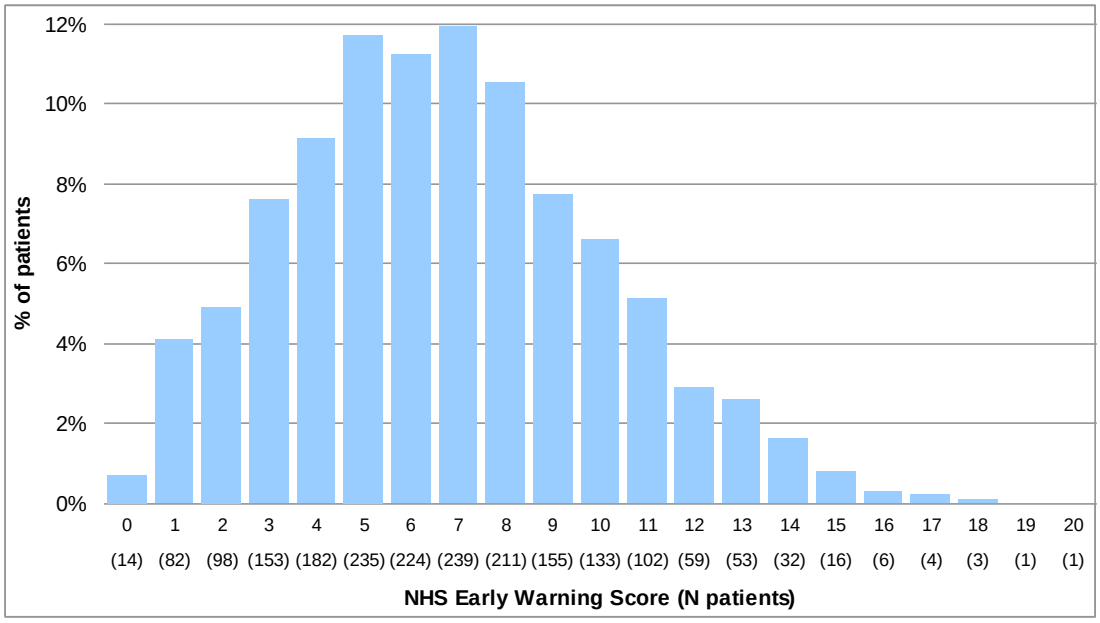
Differences between medians were tested using the Mann–Whitney *U* test. Odds ratios for each outcome were estimated using logistic regression, with NEWS group as the independent variable and age as a continuous covariate. Receiver operating characteristic (ROC) curves plotting sensitivity (true positives) against 1-specificity (false positives) were used to measure the accuracy of NEWS and age adjusted NEWS in predicting outcome. The associated ROC area under the curve was also calculated for each outcome.

Statistical significance was set at $p<0.05$ for all analyses. All results are reported along with their associated 95% confidence intervals and *p* value.

Results

2,003 patients were available for analysis; 949 (47%) were male and 1,054 (53%) female. The median age of patients was 72 years, with no significant difference in age between males and females. The Median NEWS for all patients was seven; there was no significant difference between males and females. The distribution of NEWS recorded for patients on attendance is illustrated in Figure 1-2

Figure 1-2 Frequency of NEWS (based on first set of observation taken in the Emergency Department)



Differences in age and NEWS for each outcome are shown in Table 1-0-3. Patients who were admitted to ICU within two days of attendance had a median age of 61 and were significantly younger than those who were not (61 vs. 72, $p<0.05$). ICU patients also had a significantly higher NEWS than the non-ICU group (9 vs. 6, $p<0.05$). Patients who died within 30 days were significantly older than those who did not (77 vs. 70, $p<0.05$) and had a higher NEWS (9 vs. 6, $p<0.05$).

Table 1-0-3 Median age and NEWS by gender, admission to ICU within two days, 30-day outcome and combined outcome (ICU and/or mortality).

		n	%	Patient age			NEWS		
				Median	IQR	*P*	Median	IQR	*P*
All patients	-	2003	100%	72	59-81	-	7	4 - 9	-
Gender	Male	949	47%	71	59 - 79	0.08	7	4 - 9	0.13
	Female	1054	53%	72	59 - 82		6	4 - 9	
ICU (within two days)	No ICU	1890	94%	72	59 - 81	0.00	6	4 - 9	0.00
	ICU	113	6%	61	49 - 70		9	6 - 12	
Outcome (30 days)	Alive	1706	85%	70	57 - 80	0.00	6	4 - 8	0.00
	Dead	297	15%	77	69 - 85		9	6 - 12	
Combined (ICU and/or mortality)	No	1627	81%	71	58 - 80	0.00	6	4 - 8	0.00
	Yes	376	19%	74	63 - 83		9	6 - 12	

Each rise in NEWS category was associated with an increased risk of mortality when compared to the lowest category (0-4) (5-6: OR 1.95, 95% CI 1.21-3.14) (7-8: OR 2.26, 95% CI 1.42-3.61) (9-20: OR 5.64, 95% CI 3.70-8.60). This was also the case for the combined outcome (ICU and/or mortality) (5-6: OR 1.72, 95% CI 1.14-2.60) (7-8: OR 2.17, 95% CI 1.45-3.25) (9-20: OR 5.78, 95% CI 4.02-8.31). Patients with a NEWS of 5-6 were not associated with an increased risk in ICU admission when compared to those with a NEWS of 0-4, but patients with a NEWS of 7-8 or 9-20 were (7-8: OR 2.01, 95% CI 1.02-3.97) (9-20: OR 5.76, 95% CI 3.22-10.31).

Given that age is an independent predictor of ICU admission within 48 hours and 30 day mortality, age adjusted vales of NEWS were calculated. Age adjusted odds ratios were estimated for each NEWS category are shown in Table 1-0-4

Table 1-0-4 Age adjusted odds ratios for each NEWS category for (a) admission to ICU within two days (b) 30-day mortality (c) combined outcome (ICU and/or mortality).

Variable	Reference Group	Level	*P*	Odds Ratio	95% C.I.	
					Lower	Upper
(a) ICU (within two days)						
Age (continuous covariate)			<0.01	0.96	0.95	0.97
NEWS category	0 - 4		<0.01			
		5 - 6	0.59	1.22	0.59	2.54
		7 - 8	0.04	2.01	1.02	3.97
		9 - 20	0.00	5.76	3.22	10.31
(b) Mortality (30 days)						
Age (continuous covariate)			<0.01	1.04	1.03	1.05
NEWS category	0 - 4		<0.01			
		5 - 6	0.01	1.95	1.21	3.14
		7 - 8	<0.01	2.26	1.42	3.61
		9 - 20	<0.01	5.64	3.70	8.60
(c) Combined (ICU and/or mortality)						
Age (continuous covariate)			0.01	1.01	1.00	1.02
NEWS category	0 - 4		<0.01			
		5 - 6	0.01	1.72	1.14	2.60
		7 - 8	<0.01	2.17	1.45	3.25
		9 - 20	<0.01	5.78	4.02	8.31

Patients aged 50-70 years were significantly more at risk of dying within 30-days than patients aged <50 (OR 5.38, 95% CI 2.56-11.29), as were patients aged >70 (OR 9.42, 95% CI 4.60-19.32).

ROC curves plotting sensitivity (true positives) against 1-specificity (false positives) were used to measure the accuracy of NEWS and age adjusted NEWS in predicting ICU admission within 48 hours (Figure 1-3), 30 day mortality (Figure 1-4) and a combined outcome of ICU admission within 48 hours and/or 30 day mortality (Figure 1-5).

With regard to ICU admission within 48 hours of ED presentation, adjusting the NEWS for age decreased the area under the curve from 0.67 to 0.61. Adjusting for age had little effect on the combined end point of ICU/mortality (0.71 vs. 0.70). When using the NEWS to predict 30-day mortality, the area under the curve was increased from 0.70 to 0.73 by adjusting for age, but this increase was not significant.

Figure 1-3 NEWS and age adjusted NEWS receiver operating curve (ROC) for admission to ICU within two days.

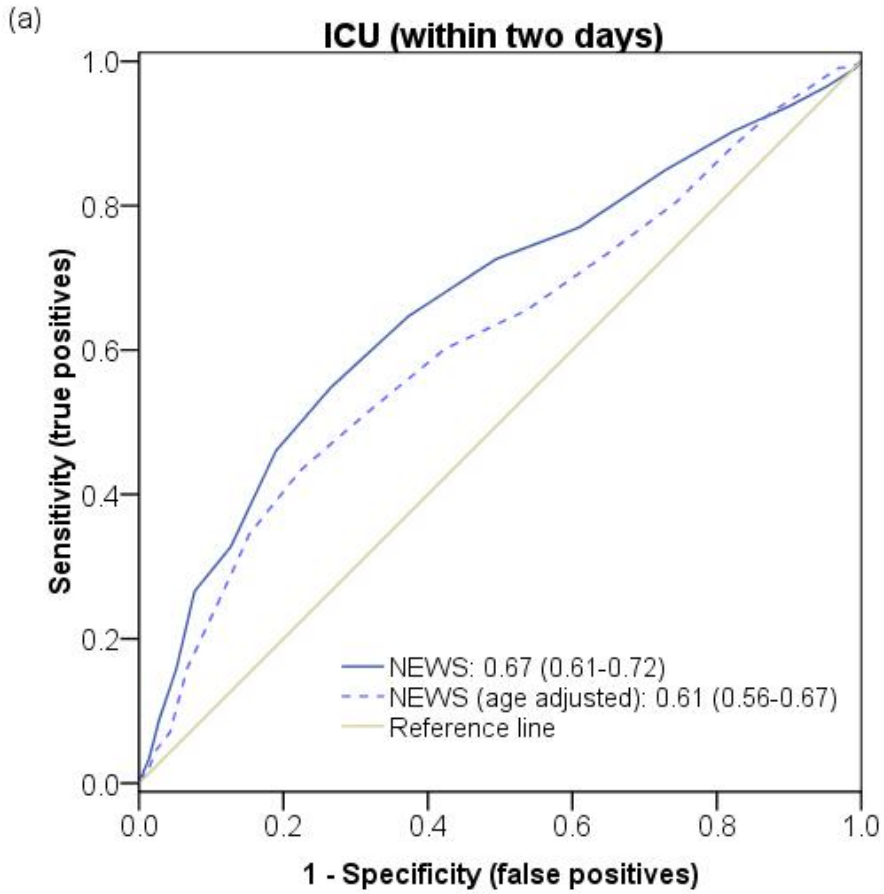


Figure 1-4. NEWS and age adjusted NEWS receiver operating curve (ROC) for 30-mortality

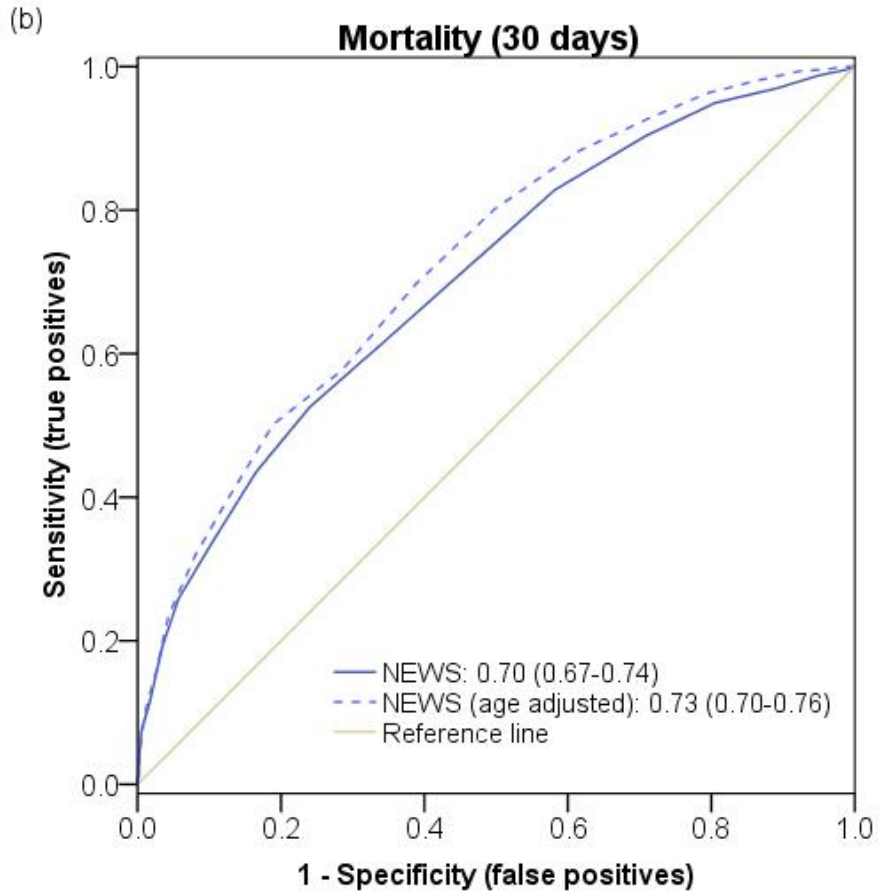
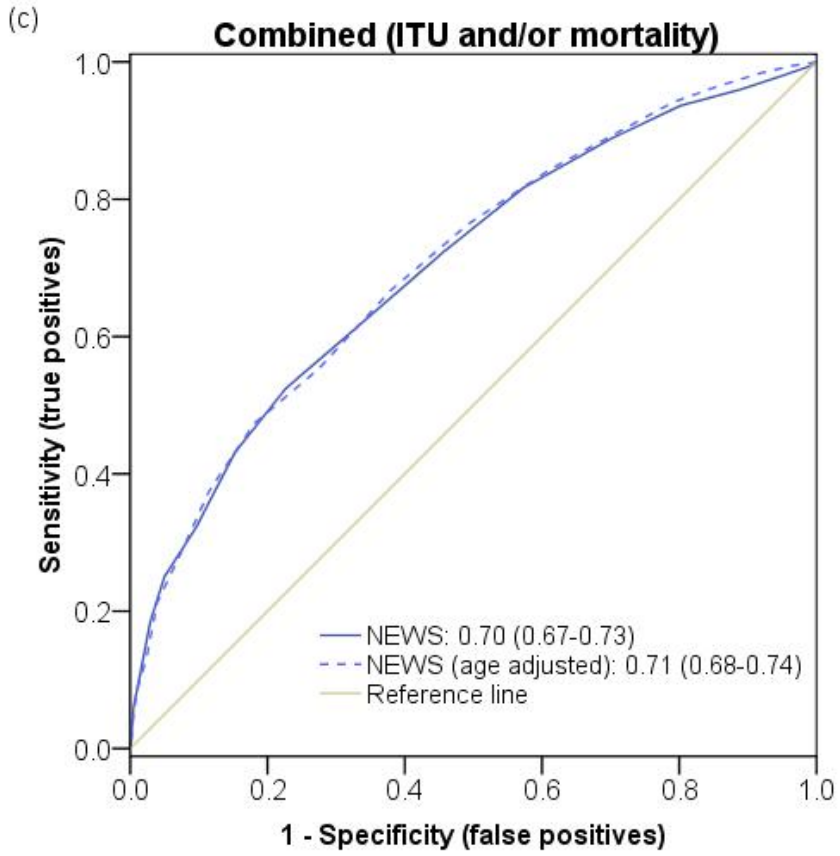


Figure 1-5. NEWS and age adjusted NEWS receiver operating curve (ROC) for combined outcome (ICU and/or mortality).



NEWS receiver operating curve (ROC) characteristics for the combined outcome of ICU and/or mortality are presented in Figure 1-5. The positive predictive value illustrates that 27% of patients with a NEWS of 7 or more were admitted to ICU within two days and/or died within 30 days. The optimal value of Youden's Index is a NEWS of 9. At this level 35% of patients were admitted to ICU within 48 hours and/or died within 30 days.

Table 1-4. NEWS receiver operating curve (ROC) characteristics for combined outcome (ICU and/or mortality).

NEWS >=	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Youden's Index
0	1.000	0.000	0.188	-	0.000
1	0.995	0.007	0.188	0.857	0.002
2	0.979	0.054	0.193	0.917	0.033
3	0.960	0.110	0.200	0.923	0.070
4	0.936	0.199	0.213	0.931	0.135
5	0.888	0.299	0.227	0.921	0.188
6	0.816	0.427	0.248	0.910	0.244
7	0.723	0.543	0.268	0.895	0.267
8	0.617	0.666	0.299	0.883	0.283
9	0.524	0.774	0.349	0.876	0.298
10	0.431	0.848	0.395	0.866	0.278
11	0.322	0.904	0.437	0.852	0.226
12	0.250	0.950	0.537	0.846	0.200
13	0.184	0.971	0.595	0.837	0.155
14	0.106	0.986	0.635	0.827	0.092
15	0.061	0.995	0.742	0.821	0.056
16	0.029	0.998	0.733	0.816	0.027
17	0.016	0.998	0.667	0.814	0.014
18	0.008	0.999	0.600	0.813	0.007
19	0.005	1.000	1.000	0.813	0.005
20	0.003	1.000	1.000	0.813	0.003

Discussion

Main findings

The data from this piece of work show that single NEWS in the Emergency Department for patients with sepsis has a moderate predictive value for adverse outcome. This is the first piece of work to look at this direct question. It is also one of the first studies to examine the NEWS as a tool.

Interpretation

The initial hypothesis was that a single NEWS was associated with adverse outcome in Emergency Department patients with sepsis, and the findings are compatible with this.

Implications

Previous research

Systems for the triaging of patients are well established in Emergency Medicine. The concept of triage dates back to the early 1800s, and at its core is the assessment of a patient by an experienced person to determine the priority and timescale of treatment and intervention based upon the severity of their condition. Over the years the concept of triage has become more scientific and a variety of tools utilising physiological data and algorithms have been developed to assist with effective triage. Previous use of early warning scores has focussed on serial measurements within an in hospital setting, rather than single values.

As outlined in the introduction, there have been previous single centres studies looking at the use of early warning scores in the Emergency Department. This is the first study that looks at multicentre data.

Practical implications and significance

Data published by Griffiths and Kidney (2012) at the time of the publication of these data, looked at the use of EWS across all UK Emergency Departments. At the time, there were 254 EDs that were surveyed, with results obtained from 145 giving a response rate of 57%. Despite this low response rate, 80% of respondents reported

they were using EWS in ED. Amongst the respondents there was strong support of EWS with 93% supporting the use of EWS in ED. This suggests that despite an evidence base lacking high quality studies, the use of EWS was already widespread and supported by the majority of ED staff.

Rotation of junior medical and nursing staff and lack of familiarity with local EWS had the potential for confusion and the introduction of the NEWS across the UK gave a single system to use, replacing large numbers of local variants of EWS.

The high sensitivity achieved with low values of NEWS (less than two) suggest that there may be utility for NEWS to be used as a rule out tool. However this would need to be clarified with further prospective work.

Limitations

This study has several potential limitations. Data were collected retrospectively which has the potential to introduce bias. Although 5,285 patients met the criteria for inclusion in the study, complete demographic data on 2,489 patients were able to be collected. Amongst this group of patients selected for this analysis (N=2,489) only 2,003 could be assessed due to missing observations on attendance. This missing information was generally only one or two of the six required physiological data points, but prevented an accurate calculation of a NEWS value. I did not attempt to impute missing data. No information is available for patients who attended and were discharged within two days of attendance. This group should by virtue of the fact that they are discharged within two days have a much lower incidence of significant illness. These data only included ICU admission within two days so I are unable to comment on patients who may have been admitted to ICU later in their hospital admission. However, for the target group of ED patients at presentation it could be argued that ICU admission more than two days after ED attendance is less linked to features of illness present at initial ED presentation.

The study only collected information on in-hospital mortality. No attempt was made to follow-up patients after discharge from hospital so any patients who were

discharged and died at home within 30 days are not included in these data. This study did not record any information on patients' comorbidity.

This patient population is representative of a UK Emergency Department population, with data collected from 20 different Scottish Emergency Departments, representing a wide spectrum of urban and rural populations, across a wide geographical area and including departments of varying size. I would therefore argue that the results are externally valid in that the population we sampled from is representative of the wider population of interest.

Conclusions of Part 1

The data presented in this study shows there is promise for the use of a single EWS in the ED, when applied to a large cohort of patients with a potentially serious condition. Amongst patients who have sepsis, a single EWS of 7 or above in the ED indicates a 27% chance of requiring admission to ICU within 48 hours and/or death within 30 days. At this level, an argument can be made for mandating senior ED clinical review for all these patients. In addition there could also be an argument for mandatory review by a critical care outreach team, regardless of ultimate destination. This study only looked at patients with sepsis, so the generalisability to other serious conditions is unknown. However given that sepsis is a common condition with potential significant morbidity and mortality but that also has a heterogeneous presentation; it does suggest that this approach may be more widely applicable and this potential warrants further research.

This concept also lends itself to extension to prehospital care and ambulance services. Most ambulance services routinely collect the physiological data required to calculate an EWS score and indeed some ambulance services have incorporated this into electronic patient record forms. An agreed EWS score of greater than a specific level could be used as a trigger for ambulance service pre-alert of a receiving Emergency Department.

Chapter 2 : Early Warning Scores in the pre-hospital environment

Introduction

Chapter 1 explored the potential for a single EWS value in the Emergency Department, and whether it was predictive of adverse outcome in a population of patients with sepsis. Early intervention and correction of physiological abnormality improves patient outcomes and this is highlighted in guidance from The Surviving Sepsis Campaign (SSC) and the National Institute for Clinical Excellence (NICE). The use of NEWS is a standardised way of detecting physiological abnormality and can be used to trigger pre-determined responses and escalation in clinical treatment.

Beyond care of patients with sepsis, early intervention and initiation of treatment has been shown to be of benefit in a number of acute presentations such as ST elevation myocardial infarction and trauma. This response is also time critical as well, in that earlier initiation of treatment confers greater benefit. There is therefore theoretical benefit to earlier identification of critically ill or injured patients to allow earlier response to deranged physiological parameters. Contact with the emergency services, which in the UK is ambulance services, is the first point where physiological parameters are routinely measured and NEWS measurement could be instituted.

The use of NEWS in the prehospital setting also remains controversial, partly due to lack of evidence. As the development of NEWS involved analysis of clinical observations in hospital inpatients, where often a diagnosis has been made and a course of treatment had already been started. Uncertainty exists as to the applicability of the NEWS to other settings, particularly the prehospital setting, where scores would be derived prior to a clear diagnosis and the institution of any treatment. In this situation the score may contribute to deciding whether a patient requires transfer to hospital or would be used as a triage aid, both of which roles differ slightly from the track and trigger (of a clinical review) role for which NEWS was originally intended.

The NEWS was based on the earlier ViEWS (VitalPAC Early Warning Score) developed in Portsmouth and stratifies patients into risk categories based on observed heart rate, respiratory rate, systolic blood pressure, arterial oxygen saturation, temperature, and conscious level; plus an additional weighting if the patient is being given oxygen therapy. Patients are then risk stratified based on the resulting aggregate score into low, medium, and high risk groups. Patients with a low aggregate score but who score in the highest category for any single observation are classified as at least medium risk.

Chapter 1 has shown potential utility for a single NEWS value in hospital Emergency Departments or in the pre-hospital phase, in predicting patients at high risk of deterioration. However other composite, ordinal scoring systems are in use.

qSOFA (quick Sepsis related Organ Failure Assessment Score) is a bedside prompt that may identify patients with suspected infection who are at greater risk of a poor outcome outside the intensive care unit (Shankar-Hari et al , 2016). qSOFA has been incorporated into consensus definitions for the assessment of clinical criteria for sepsis and the consensus task force suggested that qSOFA criteria be used "*to prompt clinicians to further investigate for organ dysfunction, to initiate or escalate therapy as appropriate, and to consider referral to critical care or increase the frequency of monitoring*". They considered that positive qSOFA criteria should also prompt consideration of possible infection in patients not previously recognised as infected. The derivation and validation cohorts for qSOFA included the pre-hospital phase of the patient journey. As the data were extracted from mainly United States of America (US) databases, the consensus task force recommended prospective validation in multiple US and non-US health care settings to determine its robustness and potential for incorporation into future iterations of the definitions. It was also felt that due to the simplicity of qSOFA, it may be particularly relevant in resource limited settings where laboratory data are not readily available, and where the literature about sepsis epidemiology is sparse.

Comparison of the performance of NEWS and qSOFA at detecting patients with sepsis at risk of adverse outcomes in an ED and ward setting of a single US centre has recently been published (Singer et al, 2016), and this revealed some disparity in

utility between the various scores used. A further study in the Emergency Department of a Norwegian Hospital (Churpek et al., 2017) revealed that qSOFA was worse than Rapid Emergency Triage and Treatment System (RETTS) in predicting severe sepsis and mortality. Finally, a study from Missouri (Askim et al 2017) in the US showed that qSOFA had a poor sensitivity for pre-hospital identification of severe sepsis and septic shock.

In the pre-hospital environment, patients are less well differentiated than in the ED, and in ED they are less well differentiated than in wards or ICU. As such, comparison could be made between the pre-hospital environment and resource limited settings. Given this fact, this study aimed to look at the performance of NEWS and qSOFA at predicting subsequent adverse outcome across an entire cohort of undifferentiated patients presenting to ED via the ambulance

Aims

This study, based in a large district general hospital in Paisley, on the western edge of the Greater Glasgow metropolitan area, Scotland, aimed to evaluate the performance of the NEWS and qSOFA in identifying unselected patients at risk of death or deterioration in the pre-hospital setting.

Methods

Details of all emergency ambulance crews dispatched with an intention to transfer to the Royal Alexandra Hospital (RAH) were obtained from the Scottish Ambulance Service data warehouse, along with details of demographics, initial patient presenting complaint, and clinical observations obtained from the ambulances' electronic patient record forms (ePRF). These were matched to a list of patients presenting to the Emergency Department of the RAH to obtain details related to the patients' hospital admissions. Patients aged less than 16 years and patients known to be pregnant were excluded, along with patients transferred from other hospitals (as these were, by definition, not from the pre-hospital setting). NEWS and qSOFA values were calculated retrospectively from the supplied clinical data. This was a retrospective cohort study over a 2-month consecutive period between October 1st and November 30th, 2012 using a convenience sample of consecutive patients.

Ambulance diversion protocols were in place to transfer patients with ST-elevation Myocardial Infarction direct to the local primary Percutaneous Coronary Intervention centre, and pregnant women in labour were diverted to the nearby maternity hospital. All other patients, including those following major trauma, were transported to the RAH.

From the identified records, information regarding discharge status, and admission to intensive care units was obtained from hospital computer systems. Clinical observations taken by ambulance personnel were obtained from the electronic patient record, and the first complete set of clinical observations used for analysis. Where a complete set had not been taken simultaneously, the first recorded value for each clinical observation was used to construct an observation set.

From the identified records, information regarding length of stay, discharge status, and admission to intensive care and high dependency units was obtained from hospital computer systems. A number of patient outcomes were identified for study – these being:

Mortality at 24 hours, 48 hours, 7 days and 30 days

ICU admission within 48 hours

A composite adverse outcome of ICU admission within 48 hours and/or death within 30 days

Data Definitions

qSOFA is scored from zero to three. One point is assigned for each of low systolic blood pressure (SBP≤100 mmHg), high respiratory rate (≥22 breaths per min), or altered mentation (Glasgow Coma Scale <15).

As described in Chapter 1, NEWS is scored from zero to twenty. Each parameter (heart rate, respiratory rate, systolic blood pressure, arterial oxygen saturation, temperature, and conscious level) can score from zero to three. An additional weighting of two is added if the patient is being delivered oxygen therapy. As well as total NEWS, categorisation of NEWS into low (total score less than or equal to 4 and no individual component score 3), medium (total score 5-6 or any component

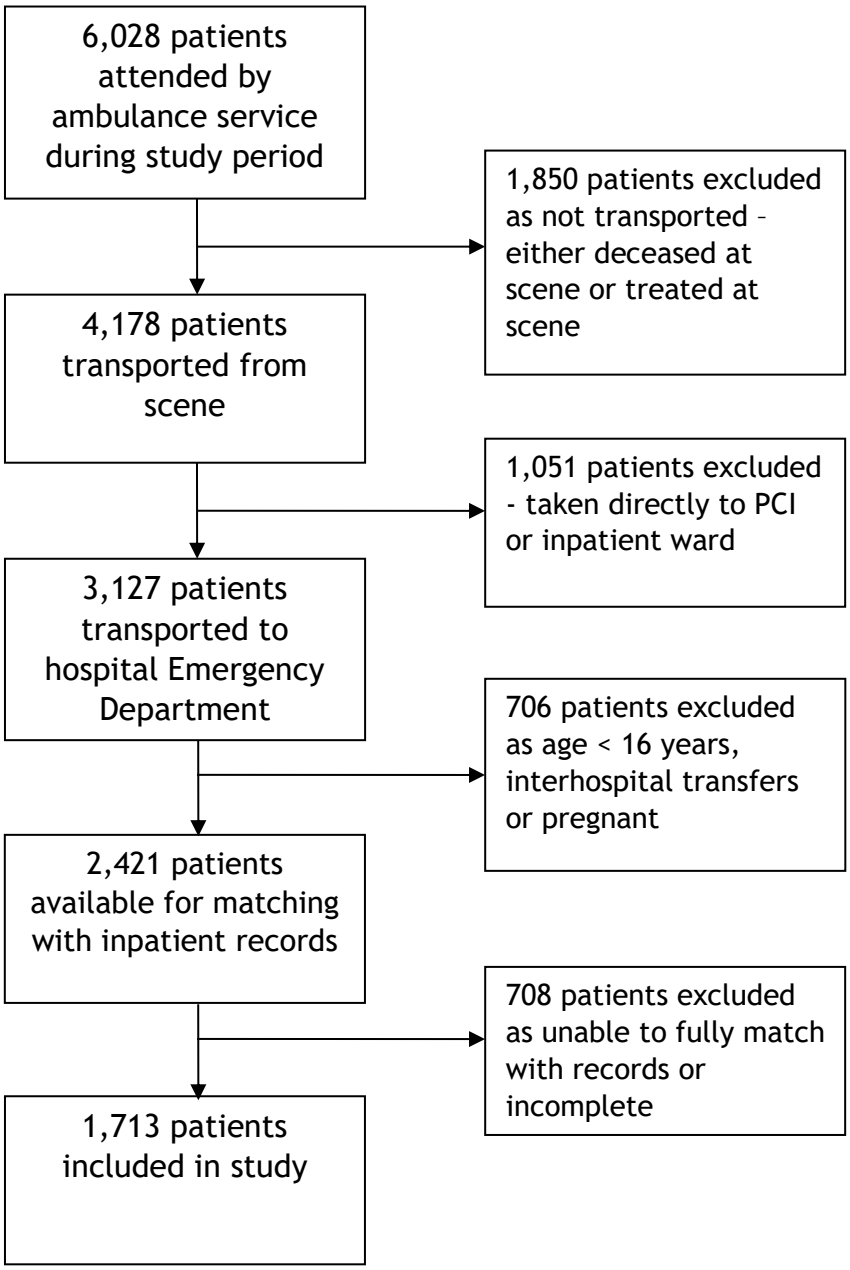
score of 3) and high (score 7 or more) clinical risk was undertaken as in the original description of the score.

Receiver operating characteristic (ROC) curves plotting sensitivity against (1-specificity) were constructed for the outcomes above, and the area under the curve (AUROC) calculated. Comparison between AUROC was done using DeLongs test. Univariate binary regression models were used to compare outcomes for the qSOFA score and the risk strata identified in the original NEWS specification. For each model, the likelihood ratio test was used to assess the model's fit and odds ratios with their 95% confidence intervals were calculated. All statistical calculation was carried out using R 3.4 for Windows. Statistical significant was defined as two-sided $p < 0.05$. No adjustment is made for multiplicity.

Results

11,052 sets of clinical observations were obtained from 6,028 unique patients. After exclusions, 1,713 complete patient encounters were identified for study (see Figure 2-1).

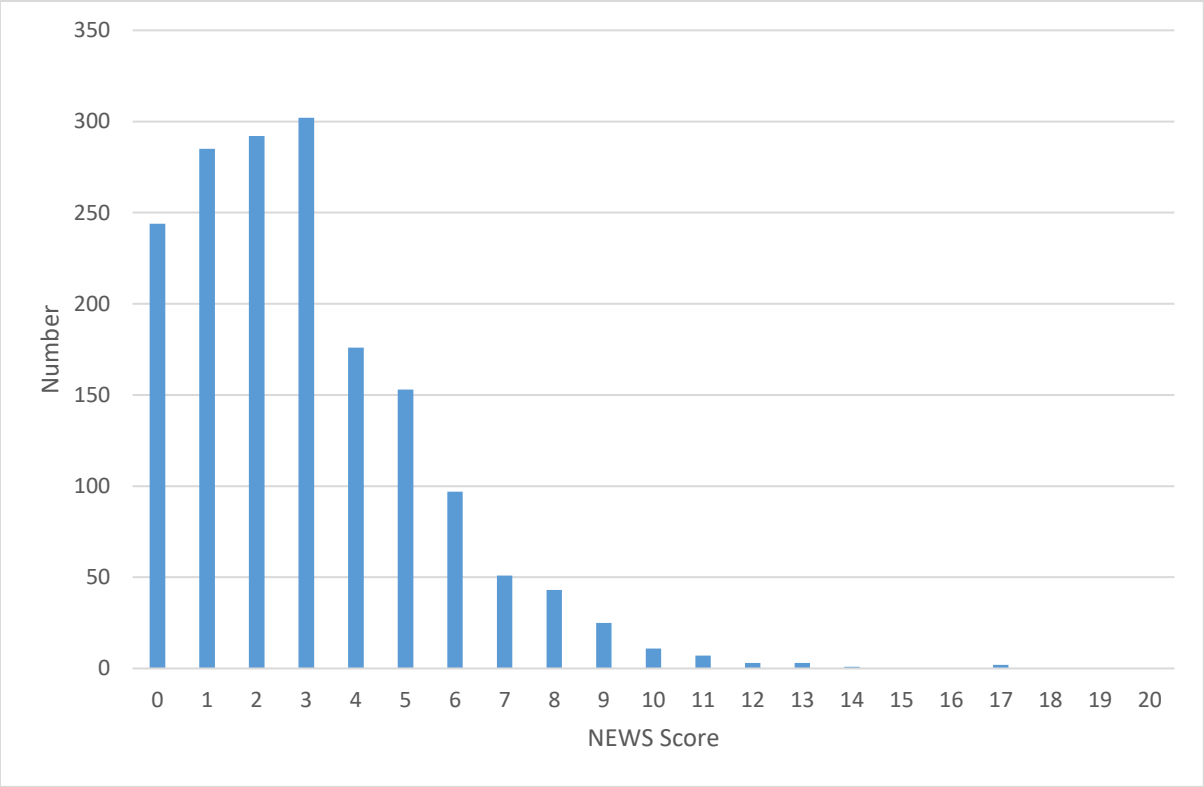
Figure 2-1. Patient pathway into the study



All patients were transported by emergency ambulances staffed either by two paramedics or one paramedic and one emergency ambulance technician. The mean age of the study population was 58.0 years (SD 20.72, median 66, IQR 47-79) with a 48.1 % male gender (95% CI 46.5 to 49.7). 65% of patients were admitted to hospital from ED. Outcome data of ICU admission within 48 hours and death within 30 days of admission were available for all studied patients.

A histogram of NEWS score is shown in Figure 2-2

Figure 2-2. Histogram of NEWS score



Section 1. Performance of NEWS

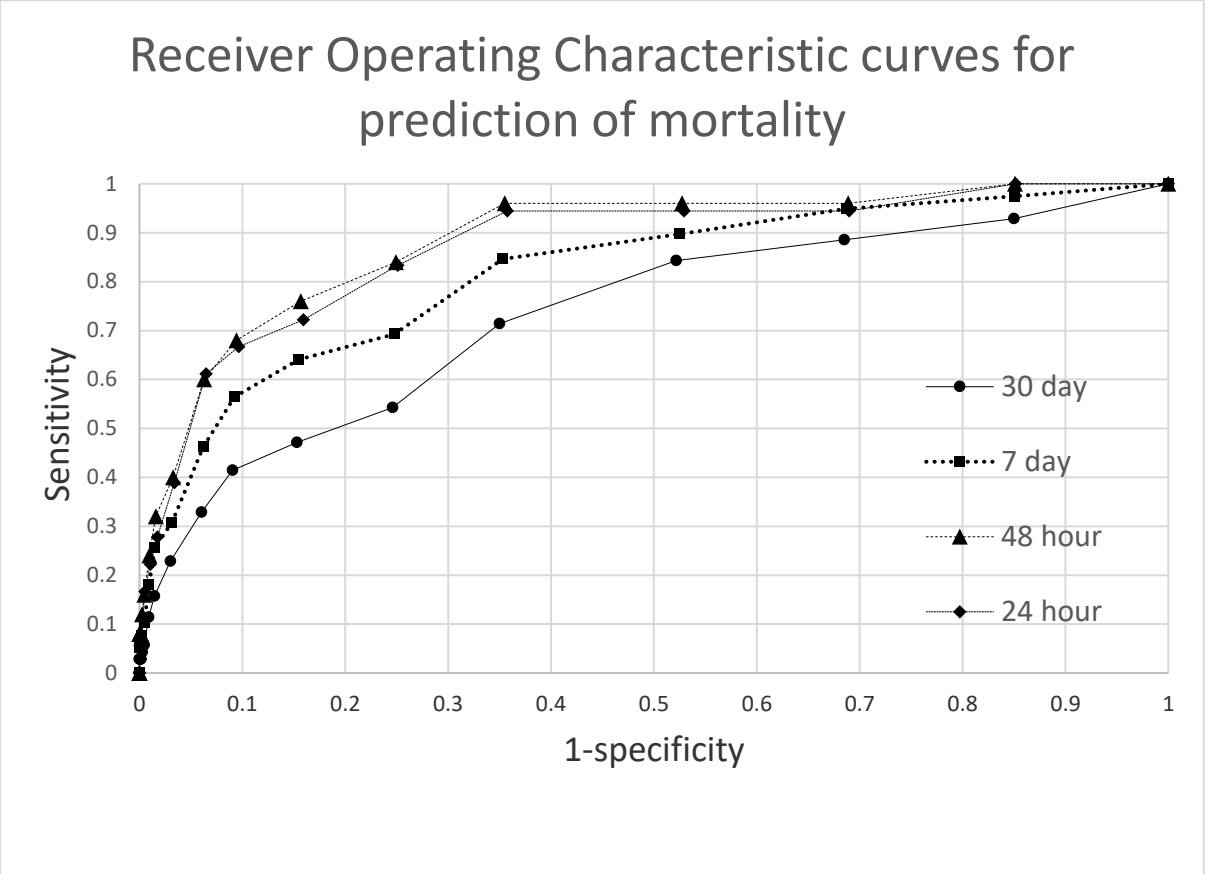
The area under the ROC was calculated for mortality at 24, 48 hours and 7 and 30 days and are shown in Table 2-1.

Table 2-1. AUROC for mortality

Mortality	AUROC	95% CI
24 hours	0.86	0.69 to 1.00
48 hours	0.87	0.75 to 0.98
7 days	0.80	0.70 to 0.89
30 days	0.74	0.66 to 0.82

The AUROC are illustrated further in Figure 2-3.

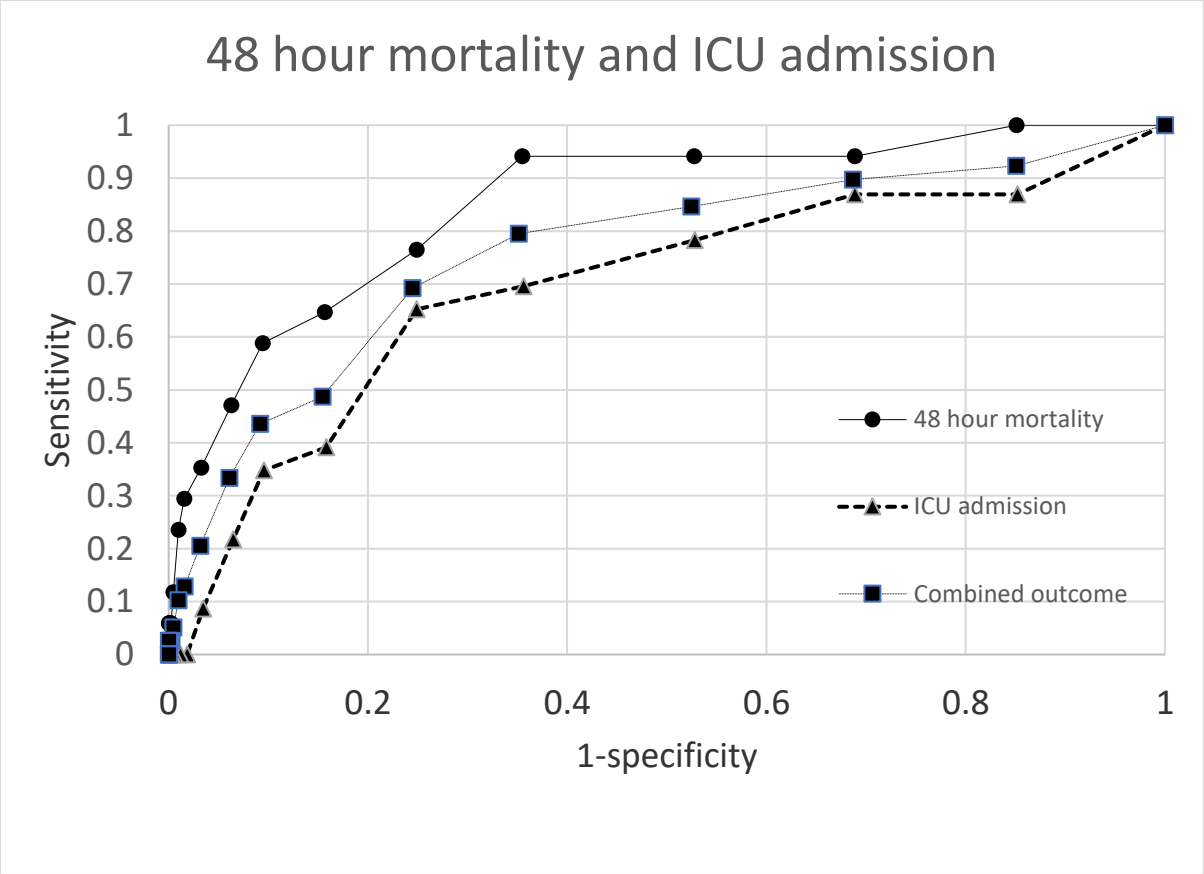
Figure 2-3 Receiver Operating Characteristic curves for mortality at 24, 48 hours, 7 and 30 days



Analysis with the Mann-Whitney test confirmed a difference in median scores between each pair and all were all of statistical significance with $p<0.0001$.

Similar results were found when looking at ICU admission within the first 48hrs of admission, and the AUROC for ICU admission was 0.774 (95% CI: 0.657-0.890) and that for the combined outcome of ICU admission or death within 48hrs was 0.815 (0.730-0.990) -see Figure 2-4. For the combined outcome of death in the Emergency Department or admission directly to ICU from the ED, the AUROC was 0.889 (0.823-0.957).

Figure 2-4 ROC curves demonstrating prediction of 48hr mortality or ICU admission within 48hrs of presentation, both individually and as a combined outcome



Outcomes in the various risk strata identified by NEWS

Outcomes for the patients in the various NEWS categories are given in Table 2-2. When the x^2 test was used to compare outcomes in the groups, there was no significant difference in 30-day or 48-hour mortality in the medium risk category compared to the low risk category, although there was a significant increase in ICU admission. The high risk group demonstrated statistically significant differences in respect of 30-day mortality, 48-hour mortality, and ICU admission in the first 48 hours, with risk ratios of 6.7, 31.2 and 4.4, respectively.

Table 2-2 Risks of each outcome at each NEWS category. AR: Absolute risk, RR: relative risk, 95%CI: 95 % confidence interval of relative risk.

		Medium risk	High risk
	N	249	146
30-day mortality	N	6	19
	AR	0.02	0.13
	RR	1.242	6.665
	95%CI	0.515-2.997	4.122-10.778
		P=0.63	P<0.001
ICU admission	N	7	8
	AR	0.03	0.05
	RR	2.588	4.413
	95%CI	1.655-6.348	1.967-9.952
		p=0.03	P<0.001
48hr mortality	N	1	12
	AR	0.004	0.08
	RR	1.726	31.257
	95%CI	0.180-16.522	10.622-91.978
		P=0.63	P<0.001

These findings were similar in trauma and non-trauma patients (Table 2-3). There were no ICU admissions in the low risk trauma group therefore it was not possible to calculate relative risks

Table 2-3 Risks of each outcome at each NEWS category. AR: Absolute risk, RR: Relative risk, 95%: 95 % confidence interval of relative risk.

		Medium risk non-trauma	Medium risk trauma	High risk non-trauma	High risk trauma
n		209	59	135	23
30 day mortality	n	6	1	17	4
	AR	0.029	0.017	0.13	0.17
	RR	1.428	0.817	7.021	8.386
	95%	0.577-3.531	0.105-6.336	3.339-11.748	2.790-25.210

	p	p=0.439	p=0.84	p<0.001	p<0.001
ICU admission	n AR RR 95% p	6 0.03 2.466 0.922-6.594 p=0.06	0 0 - - p=0.71	7 0.05 4.900 1.897-12.656 p<0.001	1 0.04 - - p<0.001
48hr mortality	n AR RR 95% p	1 0.17 1.507 0.158-14.418 p=0.72	0 0 - - p=0.61	10 0.052 4.900 1.897-12.656 p<0.001	4 0.17 37.739 7.286-195.5 p<0.001

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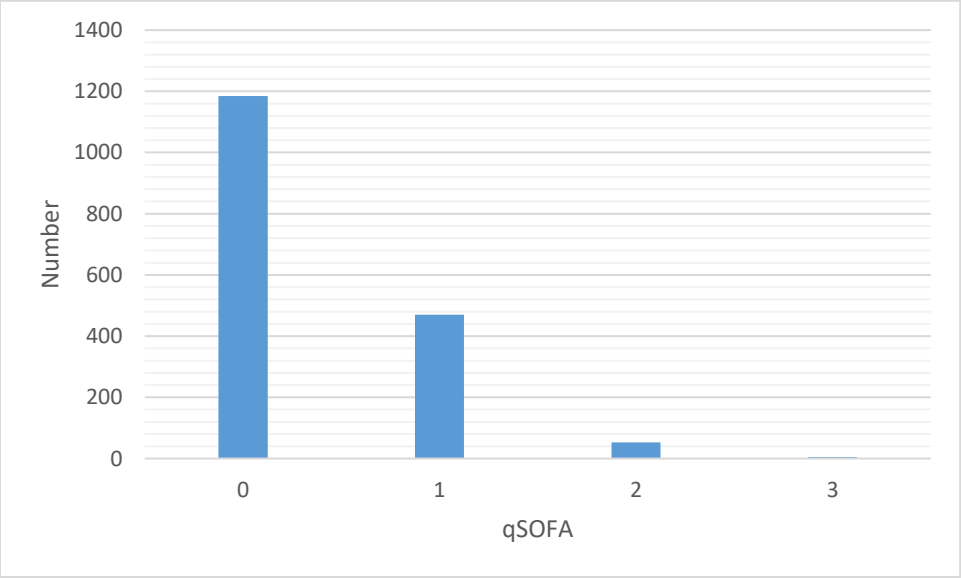
Section 2. Performance of qSOFA versus NEWS

A histogram of qSOFA scores is shown in Figure 2-5

Figure 2-5. Histogram of qSOFA scores



The NEWS risk category is significantly associated with the primary outcome of ICU admission within 48 hours of presentation and or 30-day mortality (x^2 (2) = 70.53; p <.0001). The odds ratio for the medium NEWS category, compared with the low

NEWS category was 3.30 (95% CI 2.01 to 5.43; p <.0001). The odds ratio for the high NEWS category, compared with the low NEWS category was 9.82 (95% CI 5.74 to 16.81; p <.0001). The odds ratio for the high NEWS category, compared with the medium NEWS category was 2.97 (95% CI 1.73 to 5.13; p <.0001). These data are shown in Table 2-4.

Table 2-4. Risk ratio of combined outcomes of ICU admission within 48 hours of presentation and or 30 day mortality, by NEWS category

	Survivor	Non-survivor	Risk ratio compared with NEWS category:	
NEWS category			Low	Med
Low	1162	33	-	-
Med	352	33	3.10 (1.94-4.96)	-
High	104	29	7.89 (4.96-12.58)	2.54 (1.60-4.02)

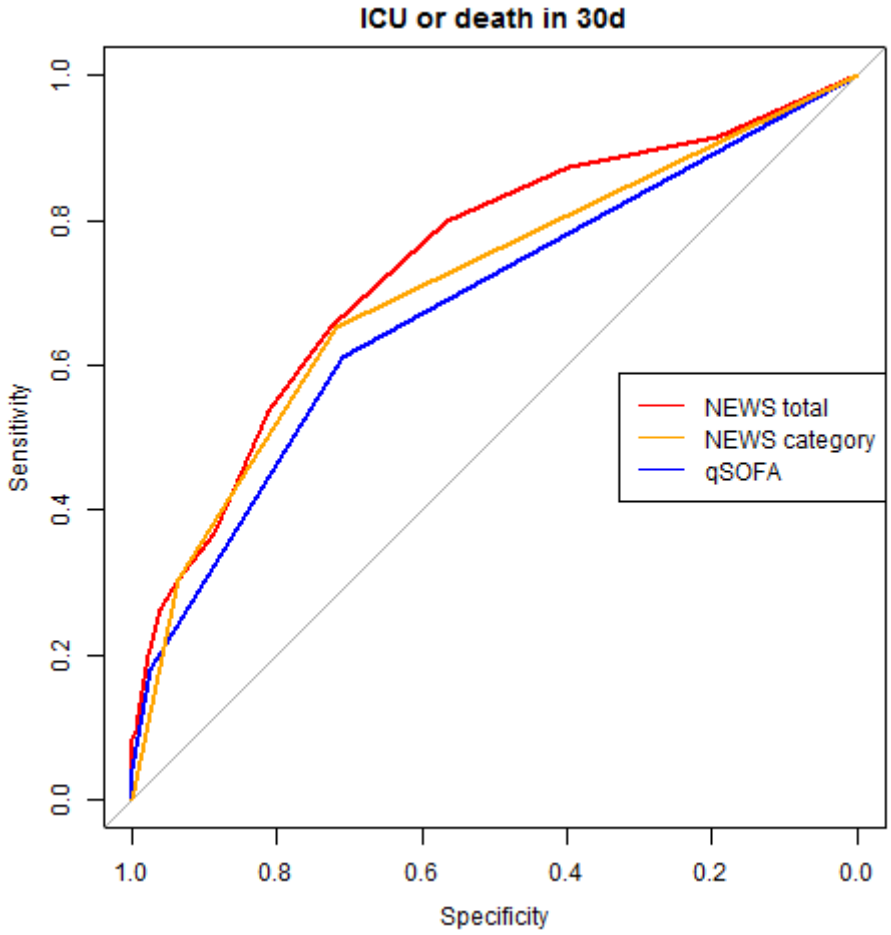
The qSOFA score is significantly associated with the primary outcome of ICU admission within 48 hours of presentation and or 30 day mortality (x^2 (3) = 61.36; p <.0001). The odds ratio for a qSOFA score of one, compared with the qSOFA of zero was 2.97 (95% CI 1.88 to 4.69; p<.0001). The odds ratio for a qSOFA score of two, compared with the qSOFA score of zero was 10.08 (95% CI 4.98 to 20.43; p<.0001). The odds ratio for a qSOFA score of two, compared with the qSOFA score of one was 3.40 (95% CI 1.68 to 6.87; p = 0.0006). The risk ratios comparing qSOFA scores for the combined outcome of ICU admission within 48 hours and/or death within 30 days are shown in Table 2-5.

Table 2-5. Risk ratio of combined outcomes of ICU admission within 48 hours of presentation and / or 30 day mortality, by qSOFA score

	Negative	Positive	Risk ratio compared with qSOFA of		
qSOFA score					
			0	1	2
0	1148	37	-	-	-
1	429	41	2.79(1.81-4.30)	-	-
2	40	13	7.86 (4.44-13.88)	2.81 (1.61-4.90)	-
3	1	4	25.62 (14.92-44.01)	9.17 (5.41-15.53)	3.26 (1.71-6.21)

The relative discriminatory value of NEWS and qSOFA was assessed by plotting AUROC for both groups, against the combined outcomes of ICU admission within 48 hours of presentation and/or 30-day mortality. This is shown in Figure 2-6

Figure 2-6. . ROC curves demonstrating prediction of combined outcomes of 30 day mortality and / or ICU admission within 48 hours of presentation



The AUROC for the primary outcome for qSOFA was 0.679 (95% CI 0.624 to 0.733), for NEWS risk category was 0.707 (95% CI 0.654 to 0.761) and for NEWS total score was 0.740 (95% CI 0.685 to 0.795). Comparison of the ROC curves between qSOFA and NEWS risk category showed no difference between NEWS risk category and qSOFA at predicting 30-day mortality (p=0.272). Comparison of the ROC curves between NEWS total score and qSOFA showed NEWS total score to be superior to qSOFA at predicting combined ICU admission within 48 hours of presentation and or 30-day mortality (z=-2.539, p=0.011).

The NEWS risk category is significantly associated with ICU admission within 48 hours (x^2 (2) = 15.22; p = 0.0005). The odds ratio for the medium NEWS category, compared with the low NEWS category was 5.51 (95% CI 1.61 to 18.94; p 0.0067). The odds ratio for the high NEWS category, compared with the low NEWS category was 11.63

(95% CI 3.08 to 43.86; p = 0.0003). The odds ratio for the high NEWS category, compared with the medium NEWS category was 2.11 (95% CI 0.66 to 6.76; p = 0.2091). This shown in Table 2-6

Table 2-6. Risk ratio admission to ICU within 48 hours, by NEWS category

	Not admitted to ICU	Admitted to ICU	Risk ratio compared with NEWS Category	
NEWS Category			Low	Medium
Low	1191	4	-	-
Medium	378	7	5.43 (1.60-18.45)	-
High	128	5	11.23 (3.05-41.31)	2.06 (0.66-6.4)

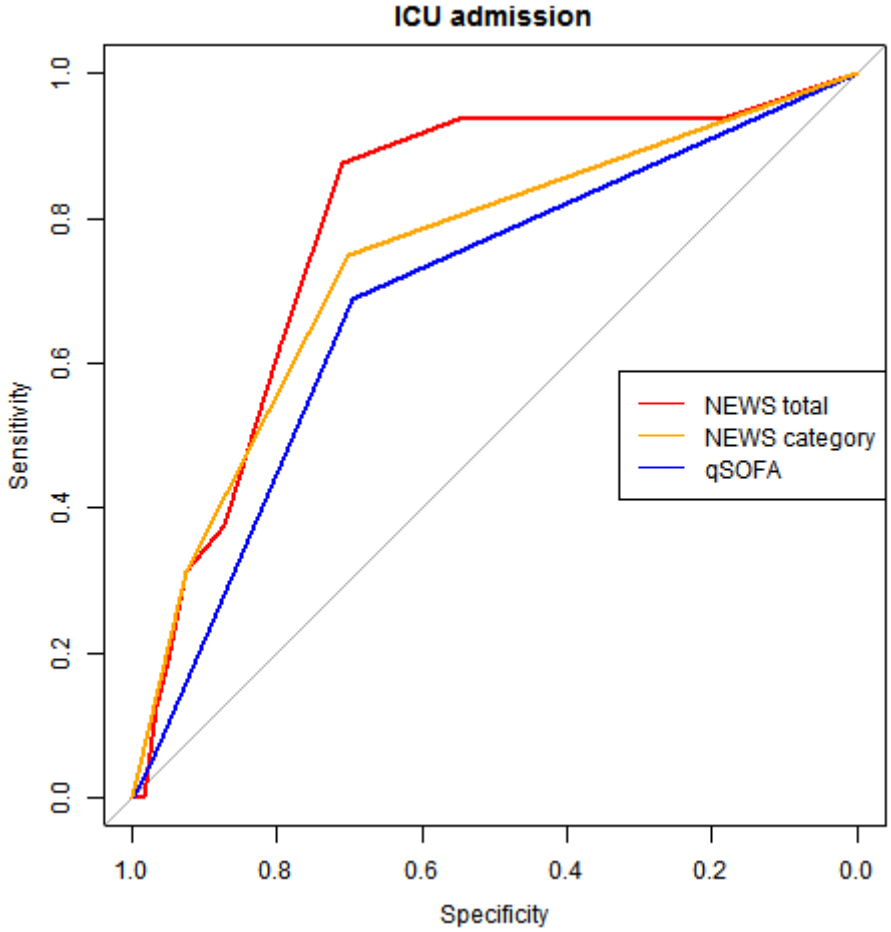
The qSOFA score is significantly associated with ICU admission within 48 hours (x^2 (3) = 10.03; p = 0.0183). The odds ratio for a qSOFA score of one, compared with the qSOFA of zero was 5.13 (95% CI 1.74 to 15.09; p = 0.0030). The odds ratio for a qSOFA score of two, compared with the qSOFA score of zero was 4.54 (95% CI 0.52 to 39.55; p = 0.1709). The odds ratio for a qSOFA score of two, compared with the qSOFA score of one was 0.88 (95% CI 0.11 to 7.05; p = 0.9078). No patients with a qSOFA of three were admitted to ICU within 48 hours. There were five patients with qSOFA=3, one died in the Emergency Department, one young patient went to the Coronary Care Unit. The three remaining patients died within 48hrs of admission without being admitted to intensive care. These data are shown in Table 2-7

Table 2-7. Risk ratio admission to ICU within 48 hours, by qSOFA score

	Not admitted to ICU	Admitted ICU	Risk ratio compared with qSOFA of		
qSOFA criteria			0	1	2
0	1180	5	-	-	-
1	460	10	5.04 (1.73-14.67)	-	-
2	52	1	4.47 (0.53-37.60)	0.88 (0.12-6.79)	-
3	5	0	0	0	0

The relative discriminatory value of NEWS and qSOFA was assessed by plotting AUROC for both groups, against the outcome of admission to ICU within 48 hours. This is shown in Figure 2-7.

Figure 2-7. ROC curves demonstrating prediction of ICU admission within 48 hours of presentation



The AUROC for qSOFA was 0.689 (95%CI 0.571 to 0.808), for NEWS risk category was 0.744 (95%CI 0.624 to 0.864) and for NEWS total score was 0.798 (95%CI 0.693 to 0.902). Comparison of the ROC curves between qSOFA and NEWS category showed no difference between NEWS risk category and qSOFA at predicting ICU admission (z=-0.751, p=0.453). Comparison of the ROC curves between NEWS total score and qSOFA showed no difference between NEWS total and qSOFA at predicting ICU admission (z=-1.896, p=0.057).

The NEWS risk category is significantly associated with 30-day mortality (x^2 (2) = 60.56; p <.0001). The odds ratio for the medium NEWS category, compared with the

low NEWS category was 2.72 (95% CI 1.59 to 4.64; p = 0.0002). The odds ratio for the high NEWS category, compared with the low NEWS category was 9.12 (95% CI 5.22 to 15.93; p<0.0001). The odds ratio for the high NEWS category, compared with the medium NEWS category was 3.36 (95% CI 1.87 to 6.02; p <0.0001). These data are shown in Table 2-8.

Table 2-8. Risk ratio 30 day mortality, by NEWS category

	Survivor	Non-survivor	Risk ratio compared with NEWS Category:	
NEWS category			Low	Med
Low	1164	31	-	-
Med	359	26	2.60(1.56-4.32)	-
High	107	26	7.54 (4.62 12.29)	2.89 (1.74-4.80)

The qSOFA score is significantly associated with 30-day mortality (x^2 (3) = 59.29; p <.0001), the odds ratio for a qSOFA score of one, compared with the qSOFA of zero was 2.90 (95% CI 1.77 to 4.74; p <.0001). The odds ratio for a qSOFA score of two, compared with the qSOFA score of zero was 10.55 (95% CI 5.07 to 21.95; p <.0001). The odds ratio for a qSOFA score of two, compared with the qSOFA score of one was 3.64 (95% CI 1.75 to 7.55; p <.0001). These data re shown in Table 2-9.

Table 2-9. Risk ratio 30 day mortality, by qSOFA score

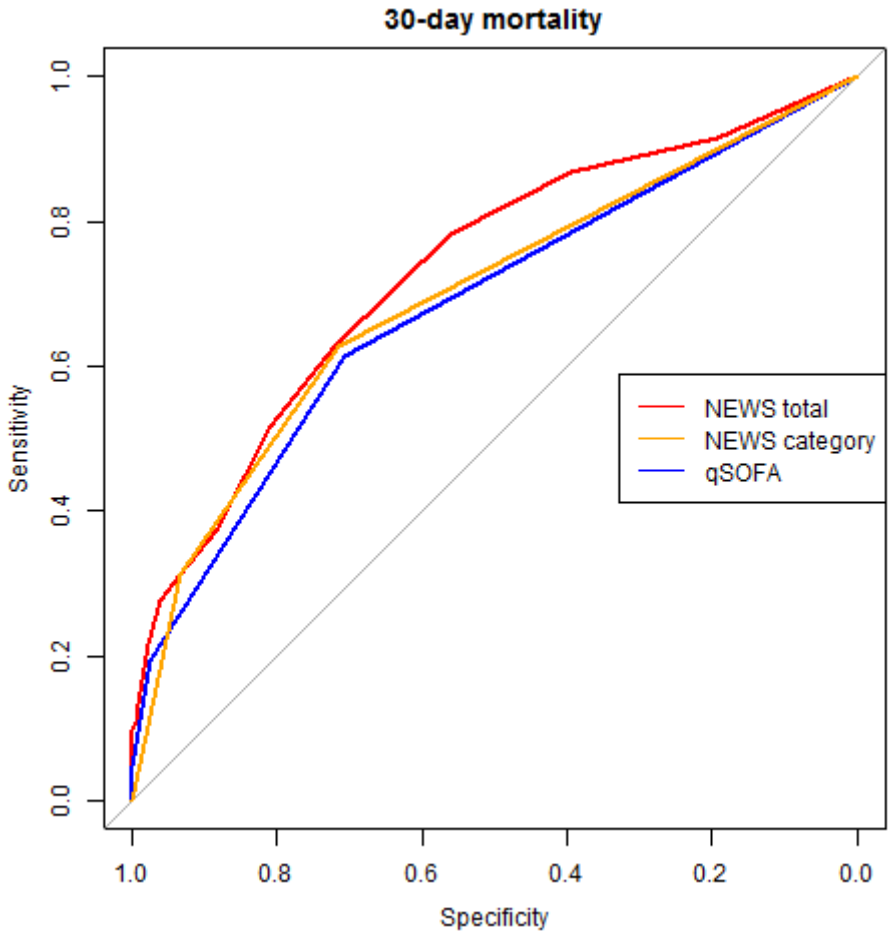
	Survivor	Non-survivor	Risk ratio compared with qSOFA of		
qSOFA criteria			0	1	2
0	1153	32	-	-	-
1	435	35	2.76 (1.72-4.40)	-	-
2	41	12	8.38 (4.58-15.33)	3.04 (1.68-5.49)	-
3	1	4	29.62 (16.99-51.64)	10.74 (6.25-18.46)	3.53 (1.82-6.85)

The odds ratio for a qSOFA score of three compared with zero was 144.2 (95% CI 15.7 to 1326.1; p <.0001). The odds ratio for a qSOFA score of three compared with one

was 49.71 (95% CI 5.41 to 456.9; p = 0.001). The odds ratio for a qSOFA score of three compared with two was 13.67 (95% CI 1.39 to 134.1; p = 0.025).

The relative discriminatory value of NEWS and qSOFA was assessed by plotting AUROC for both groups, against 30-day mortality. This is shown in Figure 2-8.

Figure 2-8. ROC curves demonstrating prediction of 30 day mortality



The AUROC for qSOFA was 0.682 (95% CI 0.623 to 0.740), for NEWS risk category was 0.695 (95% CI 0.636 to 0.753) and for NEWS total was 0.731 (95% CI 0.671 to 0.791). Comparison of the ROC curves between qSOFA and NEWS risk category showed no difference between NEWS risk category and qSOFA at predicting 30-day mortality (z=-0.458, p=0.647). Comparison of the ROC curves between NEWS total and qSOFA showed no difference between NEWS total and qSOFA at predicting 30-day mortality (z=-1.939, p=0.053).

Discussion

Main findings

This study, has revealed that among unselected pre-hospital patients, an elevated qSOFA much like NEWS, is associated with increased levels of adverse outcomes, namely, ICU admission within 48 hours of presentation and or 30-day mortality. The aggregated total NEWS score was however, superior to qSOFA at identifying patients at combined risk of either ICU admission within 48 hours of presentation and or 30-day mortality.

Interpretation

Sepsis is "*a life-threatening organ dysfunction caused by a dysregulated host response to infection*". It is a common disease, causing significant morbidity and mortality, where early recognition, early administration of antibiotics and early adequate volume resuscitation are needed to ensure good outcomes for patients. Consequently the Surviving Sepsis Campaign have recommended the development of quality improvement programmes in order to screen for sepsis in acutely ill, high risk patients. Such recommendations served as the foundations for the subsequent Sepsis-3 definition papers and the development of the qSOFA criteria to identify patients with suspected infection who are at greater risk of a poor outcome outside the intensive care unit (ICU). qSOFA was not intended to be a sepsis screening tool by the Sepsis-3 task force but as a means to identify adults with proven or suspected infection who are likely to have a prolonged ICU stay or die in hospital. However, the Sepsis-3 task force did recommend that a positive qSOFA criteria should act as a prompt for "*consideration of possible infection in patients not previously recognized as infected*". While qSOFA was validated in 4 external datasets, one of which was in the pre-hospital setting and another outside the US, the authors encouraged further prospective validation in multiple non-US settings as well as resource limited settings.

The most important finding from this study was that in unselected pre-hospital patients with their infection status unknown, the aggregated total NEWS was significantly superior to qSOFA at predicting the combined outcomes of ICU admission within 48 hours of presentation and / or 30-day mortality in unselected pre-hospital patients. This is similar to the findings of Churpek et al who revealed that qSOFA was superior to the Systemic Inflammatory Response (SIRS) criteria but inferior to MEWS and NEWS at detecting clinical deterioration in infected patients outside the ICU. These findings are not unexpected considering the fact that the qSOFA criteria are composed of 3 of the 7 parameters measured in NEWS. Indeed, a qSOFA criteria of 2 or 3 can result in a minimum NEWS score of 4 and a maximum of 9, meaning that patients with 2 or more qSOFA criteria have a medium or high clinical risk in NEWS and consequently are at increased risk of ICU admission and death. While neither NEWS nor qSOFA are the perfect risk assessment tool, NEWS is the better of the two.

Many countries now use track and trigger early warning scoring systems such as NEWS as part of their structured response to the deteriorating patient and they represent a minimum standard of care. Consequently, increased complexity and confusion will arise if healthcare professionals are asked to introduce a further aggregated score, using similar variables but different thresholds, namely qSOFA, which has not been validated in their setting, and is specific to only one cause of deterioration. Mismanaged patient deterioration is the one of the most common causes of safety related deaths. In comparison to NEWS, qSOFA would fail to identify someone at increased risk of adverse outcome namely isolated hypotension with a systolic blood pressure less than or equal to 90 mmHg and as such represents a backwards step. In the UK, NEWS is established in hospital, and increasingly pre-hospital, as the early warning score. This implementation across healthcare settings allows improved communication and handover on the patient journey. Introduction of qSOFA in addition to NEWS would potentially cause confusion with this study showing no benefit in detecting patients at risk of adverse outcome.

One potential benefit of using qSOFA over NEWS may be that it is be easier to collect only the 3 qSOFA vital sign parameters in resource limited settings, compared to the

7 vital sign parameters required for NEWS. NEWS however, is now used internationally as evidenced by its use across the world from Europe to India, South America and the USA, including the US Naval Air Forces. As such, NEWS represents a standardised approach to the assessment of acute illness severity internationally. And is a common language to communicate illness severity across the patient journey.

Patient with sepsis often present with very vague and non-specific symptoms and represent a very heterogeneous population that is often difficult to identify. Recommendations to use a different scoring system, even in a select subgroup of the population has the potential to result in staff across this patient care continuum speaking at cross purposes, with warning signs being missed, and ultimately patient care being compromised. As a result, a single generic tool such as NEWS, that is independent of patient diagnosis, is more appropriate in the undifferentiated pre-hospital population.

Finally, in this study, the aggregated total NEWS was significantly superior to qSOFA at predicting the combined outcomes of ICU admission within 48 hours of presentation rather than qSOFA, a NEWS of medium or high clinical risk (greater than or equal to 5) be used to fulfil the requirement of the Sepsis-3 definitions namely "*to prompt clinicians to further investigate for organ dysfunction, to initiate or escalate therapy as appropriate, and to consider referral to critical care or increase the frequency of monitoring*"

Implications

Triage is a crucial part of any unplanned care system, and has been developed significantly since its inception during the Napoleonic Wars. Algorithms such as the Manchester Triage System provide objective criteria for the allocation of patients to care areas, and can be sensitive enough to detect the signs of critical illness at the point of entry to the emergency department although they may still miss patients with the possibility of deterioration while still in the Emergency Department.

Early warning systems have been increasingly employed in the inpatient setting throughout the world in recent years and provide a means of identification of potential deterioration. However these scores are only effective in reducing adverse outcomes if an appropriate clinical response involving those experienced in critical care can be available to respond to the changing clinical situation. Scores developed for one patient population or healthcare system may not be applicable to other populations or healthcare systems, and even within a given healthcare system there may be individuals for whom the standard scoring points and triggers are inappropriate. Modifications may need to be made to the trigger points in certain other groups of patients with chronically deranged vital observations. Early warning scores are also reliant on clinical observations being performed at an appropriate frequency to be useful as a predictor of deterioration, and this may be limited by other workload. There is some evidence, however, that the introduction of clinical observations charts printed with early warning score calculations increases the incidence of respiratory rate being recorded, itself a valuable independent marker of deterioration.

Compared to the inpatient patient population, the adoption of early warning scoring systems has been less enthusiastic in the emergency and prehospital settings partly as there is a relative lack of robust evidence supporting their validity in this patient cohort. However usage of aggregate scoring systems such as NEWS is increasing and is developing a role in this respect as a tool to predict the need for hospital admission as well as likely outcomes, particularly in sepsis.

No early warning score can replace clinical assessment, and there are many situations where decisions about clinical management should be based on other criteria: the presence of ST-elevation myocardial infarction, major haemorrhage, or multiple trauma being only a few examples. In the absence of such presentations, signs of potentially severe illness or occult injury may occasionally be missed. In this scenario, a physiologically based score may highlight individual patients in need of more urgent care. This may form part of a pre-alert protocol or indicate specific pre-hospital treatments. Similarly at the other end of the severity spectrum, a low score in combination with an appropriate clinical assessment may safely allow treatment at a location other than an Emergency Department.

Limitations

This study does have some limitations. Data were collected retrospectively which has the potential to introduce bias. Although 2,421 patients met the criteria for inclusion in the study, only 1,713 could be assessed due to missing observations on attendance. Using basic demographics, this group of unmatched patients was not significantly different to the study population, however it is possible that this exclusion may alter these results.

This study did not attempt to impute missing data. No information is available for patients who attended and were discharged within two days of attendance. This group should by virtue of the fact that they are discharged within two days have a much lower incidence of significant illness.

qSOFA was designed as a tool to identify those with infection who are at risk of adverse outcomes. As such, it may be inappropriate to use qSOFA in unselected patients. However, the authors of the Sepsis 3 papers state that a positive qSOFA should also prompt consideration of possible infection, suggesting it can be used in unselected patients.

This study did not adjusted for age or sex differences between the low, medium and high risk NEWS groups, and this may account for some of the difference in mortality. However, the absence of age or gender adjustments is a feature of the NEWS that this study aimed to validate. As one of the end-points was survival to discharge and only in-hospital death was considered, the mortality rate, particularly the 30 day mortality rate, may be underestimated. Similarly, due to the method of data collection, it was not possible to conclusively identify all patients who were re-admitted following discharge, although there were no deaths among those that could be identified as being repeat attenders. The overall mortality rate was low, as was the proportion of people with high NEWS scores and the total numbers in these categories was also low, particularly among trauma patients.

The study population is representative of an adult pre-hospital ambulance population transported to hospital. There were limited exclusions (direct to PCI, cardiac arrests and inter hospital transfers). This study was conducted within a single

centre, and therefore may not represent all external populations. However, the single centre represents a medium sized UK hospital serving mixed rural and urban population.

Finally, this study was a retrospective convenience sample of 1713 consecutive patients from 2012. As such, it was performed in a patient population before qSOFA existed and while NEWS was only beginning to gain traction, making it an advantage in terms of clinicians blinding and reducing bias.

Conclusions of Part 2

In this cohort among unselected pre-hospital patients, elevated qSOFA is associated with increased levels of adverse outcomes. Comparison with NEWS shows qSOFA has an inferior performance at identifying patients at risk of adverse outcomes. Calculation of an early warning score prior to transfer to hospital is straightforward and may be a useful triage tool with potential to facilitate earlier recognition of at-risk or deteriorating patients, possibly allowing earlier involvement of appropriate ED and critical care staff. These data suggests that development of pre-hospital early warning scores should focus on NEWS, rather than qSOFA.

Chapter 3 : PEWS in the pre-hospital environment

Introduction

Each year approximately 350 to 450 infants, children and young people (CYP) die in Scotland. Similar to figures across the UK, the majority of deaths occur in children under one year of age, with the second largest number of deaths occurring in the 15 to 18 year old age group (RCPH report 2014) .Child mortality rates fare particularly poorly in the UK compared to the rest of Europe and the UK has the greatest "excess mortality" of any country in western Europe. A recent report by Healthcare Quality Improvement Partnership (HQIP) Clinical Outcome Review Programme (CORP): Child Health, confirmed there are also variations between the 4 home nations with Scotland having the greatest "excess mortality". It is important, therefore that measures are taken to improve recognition and management of the seriously ill or injured child across the health service.

NHS Scotland is committed to improving the outcome of Child and Maternal Health as evidenced by their inclusion in the Scottish Patient Safety Programme. An important element in improving the care of any deteriorating patient is early identification and early intervention. This has been followed through with a commitment from the Scottish Patient Safety Programme to make the development and implementation of a single national Paediatric Early Warning Score (PEWS Scotland) a priority.

Literature Review

As outlined in Chapter 1 and Chapter 2, physiological deterioration often precedes clinical deterioration as patients develop critical illness. Recognition of this has led to the development of Early Warning Scoring (EWS) systems for use in adult patients in a hospital setting. These assign a numerical value to various physiological parameters, and when combined to a composite score for a patient, allow early identification of those at risk of critical illness.

Data presented in Chapter 1 and Chapter 2 examined the use of EWS in the Emergency Department (ED) and the pre-hospital environment. These studies have shown some success at identifying adult patients at risk of adverse outcome such as ICU admission or death, however this has not been without controversy. The use of multiple different scoring systems has the potential to result in staff across the patient care continuum speaking at cross purposes, with warning signs being missed, and ultimately patient care being compromised. This has led to a standard National EWS (NEWS) for adults across the NHS in the United Kingdom being recommended to improve patient care. Due to the standardised approach to the assessment of the critically ill adult, NEWS has become a common language to communicate illness severity across the patient journey.

Children and young people have different physiological responses to illness and injury compared to adults. Paediatric Early Warning Scores (PEWS) have been developed in response to this to detect the early deterioration of the hospitalised child (Lillitos et al., 2014). Subsequent studies have looked specifically at PEWS in the ED (Bradman and Maconachie., 2008) and whether this can be useful in predicting outcomes such as need for admission to hospital and significant illness (Bradman et al., 2014). They have shown PEWS to be specific but not sensitive for these outcomes in the ED. Whilst need for admission for ED patients is an important outcome, need for critical care and mortality are arguably more so. In the paediatric population, using the outcome of critical care need and death are challenging due to their low incidence in the general paediatric population.

PEWS also has the potential to be used in pre-hospital care and ambulance services. Most ambulance services routinely collect the physiological data required to calculate a PEWS. An agreed PEWS score of greater than a specific level could be used as a trigger for ambulance service pre-alert of a receiving ED.

As was initially seen with adult early warning scores, a national study showed a plethora of paediatric scores and systems in use within hospitals in the UK (Roland et al., 2014). The NHS within Scotland have agreed a standardised paediatric single scoring system to be used in all hospitals within Scotland – PEWS (Scotland).

In summary, the identification of unwell children can be challenging, particularly as the proportion of paediatric patients with serious illness or injury is lower than that

in a general adult population, and especially in the pre-hospital environment where information can be less easily available than in the hospital environment. I investigated the utility of PEWS (Scotland) at identifying children at risk of an adverse outcome in an unselected paediatric ambulance population.

Aims

Is PEWS (Scotland) a predictor of ICU admission within 48 hours or mortality within 30 days, for unselected paediatric patients transported by the Scottish Ambulance Service?

Methods

Setting & Population

All paediatric patients aged less than 16 years old on the date they are conveyed by the Scottish Ambulance Service (SAS) to hospital over a 5 year period from 2011 to 2015. The design was a retrospective cohort study.

Data Definitions:

The national PEWS (Scotland) contains seven physiological parameters; respiratory rate, peripheral oxygen saturations, heart rate, blood pressure, capillary return, conscious level, temperature (Table 7), each of which is assigned a value of between 0,1 or 3 inclusive as observations deviate outwith the 5th and 95th centiles or 1st and 99th centiles

Figure 3-1. PEWS (Scotland)

Respiratory Rate

Age	3	1	0	1	3
0-11m	<20	20-29	30-49	50-69	>70
12-24m	<20	20-24	25-39	40-59	>60
2-4y	<15	15-19	20-34	35-49	>50
5-11y	<15	15-19	20-29	30-39	>40
>12	<10	10-14	15-24	25-34	>35

Oxygen Saturations (SpO_2)

Age	3	1	0
all ages	<92	93-94	>94

O_2 Delivery

Age	0	1
all ages	Air	O_2

Temperature

Age	3	1	0	1
all ages	<35	35-35.9	36-37.9	>38

Systolic BP

Age	3	1	0	1	3

0-11m	<60	60-69	70-99	100-109	>110
12-24m	<60	60-69	70-99	100-109	>110
2-4y	<70	70-79	80-99	100-119	>120
5-11y	<80	80-89	90-109	110-129	>130
>12	<90	90-99	100-119	120-139	>140

Heart Rate

Age	**3**	**1**	**0**	**1**	**3**
0-11m	<100	100-109	110-159	160-169	>170
12-24m	<80	80-99	100-149	150-159	>160
2-4y	<70	70-89	90-139	140-149	>150
5-11y	<60	60-79	80-129	130-139	>140
>12	<50	50-70	70-109	110-129	>130

Capillary Return

Age	0	1	3
All ages	<2 seconds	2-4 seconds	>4 seconds

Conscious Level

Age	0	3
All ages	Alert	V/P/U

In addition, a score of 0 or 1 is added for being on supplemental oxygen or not. An aggregated score is then calculated by adding the value for each of these

parameters. Hence, the total PEWS can vary between 0 and 22. As physiological parameters vary with age there are 5 different age banded scores.

For the purposes of the primary outcome, the first complete record of PEWS (Scotland) within each incident was used for analysis. This is defined as the first set of observations taken by an attending ambulance crew where all eight parameters required for a PEWS (Scotland) score to be calculated were taken.

Thirty-day mortality was defined as death within 30 days of SAS attendance to a patient, including all causes and those deaths occurring in the community. ICU admission was defined as admission to a level 3 (ICU) bed within 48 hours of SAS attendance to a patient.

Data Collection / Data Linkage

SAS Paramedic crews routinely collect patient observations in an electronic Patient Report Form (ePRF) on every patient encounter. This occurred for the duration of the study period.

The data from the time period required for the study were extracted from the SAS ePRF, by an Information Services Manager within the SAS National Headquarters. They were then encrypted and sent via secure transfer to the research nurse. The data were then extracted into individual patient datasets, in order to be able to supply identifiers for data linkage. They were then anonymised, and the required variables necessary for linkage were transferred to Information Services Division (ISD) Scotland. ISD provides health information, health intelligence, statistical services and advice that support the NHS in progressing quality improvement in health and social care. Data were linked for mortality, hospital admission, total length of stay, ICU admission, length of stay in ICU and death in ICU, using the Unscheduled Care Datamart. The linked data were then sent back to the research nurse, where they were then matched to the full dataset. This dataset contained all

physiological parameters for patients and these were used to calculate PEWS retrospectively.

Linkage Process: SAS incident numbers and Call Start Date were matched into a database held by ISD: the Unscheduled Care Datamart (UCD). Where this linking process produced a valid Community Health Index (CHI) or NHS number, further information on the inpatient admission/deaths associated with that SAS incident was extracted. The UCD is a collaboration between Information Services Division, NHS 24 and the Scottish Ambulance Service (SAS). The UCD securely links data from NHS 24, the Scottish Ambulance Service, Out of Hours Primary Care services, Accident and Emergency services, Acute Hospital Admissions, Mental Health and Deaths to show patient journeys.

Statistical Analysis

Demographic variables are presented as mean ± standard deviation or quartiles or frequency and percentage as appropriate.

The odds ratios (with 95% confidence interval) are presented from a multivariable logistic regression models for the primary outcome with age, gender and PEWS. The area under the Receiver Operating Characteristic (AUROC) curve and 95% confidence intervals were found. Youden's index was used to determine the optimum threshold. The statistical analyses were performed using the statistical package SAS, version 9.4. All tests were applied with a 2-sided significance level of 5%.

Results

Over the study period, a total of eligible 126,563 patients were attended by SAS. After exclusions, 21,202 children had fully matched data that were available for analysis. A breakdown of the reasons for exclusion is given in Figure 3-2.

The demographics for the study group of 21,202 patients where all required PEWS (Scotland) data were available and the population of 102,993 patients with known outcome data are summarised in Table 3-1.

Table 3-1 Demographics of study population

	Full PEWS (Scotland) data available	Known outcome data	Comparison between full PEWS (Scotland) data available or not
Number of patients	21,202	102,993	
Mean Age (years) ± SD	10.0 ± 4.6	5.8 ± 5.1	p< 0.001 [1]
Gender: Male (%)	11,130 (53.8)	58,108 (57.0)	p< 0.001 [2]
Admission to ICU within 48 hours (%)	151 (0.7)	1053 (1.0)	p< 0.001 [2]
Death within 30 days (%)	26 (0.12)	153 (0.15)	p = 0.317 [2]
Primary outcome (%)	176 (0.83)	1178 (1.14)	p< 0.001 [2]
Median PEWS (Scotland) score (Q1, Q3)	2 (1, 4)	n/a	

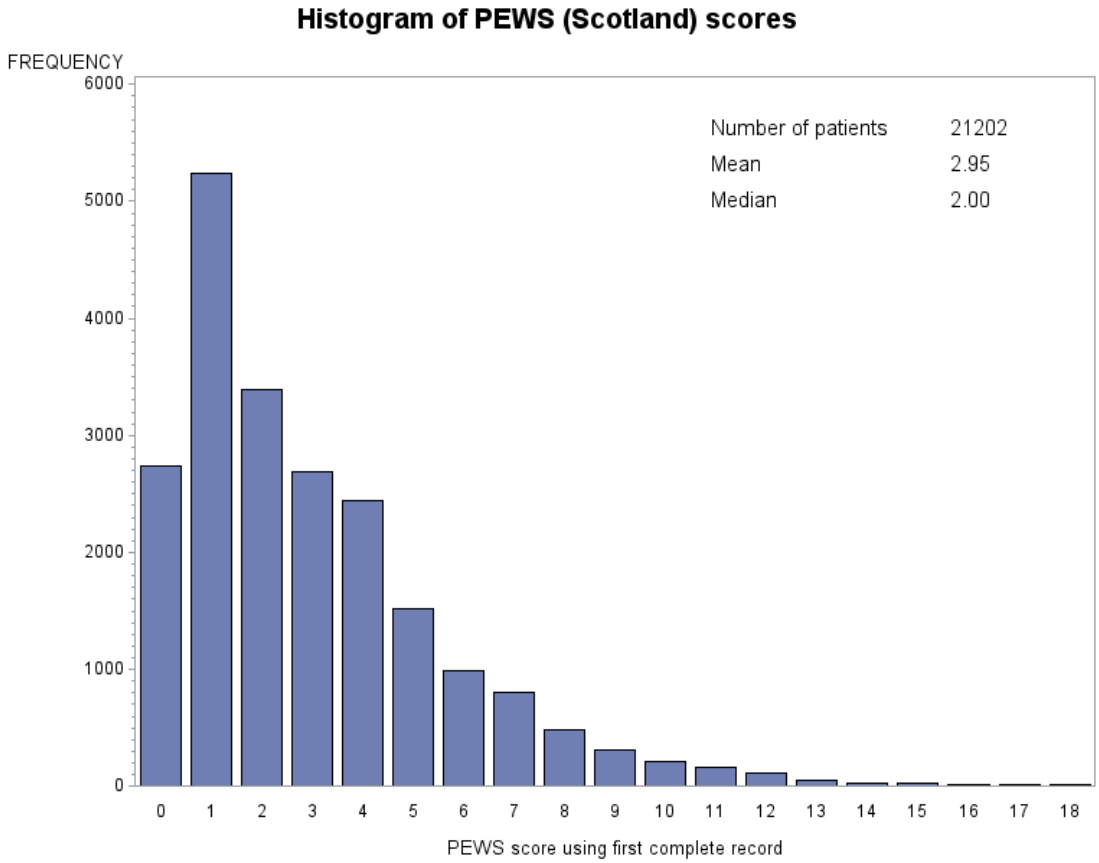
Figure 3-2. Patient inclusion in the study

For the primary outcome of ICU admission within 48 hours and / or death within 30 days, there were 102,993 patients with a known outcome. Of these 102,993 patients, 1053 (1.02%) were admitted to ICU within 48 hours and 153 (0.15%) died within 30 days. 1178/102993 (1.14%) had the primary outcome of ICU admission and or death within 30 days.

Within the study group where a first complete set of observations was made, the primary outcome measure of ICU admission within 48 hours and / or death within 30 days occurred in 176/21202 (0.83 %).

The mean PEWS (Scotland) score in the study group of 21,202 patients was 2.95, and the distribution of PEWS (Scotland) in this group is shown in Figure 3-3.

Figure 3-3 Histogram of PEWS (Scotland)



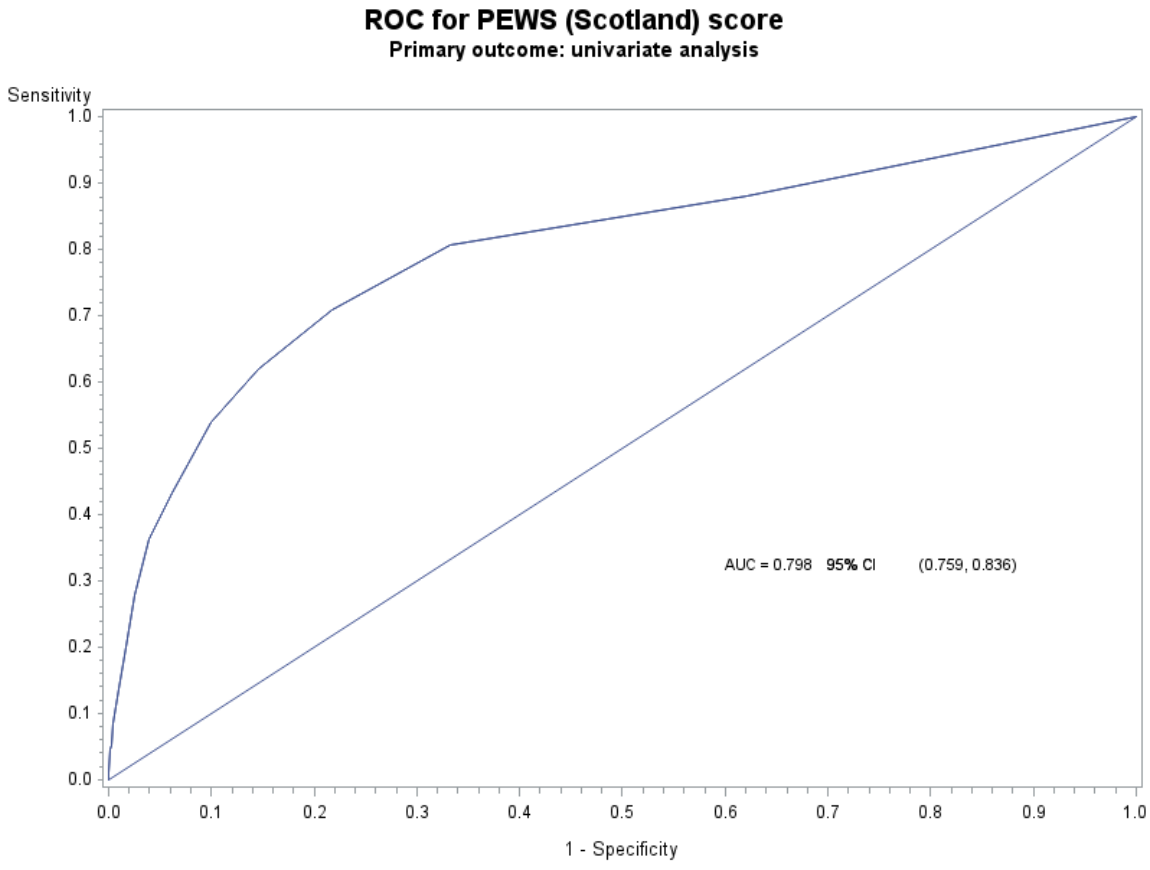
Multivariable logistic regression analysis showed that PEWS (Scotland) but neither age nor gender were independent predictors for the primary outcome– see Table 3-2.

Table 3-2 Multivariate analysis of primary outcome

Effect	Odds Ratio	95% CI and p value
Gender Female vs Male	0.930	(0.686 - 1.261) ; p = 0.639
PEWS (Scotland)	1.403	(1.349 - 1.460) ; p = <0.001
Patient Age	1.003	(0.972 - 1.035) ; p = 0.854

Using the PEWS (Scotland) composite score as the explanatory variable showed an area under the curve (AUROC) for the primary outcome of 0.797 (95% CI 0.759 to 0.836, p<0.001). This is shown in Figure 10.

Figure 3-4. Area under Curve for PEWS (Scotland) total score



Sensitivity, specificity, positive predictive value and negative predictive value are shown in Figure 3-5. The optimal value for PEWS using Youden's index was 5.

Figure 3-5. Sensitivity and Specificity of PEWS (Scotland) by PEWS value

PEWS score	Frequency	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
0	2740	1.000	0	0.0083	.
1	5235	0.960	0.130	0.009	0.997
2	3396	0.881	0.378	0.012	0.997
3	2686	0.841	0.539	0.015	0.998
4	2447	0.807	0.667	0.020	0.998
5	1516	0.710	0.783	0.027	0.997
6	985	0.619	0.854	0.034	0.996
7	809	0.540	0.900	0.043	0.996
8	487	0.432	0.938	0.055	0.995
9	306	0.364	0.960	0.071	0.994
10	212	0.278	0.974	0.082	0.994
11	161	0.199	0.983	0.091	0.993
12	111	0.136	0.991	0.108	0.993
13	48	0.085	0.995	0.135	0.992
14	27	0.051	0.997	0.143	0.992
15	23	0.045	0.999	0.222	0.992
16	8	0.011	0.999	0.154	0.992
17	4	0.000	0.99976	0.000	0.992
18	1	0.000	0.99995	0.000	0.992
19	0	0.000	1	.	0.008

Discussion

This to be the first study to demonstrate that a complete eight point PEWS recorded in paediatric ambulance patients can predict outcome on a population basis; specifically ICU admission within 48 hours or death within 30 days for an unselected group of paediatric ambulance patients aged under 16 years. The study group are a national cohort with a robust follow up of 30 days.

Despite their widespread adoption, the utility of PEWS in inpatient settings for which they are designed has long been debated. A number of systematic reviews have examined PEWS in the in hospital context.

Thirty three different Paediatric Track and Trigger Systems (PTTS) were reviewed (Chapman et al., 2016). PTTS describes an early warning component, tracking – equivalent to PEWS - and a trigger component, which is the response. There was considerable heterogeneity in the parameters used in the PEWS component. The variety of different PEWS made comparison between different systems difficult to make. Overall their conclusion was that there was limited evidence for the validity and clinical utility of PEWS. Further research was needed around the thresholds used for the vital signs and the reliability, accuracy and calibration of PTTS in different settings.

A systematic review (Lambert et al.,2017) conducted a review, looking at PEWS. This group identified 90 separate papers as eligible for analysis. They concluded that there was no clear evidence of superiority of one PEWS system over another. The studies examined did however highlight some evidence of improvements in clinical and process-based outcomes for clinically deteriorating children. Favourable outcomes were also identified for enhanced multidisciplinary team work, communication and confidence in recognising, reporting and making decisions about child clinical deterioration.

The lack of clarity around evidence supporting the use of PEWS extends to their use in the ED. This also extends into pre-hospital practice where, there remains scepticism about the validity of PEWS (Roland and Jahn, 2012). If early warning

scores are to live up to their name then identifying an ill child at the earliest point in their health care journey has the potential to lead to earlier intervention and improved outcomes. Demonstrating the utility of PEWS (Scotland) to identify patients at the time of ambulance conveyance is therefore an important new contribution.

In the case of ambulance patients it can be postulated that PEWS (Scotland) may be of benefit in giving ambulance crews an objective measure on which to pre-alert a receiving ED to the arrival of an unwell paediatric patient. With the changing structure of receiving arrangements for paediatric patients, PEWS (Scotland) could allow for re-routing patients to appropriate receiving centres, when it is recognised that there is an increased risk of requiring active intervention including admission to intensive care, or the skills of a trauma team. Children have higher physiological reserve than adult patients and can often cope well in the early phases of illness or injury but then demonstrate a rapid decompensation, with measurable changes in physiological markers or PEWS. Reversing the decompensation in, for example sepsis, at this stage can be challenging and time critical. In an attempt to maximise "early warning", the design of paediatric scoring systems take this compensation phase into account and are often criticised for being too sensitive and non specific at low scores, or too specific but not sensitive enough at higher scores. In addition using a PEWS in a group of patients or environment for which they were not designed can also cause issues as sensitivity and specificity varies with underlying diagnosis (trauma, surgical, medical), environment or outcome measure used for validation (admission to hospital, significant illness). As such each PEWS system has a recommended score to escalate care within that environment, with the assumption that specificity increases with increasing score.

Youden's index in this study of PEWS (Scotland) demonstrates optimal sensitivity (0.71) and specificity (0.78) at a PEWS of 5. It is conceivable therefore that a PEWS (Scotland) of 5 could be recommended as the threshold for pre-alert or enhanced pre-hospital professional to professional advice irrespective of age and gender. As the PEWS (Scotland) increases it becomes less sensitive but more specific so setting

inflexible thresholds risks increasing proportions of patients with false negative scores. As such, using a PEWS (Scotland) of 5 as the sole criteria to pre-alert receiving EDs could cause children with significant illness or injury to be missed. Studies in ED suggest PEWS may be better at identifying medically unwell patients than surgically unwell/trauma, and that therefore suggests that PEWS (Scotland) can support, but not replace, triage.

All teaching on PEWS (Scotland) in hospital settings reiterates the importance of "staff or carer concerns" which are seen to "trump" a low score when present and contribute to the in-hospital PEWS (Scotland) system. As this study population is an unselected group transferred by ambulance, it is likely that parent/ carer concern will be high, however it may be that the sensitivity of the score could be enhanced by the tacit knowledge input of the paramedic crew. Further research in this area is ongoing in hospital settings and could enrich this study if replicated in the ambulance service.

A survey of paramedics (McLelland and Haworth, 2016) has shown that NEWS is used to support but not replace or override their clinical knowledge and pre-hospital assessment tools. This is consistent with teaching on PEWS to clinical staff caring for children in hospital.

Limitations

Internal validity

Despite identifying in excess of 100,000 patients with matched data, only 21% had a complete set of observations to calculate a PEWS. Comparing the whole study population with those where full physiological and outcome data is available, the demographics are similar. However it is, by definition, impossible to state that the PEWS values would be similar in both groups. Whilst the outcomes for those with a PEWS (Scotland) appear representative for the whole sample it is not clear this would hold true for the PEWS (Scotland) score itself. During the development of PEWS (Scotland) concern has been raised by pre-hospital clinicians that a PEWS would be difficult to calculate. It is recognised that even in hospital a full set of

observations may not be taken. There are particular issues with reliable blood pressure measurement in hospitalised children (Bird and Michie, 2006) along with capillary return (Fleming et al., 2015). This is in addition to difficulties with monitor pickup in small infants with cool peripheries. PEWS may have better predictive values in acute medical illness compared with trauma. All of these factors may contribute to whether a full set of observations are recorded in the pre-hospital environment.

External validity

This study has defined the primary outcome as admission to ICU within 48 hours or death within 30 days. These significant outcomes are thankfully rare in children and young people. PEWS (Scotland) has been shown to recognise these outcomes for children in hospital but this is the first evidence that PEWS (Scotland) can also identify admission to ICU within 48 hours or death within 30 days, in the pre-hospital environment as well. It could be hoped that critically ill children would be transferred to hospital by ambulance, and those less unwell present via other modes of transport. It is not known how many critically ill children self-present but it is recognised that many children taken to hospital by ambulance are discharged home without hospital admission. As this population is an unselected ambulance cohort it is not clear how the results generalise to all unwell or injured children. Care should be taken if applying the results to other pre-hospital settings, for example GP practice, out of hours services or minor injuries units, where a higher proportion of lower acuity illness may be seen.

The PEWS (Scotland) was developed for inpatient units drawing on the combined expertise of front line clinical staff and clinical academics, a Delphi process and extensive testing. It was validated for in hospital use by Chapman et al (2017) in their comparative paper. Similar to the findings in this study, the optimal sensitivity and specificity as per Youden's Index is 5 for predicting death or ICU admission for paediatric inpatients included in that inpatient study population. This comparative study demonstrates that some PEWS are better at predicting outcome than others. The PEWS (Scotland) had an AUROC of 0.81 which would place it 9th in the comparison table (unpublished data). It cannot be assumed that all PEWS would

predict outcome in this, or any other, group of unselected ambulance patients. It was intended that PEWS (Scotland) would be validated for pre-hospital use in various settings once established in hospital practice. As a score of 5 shows optimal sensitivity and specificity in both ambulance and inpatients, this permits a shared understanding of clinical staff throughout the patients' journey of what a score of 5 may mean.

Whilst any recognition system should be designed to identify those at highest risk of adverse outcome, many PEWS studies also seek to use PEWS to predict hospital admission. Unlike the pre-hospital ability of PEWS (Scotland) to predict adverse in-hospital outcome, it is not known whether PEWS (Scotland) can also be used to predict which patients transferred by ambulance require hospital admission. Should PEWS (Scotland) be used to support pre-hospital triage, recognition and decision making for patients requiring admission, appropriate validation should be undertaken to support safe transfer to an appropriate centre without either increasing secondary transfers or overloading major paediatric receiving units.

Lastly, as a single PEWS has been adopted through all paediatric units in Scotland, this study supports the use of this scoring system in children transferred by ambulance. Whilst many teams continue to work on identifying the best PEWS for use in hospital, it is recommended that we continue to move towards a UK standardised score, both in hospital and pre-hospital as is seen in NEWS.

Conclusions of Part 3

These data show PEWS (Scotland) to be a useful tool in a pre-hospital setting. A single set of physiological observations undertaken prior to arrival at hospital can identify a group of children at higher risk of an adverse in-hospital outcome. Paediatric care is becoming more specialised and focussed on a smaller number of centres. In this context, use of PEWS in the pre-hospital phase may allow changes to paediatric pre-hospital pathways to improve both admission to ICU and child mortality rates.

Chapter 4 Modification of PEWS: qPEWS prediction of adverse outcome

Introduction

Chapter 3 demonstrated that a single PEWS in the prehospital environment was predictive of adverse outcome in unselected paediatric ambulance patients.

The utility of Paediatric Early Warning Scores (PEWS) in hospitals remains contentious, but there is growing evidence to support their role in recognising deterioration hours before a critical event in children. One might expect that most UK paediatric units will use an early warning score following the recommendations of the UK report "Why children die". Despite their profusion only a minority of scores have been tested before their introduction into clinical practice. Within Scotland, Clements et al (2008) found that only 2/14 paediatric early warning scores had published their retrospective testing.

The variables used and the outcomes measured vary between scores. However, all scores use heart rate and respiratory rate and most included oxygen saturations, supplemental oxygen and conscious level. Fewer scores included blood pressure, respiratory effort, capillary return and temperature. Clinical opinion has largely determined which variables to test. Variables with prognostic significance in one disease, for example bacterial or viral respiratory infections, may be inappropriately included in scores for other diseases. Doubt as to which variables to use has led to large multicentre studies. The performance of any score depends upon the reliability with which its components are measured. In the initial bedside study all variables were recorded for only 1 in 20 children, the reasons for which are complex. Variables measured infrequently and that are subject to systematic error, such as blood pressure, are more likely to impair a score's performance.

Literature Review

The Paediatric Early Warning Score (Scotland) was introduced with the intention of creating a single score with the ability of differentiating unwell children through

the whole patient journey and create a common language for communicating this. It is now embedded in inpatient practice in Scotland and therefore this piece of work aims to assess the validity of PEWS in the pre-hospital environment. In the data presented in Chapter 3, 21,202/102,993 (21%) children had all eight components of a paediatric early warning score recorded when transported by ambulance to hospital. Some variables were measured less often than others, which might reflect the difficulty of measuring blood pressures in crying children, unreliable pulse oximetry in moving vehicles and a disbelief that temperature in a recently-injured child might be useful. The eight point PEWS may have compromised the utility of this early warning score in the pre-hospital environment by including some variables that cannot be reliably measured by paramedic crews in ambulances

The basis for developing PEWS has always been "making it easier to do the right thing and more difficult to do the wrong thing" and in paediatrics in particular, to reduce the cognitive load of applying age related values. Whilst some of the cognitive load is removed by the electronic patient report form (ePRF) in the pre-hospital setting calculating the PEWS, it could be argued that the low rate of fully completed all eight point PEWS scores reflects that we have either not created an understanding of the need for collecting all of the vital sign parameters or not made it easier for paramedic crews thereby compromising both the utility and applicability of the PEWS score. Abbreviation of the score by reducing the number of components could increase the number of children with calculable scores.

Aims

The aim of this study was to determine the discrimination of abbreviated versions of the paediatric early warning score for the outcomes assessed in Chapter 3: admission to intensive care within 48 hours of ambulance transfer or death within 30 days.

Methods

The methods were outlined in the Chapter 3. Briefly, this study included all children (< 16 years) conveyed by the Scottish Ambulance Service to hospital from 2011 to 2015. The study did not include children in cardiac arrest or children transferred

between hospitals. Risk scores of 3 and 1 for each (of seven) physiological variables were assigned if they deviated outside their 99%CI and 95%CI, respectively, adjusted for five age categories: Glasgow coma score; heart rate; systolic blood pressure; respiratory rate; pulse oxygen saturation; temperature; time to capillary reperfusion. The study assigned a score of 1 if supplemental oxygen was given. The study analysed the association of scores with a composite of all-cause mortality within 30 days or admission to intensive care within 48 hours of ambulance attendance, identified by linking records with the Community Health Index or NHS number. The physiological values recorded from the first instance that all eight variables were recorded. Missing values were not imputed.

The area under the receiver operating characteristic (AUROC) curve was used to calculate the associations of variables and their combinations with outcome. For patients with all eight variables recorded, variables were entered sequentially into a multivariable binary logistic model, adding the variable that in combination with the existing model associated most with outcome, if $p<0.05$ and removing variables if $p>0.1$. The AUROC for each cumulative model was compared to using all eight components using DeLong's test. Sensitivity analyses were performed for each model with and without supplemental oxygen delivery. SAS® software was used for all analyses (version 9.4, SAS Institute Inc.; Cary, NC, USA) and assumed two-sided $p < 0.05$ statistically significant. We did not test differences in the AUROC curves for different abbreviated models as the number of children (and outcomes) were different.

Results

Data were available for 102,993 children. The number of children who had values recorded were: supplemental oxygen 102,993 (100%); Glasgow coma score 83,648 (81%); heart rate 83,330 (81%); systolic blood pressure 37,088 (36%); respiratory rate 90,358 (88%); pulse oxygen saturation 71,372 (69%); temperature 60,402 (59%); time to capillary reperfusion 81,685 (79%). Recorded observations varied considerably by age (Figure 4-1)

Figure 4-1 . Percentage of value observed against age for all eight PEWS components

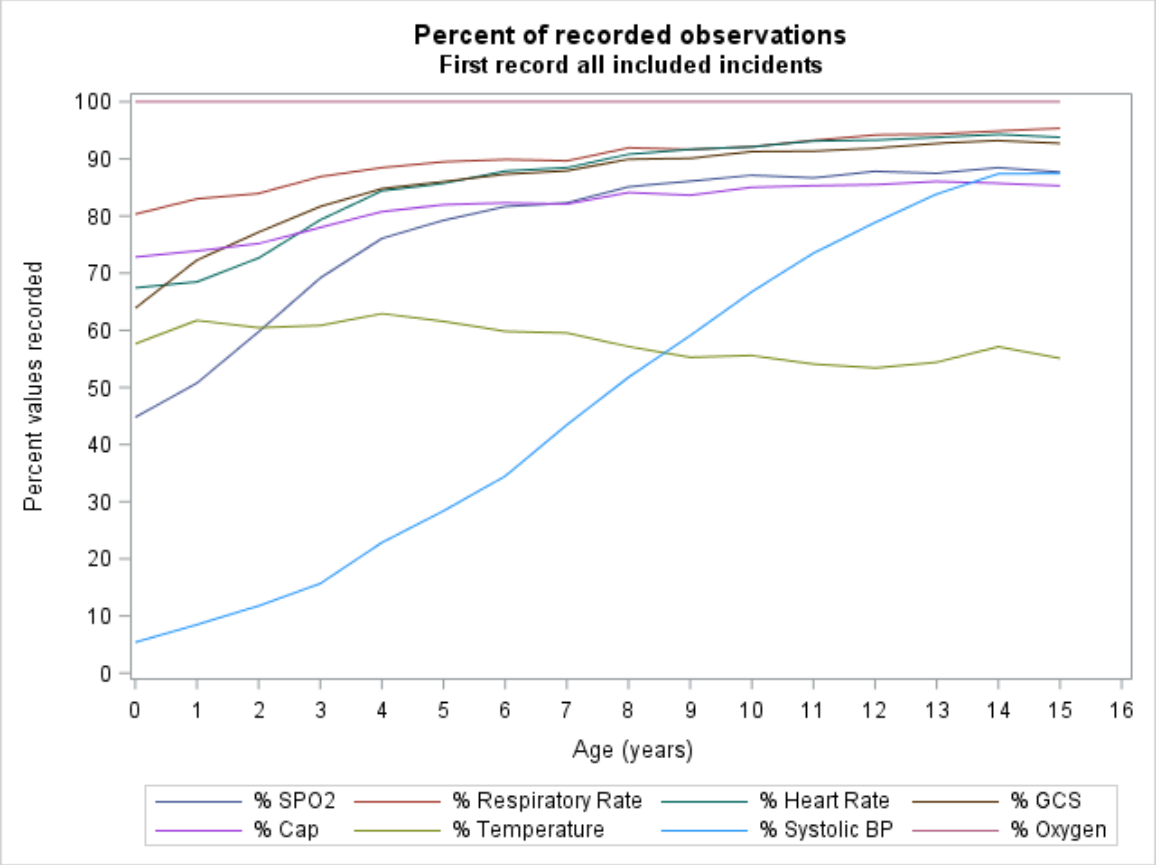


Table 4-1 demonstrates the number of sets of complete observations recorded by using different combinations of variables. This varies from 20.5% for the full 8 components of PEWS to 72.3% for a combination of 3 vital signs.

Table 4-1 PEWS components combinations data capture rates

PEWS Components required		N	%
All included incidents		102993	100.00
3 vital sign parameters	GCS,HR, RR (GHR)	74508	72.34
ABCD approach	GCS, HR, RR, SpO2 (GSHR)	64202	62.34
5 vital sign parameters	GCS, HR, RR, Temp, Cap	45734	44.40
4 of the above 5 parameters	GCS, HR, RR, Cap (GHRC)	66449	64.52
	GCS, HR, RR, Temp	51007	49.52
	HR, RR, Temp, Cap	48242	46.84
	GCS, RR, Temp, Cap	47588	46.21
	GCS, HR, Temp, Cap	47028	45.66
All PEWS components		21202	20.59

GCS=Glasgow Coma Score, HR=Heart Rate, RR=Respiratory Rate, SpO_2=pulse oximetry, temp=temperature, cap=capillary return

As described in Chapter 3, the event rate for this cohort was 1178 for the primary outcome of ICU admission within 48 hours or death within 30 days. Admission to intensive care within 48 hours of ambulance transfer occurred in 1053 patient and death within 30 days occurred in 153 patients. Some patients experienced both ICU admission and death within 30 days.

For the 21202 complete records, a stepwise analysis was undertaken using the first available known PEWS(Scotland) component. All eight components of the PEWS were independent predictors of the primary outcome. However, Table 4-2 shows that from step 4, none of the AUROC are significantly different from that using all components.

Table 4-2 Stepwise analysis of individual PEWS components

Step	PEWS component Entered	Entry into stepwise model p-value [1]	AUROC for cumulative model	Comparison with all PEWS components known p-value [2]
1	O_2 Delivery	<.0001	0.6916	<.0001
2	Conscious level (GCS)	<.0001	0.7529	<.0001
3	Heart rate (HR)	<.0001	0.7943	0.0126
4	Oxygen Saturations (SpO_2)	<.0001	0.8019	0.0799
5	Systolic BP	0.0053	0.8107	0.4281
6	Respiratory Rate (RR)	0.0222	0.8114	0.4769
7	Temperature score (Temp)	0.0490	0.8139	0.9580
8	Capillary Return (Cap)	0.0430	0.8138	N/A

Although some individual PEWS(Scotland) components performed well in the stepwise regression, the data in Figure 4-1 shows an age-related variation in rate of recording of the variables. The information from component data capture rate, individual PEWS component performance as well as clinical consideration, including ease and importance of collection, were combined to create qPEWS candidates in addition to PEWS(Scotland). The data capture rates within this dataset for combinations of individual PEWS components are given in Table 4-1. As well as a data driven combination of physiological components, an Airway-Breathing-Circulation- Disability (ABCD) approach of PEWS components was included, as this

was felt to be a clinically important structured approach. These combinations of individual components were all investigated as potential qPEWS.

Whilst it may be a proxy for parental or practitioner concern, oxygen delivery is not a true physiological observation, it is a delivered therapy. In some settings, oxygen may also not be available to be delivered. Therefore, when testing the potential qPEWS, oxygen delivery was analysed as another variable – each qPEWS was tested with and without oxygen therapy.

A comparative model was constructed to compare the various potential qPEWS (each qPEWS is the sum of the PEWS components used) as well as the original 8 component PEWS(Scotland):

4 best scoring components using stepwise regression – **O**xygen therapy, Conscious Level (**G**CS), **H**eart Rate, Oxygen **S**aturation (OGHS)

Highest data capture 4 components – Conscious Level (**G**CS), **H**eart Rate, **R**espiratory Rate, **C**apillary Return with and without **O**xygen (GHRC & GHRCO)

ABCD approach – Conscious Level (**G**CS), Oxygen **S**aturation, **H**eart Rate, **R**espiratory Rate with and without **O**xygen (GSHR & GSHRO)

"Resource Limited" approach – Conscious Level (**G**CS), **H**eart Rate, **R**espiratory Rate with and without oxygen (GHR & GHRO).

These data are shown in Table 4-3

Table 4-3 Comparison of Utility of PEWS components combination

Components	N	AUROC [1]	Youden's index	Sensitivity at Youden's index	Specificity at Youden's index
PEWS	21202	0.7976	5	0.710	0.783
OGHS	67265	0.7833	2	0.757	0.692
GHRCO	66449	0.7711	2	0.759	0.667
GHRC	66449	0.7529	3	0.659	0.741

GSHRO (= ABCDO)	64202	0.7990	4	0.666	0.800
GSHR (= ABCD)	64202	0.7921	3	0.744	0.697
GHRO	74508	0.7683	2	0.748	0.672
GHR	74508	0.7480	3	0.661	0.738
O = oxygen delivered, G = GCS, H = heart rate, S = SpO_2, R = respiratory rate C = Cap return time					

The outcome rate in all model cohorts was around 1%: threshold scores discriminated children with an outcome rate < 1% (in about two thirds) from children with an outcome rate 2%-3% as shown in Table 4-4Table 4-4).

Table 4-4. The performance of different models for how variables recorded for 102,993 children transported by ambulance to hospital associated with subsequent admission to paediatric intensive care (48 h) or death (30 days).

Variables	Number	Events	AUROC	Threshold Value	Sensitivity	Specificity	PPV	NPV
GCS, HR, RR	74,508	799	0.75	3	0.66	0.74	2.7%	99.5%
GCS, HR, RR, O_2	74,508	799	0.77	2	0.75	0.67	2.4%	99.6%
GCS, HR, SpO_2, O_2	67,265	728	0.78	2	0.76	0.69	2.6%	99.6%
GCS, HR, RR, CRT	66,449	684	0.75	3	0.66	0.74	2.6%	99.5%
GCS, HR, RR, CRT, O_2	66,449	684	0.77	2	0.76	0.67	2.3%	99.6%
GCS, HR, RR, SpO_2	64,202	679	0.79	3	0.74	0.70	2.6%	99.6%
GCS, HR, RR, SpO_2, O_2	64,202	679	0.80	4	0.67	0.80	3.4%	99.6%
GCS, HR, RR, Temp	51,007	513	0.74	3	0.72	0.68	2.2%	99.6%
HR, RR, Temp, CRT	48,242	492	0.69	2	0.68	0.63	1.9%	99.5%
GCS, RR, Temp, CRT	47,588	461	0.72	3	0.55	0.83	3.1%	99.5%
GCS, HR, Temp, CRT	47,028	474	0.73	3	0.68	0.72	2.4%	99.5%
GCS, HR, RR, Temp, CRT	45,734	450	0.75	3	0.72	0.68	2.2%	99.6%
GCS, HR, SpO_2, O_2*	21,202	176	0.80	5	0.71	0.78	2.7%	99.7%

*For the 21,202 children for whom all eight variables were recorded.

AUROC, area under the receiving operator characteristic curve; CRT, capillary refill time; GCS, Glasgow coma score; HR, heart rate; O_2, supplemental oxygen; RR, respiratory rate; SBP, systolic blood pressure; SpO_2, oxygen saturation; Temp, temperature.

Discussion

This study shows that in an unselected population of ambulance patients, four components of the paediatric early warning score (PEWS) were as good as all eight components for discriminating between children who died within 30 days or were admitted to intensive care within 48 hours of emergency ambulance transfer to hospital: oxygen delivery; conscious level; heart rate; and oxygen saturations.

Which components of the multiple PEWS scores, in use internationally, best predicts outcome remain under debate. This study has demonstrated that each of the 8 components which contribute to the PEWS(Scotland) are independent predictors of the adverse outcomes of admission to PICU within 48 hours or death within 30 days in unselected children and young people < 16 years old transferred to hospital by ambulance. Furthermore, this study has demonstrated that the stepwise AUROC

increases little after the first 4 components of oxygen delivery, conscious level, heart rate and oxygen saturations. Reducing the number of PEWS components from eight to four increases greatly the number of valid observations from this study (at least one record with a complete set of values), especially as systolic blood pressure and oxygen saturation, in particular, have very low observation rates in the early years.

As the AUROC increases little after these first 4 components, consideration has to be given as to the ease of collecting the vital sign parameter as well as their relative contribution to the AUROC when determining what to include in a qPEWS. Taking all of this into account, this study has demonstrated that it is worth considering the following vital signs when deriving and further testing a qPEWS:

OGHS (Oxygen Delivery, Conscious Level, Heart Rate and Oxygen Saturation)

ABCD (Conscious Level, Respiratory Rate, Oxygen Saturation and Heart Rate)

GHRC (Conscious Level, Heart Rate, Respiratory Rate, Capillary Return)

GHR (Conscious Level, Heart Rate, Respiratory Rate)

The development and use of a qPEWS is a pragmatic approach as reducing the number of parameters/vital signs recorded will increase the reliability of the vital sign documentation due to the simplification of the process. In the pre-hospital assessment of sick children and young people, it can be challenging to complete a full set of eight observations which is reflected in the relative proportions of patients who do not have a full set recorded not only in this paper, but in the original PEWS paper. Failure to perform and document the eight observations can be due to challenges with accessing age appropriate equipment for example blood pressure cuffs and pulse oximetry probes, difficulty in interpreting observations when children are crying and distressed, and finally due to the perceived relative importance of some physiological parameters over others in various circumstances. The issue of crying and distress impacting upon vital sign observations is reduced in hospital where PEWS scores are used to track physiological changes over time compared to a single set of vital sign recordings in the pre-hospital setting.

It is recognised that some PEWS scoring systems are more predictive than others for children and young people who deteriorate in hospital. Interestingly two of the top performing three scores in that comparison do not score for conscious level which led to me assessing the aforementioned combinations of variables which may be felt to be more clinically relevant, useful or more easily measured.

Simplification of vital sign recording to just 3 or 4 parameters (OGHS, ABCD, GHRC or GHR) will not just improve the chances of reliable observations, but may also enhance the timeliness of the recordings of all four observations in a pre-hospital setting (Hoffmann et al., 2016). These four simple vital signs can be completed quickly with conscious level measured via an AVPU score, and both heart rate and oxygen saturation being measured with a pulse oximeter whilst also determining the need for oxygen therapy.

In a resource limited setting, the implementation of PEWS has been shown to improve outcomes (Agulnik et al., 2017). The "Resource Limited" approach (GHR) to qPEWS scoring lends itself to remote, rural and resource limited settings where the lack of technology to perform vital sign measurement may make it easier for staff to undertake track and trigger, enhancing compliance whilst also expediting the recognition and ultimately treatment of the acutely ill child or young person. In the situation where further observations may not significantly improve the AUROC and lead to better prediction of adverse events, it could be suggested that taking further observations which may not enhance the qPEWS score could take more time and lead to delays in transfer to definitive care. Meanwhile a simplified three or four point qPEWS score could contribute to pre-hospital clinical decision making including when and where to transfer an acutely ill child or young person.

This study has shown that for the 4 different types of qPEWS, whether oxygen delivery as a parameter is included or not, each qPEWS compares well to PEWS with a similar AUROC, specificity and sensitivity and approximately three times the

completion rate of PEWS. This study has shown that simplification of PEWS(Scotland) to the various qPEWS does not sacrifice the accuracy of qPEWS as a tool to predict adverse outcomes. The decision on which qPEWS to use in the pre-hospital setting depends on ease of use, practical and clinical considerations such as the availability of technology such as pulse oximeters, non-invasive blood pressure monitors or sphygmomanometers and stethoscopes. As such, GHR qPEWS will most likely have the greatest applicability in both resource intensive and certainly resource limited settings

Limitations

This study has defined the primary outcome as admission to PICU within 48 hours or death within 30 days. Thankfully these adverse events are rare in children and young people. Not all unwell or injured children present to hospital via ambulance and as this population are unselected paediatric ambulance patients from Scotland, it is not clear how the results generalise to all children and young people. Care should therefore be taken in extrapolating the results to other pre-hospital settings, such as resource limited settings or indeed GP practices or, minor injuries units, where a higher proportion of lower acuity illness may be seen. A large number of patients conveyed to hospital by ambulance are not subsequently admitted to hospital – in this cohort only 29.9% of patients were admitted to hospital. This study has not looked at the utility of pre-hospital qPEWS in predicting hospital admission or discharge.

It cannot be presumed that any of these qPEWS are transferrable to inpatient settings or whether each physiological parameter would remain independent predictors of adverse outcome in an inpatient setting. This study has only looked at the physiological parameters and ranges included in the PEWS(Scotland). Each PEWS varies with which parameters are included, but also the thresholds for triggering a score by age. It therefore cannot be assumed that simplifying any PEWS to a qPEWS would convey the same degree of prediction. It is conceivable that it is the proportionate weighting and trigger thresholds of each physiological parameter which results in the contribution to outcome prediction. PEWS(Scotland) is

relatively weighted to tachycardia which triggers at 90th centile where the other physiological parameters trigger at 95th centiles,[33] and conscious level where anything less than *alert* on the AVPU scale is weighted the same (whereas some scoring systems grade V to U).

Finally, PEWS scores have been traditionally used to predict deterioration in hospital where the scores are monitored over time looking for trends to highlight deterioration. In this study of PEWS(Scotland) and qPEWS in unselected ambulance patients, a single set of observations is used to calculate both PEWS, qPEWS and predict outcome. Although there is evidence that a single set of observations can predict outcome, it is conceivable that the same core measures may not be as sensitive nor specific at predicting inpatient deterioration of the child and young person.

Conclusions of Chapter 4

This is the first study which looks at the relative predictive value for each physiological parameter contributing to a Paediatric Early Warning Scoring System. It highlights that a score including conscious level, heart rate and respiratory rate is as robust in this pre-hospital group of children and young people, as a scoring system including all eight parameters. It is not clear how transferable these data are to other pre-hospital or in hospital settings including Emergency Departments, but these results offer a platform for further exploration of simplified scoring systems such as the qPEWS.

The simpler a system is, the more likely it is to be adhered to. A simplified qPEWS of conscious level, heart rate and respiratory rate may offer potential to be used in both primary care and resource limited settings but it is recommended that this is explored further in those populations prior to adoption and implementation.

Chapter 5 Prehospital PEWS as a predictor of the need for hospital admission

Background

Chapter 3 showed that the PEWS(Scotland) was able to identify those children at higher risk of an adverse outcome, ICU admission and/or death within 30 days. In Chapter 4 this concept was developed further and looked at the eight individual components of the PEWS(Scotland) and their predictive value. Chapter 4 showed that using a smaller number of components did not lead to a loss of discriminative ability in predicting adverse outcome. However, by using a smaller number of components this allows an improved rate of data completion, compared with using the full eight components.

Early Warning Systems (EWS) were initially developed to recognise physiological deterioration early in order to facilitate identification of those at risk of critical illness and trigger clinical review. As outlined in the previous chapters, these systems were created in order to track adult ward patients and previous chapters have explored their utility in an Emergency Department and pre-hospital setting.

The EPOCH cluster, randomised controlled trial into the effect of PEWS versus usual care across twenty one hospitals found similar results to the adult population with no effect on overall mortality but was associated with earlier ICU admission (Parshuram 2018). Overall 350-450 children die in Scotland, with around 2000 requiring admission to a paediatric intensive care unit. Both ICU admission and death within 30 days thankfully remain a relatively rare event.

However, there are approximately 70,000 emergency admissions of children and young people to hospital every year in Scotland. Approximately 35% of these emergency admissions arrive at hospital by ambulance. As outlined in previous chapters, PEWS also has the potential to be used in pre-hospital care and by ambulance services. Most ambulance services routinely collect the physiological data required to calculate a PEWS. Chapter 3 showed that a single elevated PEWS Scotland when a patient is assessed by ambulance staff is associated with a higher

risk of adverse outcome (ICU admission or death within 30 days). There is also potential to simplify the process with the use of an abbreviated, or quick PEWS (qPEWS) which Chapter 4 has shown to be associated with a higher risk of an adverse outcome.

Literature Review

There are a number of different studies that have examined the utility of Paediatric EWS at predicting hospital admission in children and young people.

The earliest study (Bradman 2008) was a prospective cohort in a single UK centre over a period of 2 weeks. 774 children attended during this period but only 424 were included in the study, the remainder being redirected or discharged during the triage process. The admission rate was 13.9% (59/424). A PEWS of 2 or more was associated with a likelihood ratio of admission of 3.1 compared with a PEWS of 0. This incremental increase was also seen with a PEWS of 3 or more (LR 4.6) and PEWS of 4 or more (LR 4.75).

A single centre study from Netherlands (Seiger et al., 2013) examined 10 different PEWS in a prospective cohort. All children presenting to a paediatric tertiary centre in the Netherlands over a 3 year period were included. One of the outcome measures used was predicting need for hospitalisation. A total of 17943 patients were included with an event rate of 16% admission to hospital and 2% admission to ICU. The area under the ROC curves for predicting hospitalization was poor to moderate (range: 0.56 [95% CI: 0.55-0.58] to 0.68 [95% CI: 0.66-0.69]). The sensitivity and specificity derived from the ROC curves ranged widely for hospital admission (sensitivity: 36.4%-85.7%; specificity: 27.1%-90.5%). None of the PEWS had a high sensitivity as well as a high specificity.

Further data from a single Norwegian centre (Solevag et al, 2013) examined the association of PEWS with an adverse outcome. This was a retrospective cohort study over 3 months and included 761 patients. In this study a PEWS >2 was associated with a higher incidence of surrogate markers of severe illness such as fluid resuscitation and intravenous antibiotics when compared to PEWS <3. The rate of admission to critical care was also significantly higher in the PEWS >2 group.

A North American study (Breslin et al., 2014) examined the association between the PEWS at the time of Emergency Department attendance and disposition. This was a single centre study undertaken over 8 months in an urban, tertiary care paediatric centre in the United States of America. 383 patients were included with an event rate of admission to hospital of 33% (126/383). The area under the ROC curve was 0.68 (95% CI, 0.63 to 0.73).

Comparison of a number of different approaches (Bradman et al., 2014) aimed to compare triage nurse predictions against a PEWS, Manchester triage category and also two other tools, the Paediatric Risk of Admission Score (PRISA) and updated version, PRISA II. This was a prospective observational study undertaken in a single tertiary, paediatric Emergency Department in Australia over a single week. The outcomes of interest were hospital admission, including admission to critical care. A total of 946 patients were included for analysis. Cutoffs for positive predictive tools were PEWS>4, triage category 3 or above, PRISA>=9 and PRISA II >=2. Sensitivity varied from 10.6% (95% CI 6.0 to 15.6) for triage category to 77.5% (95% CI 70.5 to 83.6%) for triage nurse. Specificity also varied from 87.1% (95% CI 84.6 to 89.4%) for PRISA I to 98.7% (95% CI 97.7 to 99.4%) for triage category. AUROCs were not given for the various methods.

Further data (Chaiyakulsil et al., 2015) reported on the validation of PEWS in the Paediatric Emergency Department. The setting for this study was a single centre tertiary, paediatric ED in Thailand over a 3 month period, with data collected prospectively. This study excluded trauma and surgical patients, including only those with medical illness. 1136 patients were available for inclusion, however the event rate for admission is not explicitly stated. The AUROC for predicting overall admission was 0.73 (95%CI: 0.68–0.77). The sensitivity and specificity in predicting overall admission with a cut-off of PEWS ≥1 were 78% and 59.6%, respectively. PPV was 27.7% and NPV was 94.8%.

Two versions of PEWS (Lillitos et al., 2016) were used to assess ability of PEWS to predict need for hospital admission. This was a single centre UK study based on retrospective data for a single month. Patients were grouped on medical and surgical diagnoses. Results were available for 1921 patients with an admission rate of 11% (211/1921). For hospital admission overall a PEWS of ≥3 was specific (93%) but poorly

sensitive (32%). The area under the receiver operating curve (AUROC) was low at 0.690. Significant illness: for medical illness, PEWS ≥3 was highly specific (96%) but poorly sensitive (44%). The AUROC was 0.754 and 0.755 for the two local PEWS, respectively. Both scores performed poorly for predicting significant surgical illness (AUROC 0.642). Subgroup analysis showed PEWS ≥3 performed well in predicting respiratory illness requiring admission: AUROC of 0.900 and 0.866 for the two local PEWS with sensitivity 75%, specificity 91%.

There is also evidence regarding respiratory illness specifically in children (Van der Loeff and Campbell, 2017). This was a prospective observational study of children admitted to a single UK centre over a 4 month period, during peak RSV season. Data were available for 73 patients. This showed that increased PEWS was associated with length of hospital stay ($p<0.001$). Need for critical care admission (level 2 high dependency care) was associated with a mean PEWS of 4.2 compared with 2.3 for those not needing critical care ($p<0.001$).

These studies show there is no clear consensus regarding a cut off for PEWS which indicates hospital admission, but that higher PEWS scores are associated with an increased likelihood of hospital admission. The issue is further complicated by the heterogeneous nature of the PEWS components and weightings.

No studies were identified specifically on pre-hospital PEWS and likelihood of hospital admission. As described in Chapter 2, Adult National Early Warning Scores (NEWS) have been validated in the pre-hospital environment and high NEWS scores are associated with poorer clinical outcomes (measured by ICU admission or death).

In summary, available evidence suggests that a higher PEWS in the Emergency department is associated with hospital admission.

Aims

Therefore this study examined whether pre-hospital PEWS Scotland is predictive of the need for hospital admission in children and young people being transported by ambulance. Is PEWS Scotland a predictor of hospital admission or length of stay for paediatric patients transported by the Scottish Ambulance Service?

Methods

The methods of data collection were outlined in Chapter 3. Briefly, this study included all children (< 16 years) conveyed by the Scottish Ambulance Service to hospital from 2011 to 2015. The study did not include children in cardiac arrest or children transferred between hospitals. Risk scores of 3 and 1 for each (of seven) physiological variables were assigned if they deviated outside their 99%CI and 95%CI, respectively, adjusted for five age categories: Glasgow coma score; heart rate; systolic blood pressure; respiratory rate; pulse oxygen saturation; temperature; time to capillary reperfusion. The study assigned a score of 1 if supplemental oxygen was given. The study analysed the association of primary outcome of inpatient hospital admission identified by linking records with the Community Health Index or NHS number. The physiological values recorded from the first instance that all eight variables were recorded. Missing values were not imputed.

Statistical Analysis:

SAS® software was used for all analyses (version 9.4, SAS Institute Inc.; Cary, NC, USA). Categorical data are reported as percentages. Odds ratios, their 95% confidence intervals and p-values for each outcome are estimated using logistic regression. The PEWS group and gender are considered independent variables and age as a continuous covariate. Receiver operating characteristic (ROC) curves plotting sensitivity (true positives) against 1-specificity (false positives) are used to measure the accuracy of predicting outcomes. Differences among areas under the ROC are compared using DeLong's test. Results are considered significant at a $p<0.05$ threshold (two tailed).

Results

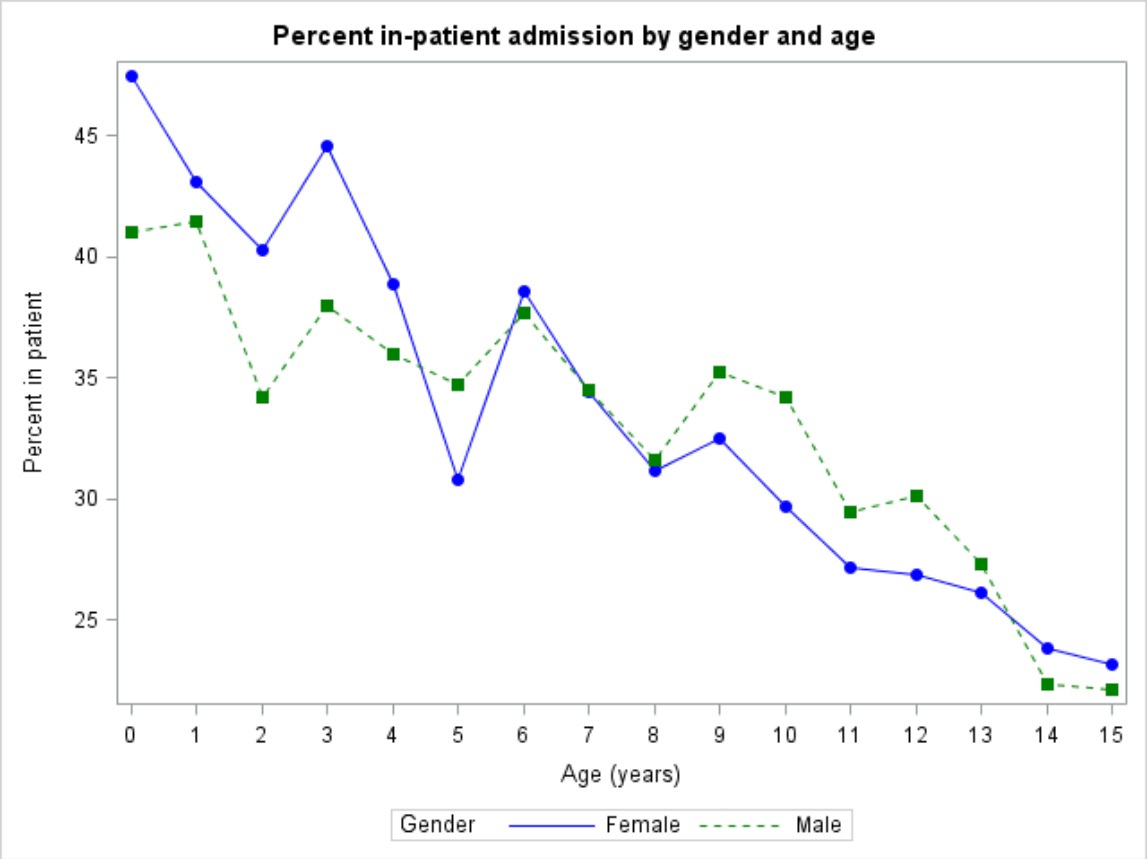
Over the study period, 126,563 patients were conveyed by the Scottish Ambulance Service, of whom 21,202 had at least one full set of eight observations required to calculate PEWS Scotland. Regarding the final outcome of hospital admission, 102,993 had a known outcome, of whom 34,655 were admitted (33.65%). Within the study group of patients with a complete set of pre-hospital observations, 6,340 of 21,202

(29.9%) were admitted to hospital. See Figure 1. There was a statistically significant difference in the rate of hospital admission between these groups (p<0.001).

Demographics

The rate of admission varied considerably with age as shown in Figure 5-1

Figure 5-1 Proportion of patients admitted by age



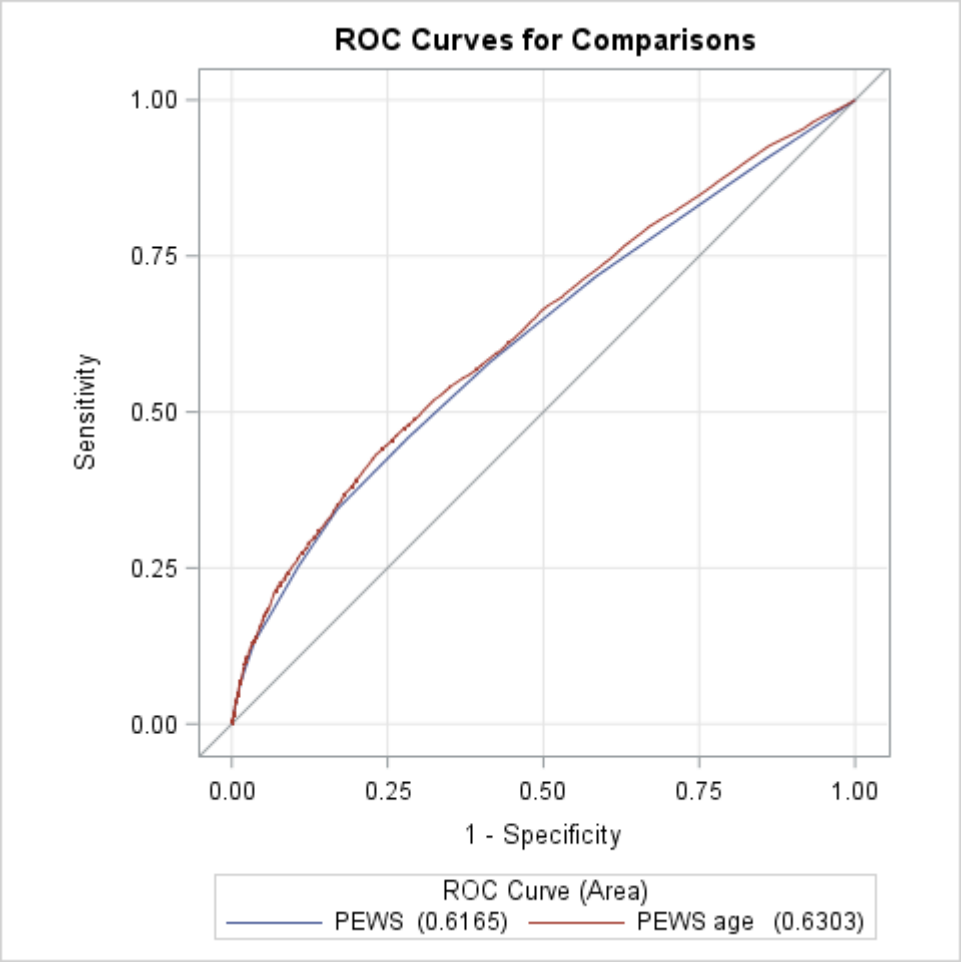
On univariate analysis, pre-hospital PEWS and age are independent predictors of the outcome of hospital admission, but gender is not (Figure 5-2).

Figure 5-2. Odds Ratio for hospital admission

Effect	OR	95% CI and p value
PEWS score	1.189	(1.176 - 1.202); p <0.001
Gender Female vs Male	0.973	(0.915 - 1.034); p = 0.373
Patient Age	0.955	(0.949 - 0.962); p <0.001

Further analysis of PEWS shows AUROC of 0.617 (95% CI 0.6081 - 0.6249; p<0.001), suggesting poor predictive ability of hospital admission. Gender does not significantly alter this (p=0.322) whereas addition of age increase the AUROC to 0.630 (p<0.001). This shown in Figure 5-3

Figure 5-3 AUROC for PEWS and PEWS Age



Analysis of sensitivity and specificity shows a PEWS of 4 to have optimal Youden's Index, in the whole cohort. At this threshold the sensitivity is 46% and specificity is 72% to predict hospital admission. This value varies with age as shown in Table 5-1

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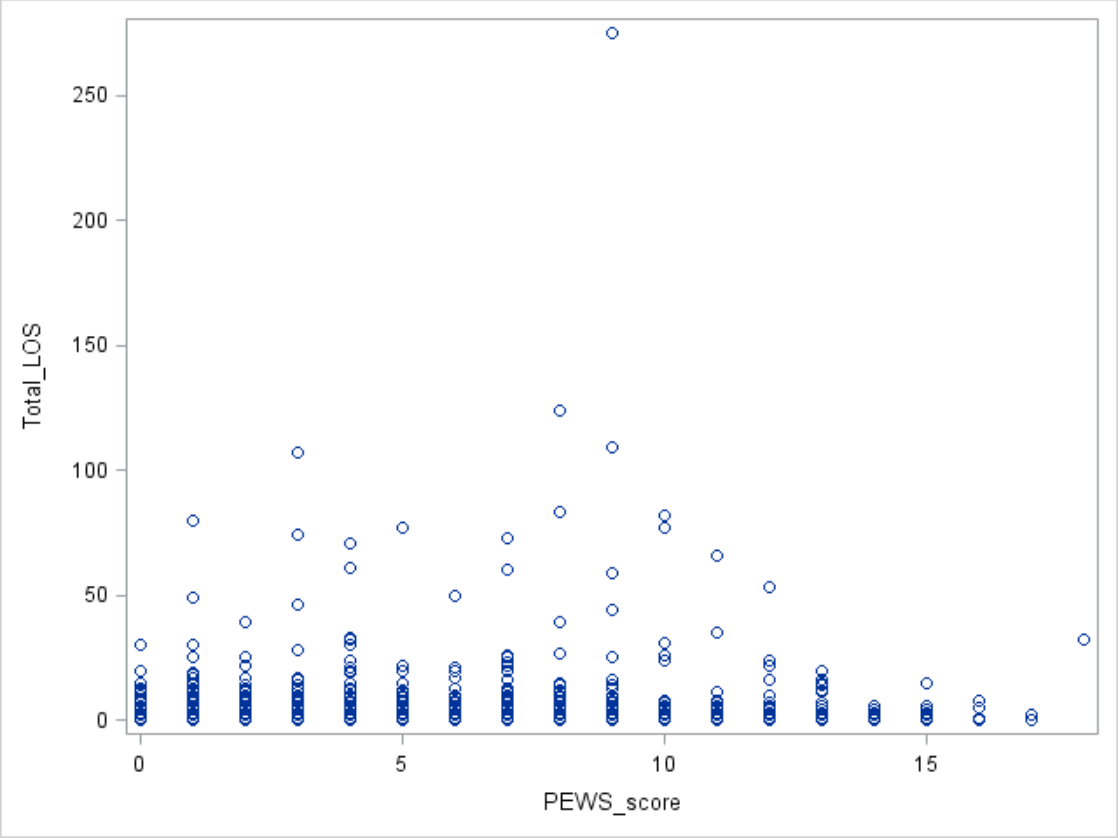
Table 5-1 Youden's value for hospital admission by age

Age (years)	Number	Events	AUROC	Threshold value	Sensitivity	Specificity	PPV	NPV
0	471	207	0.66	5	0.58	0.67	0.58	0.67
1	801	340	0.62	5	0.60	0.59	0.52	0.67
2	788	290	0.66	5	0.56	0.69	0.51	0.73
3	846	341	0.69	5	0.56	0.76	0.61	0.72
4	900	334	0.67	5	0.48	0.79	0.58	0.72
5	828	277	0.63	3	0.58	0.64	0.44	0.75
6	805	305	0.64	3	0.56	0.66	0.50	0.71
7	807	277	0.63	3	0.53	0.70	0.48	0.74
8	835	263	0.60	5	0.29	0.88	0.53	0.73
9	947	324	0.60	3	0.52	0.64	0.43	0.72
10	1107	359	0.60	4	0.37	0.79	0.46	0.72
11	1344	383	0.64	5	0.34	0.88	0.53	0.77
12	1717	494	0.60	3	0.49	0.68	0.38	0.77
13	2228	595	0.59	3	0.51	0.63	0.33	0.78
14	3111	720	0.56	5	0.26	0.84	0.33	0.79
15	3667	831	0.57	3	0.55	0.56	0.27	0.81

There was no correlation between pre-hospital PEWS and length of stay in hospital (r=0.092) (95% CI 0.068 - 0.117). A scatterplot of length of stay against PEWS is shown in Figure 5-4

Figure 5-4 PEWS Score against total length of hospital stay



Discussion

Main findings

This study finds that pre-hospital PEWS Scotland in an undifferentiated population of paediatric ambulance patients in Scotland is a poor predictor of hospital admission. Although age improves this statistically, it remains a poor predictor.

Interpretation

There are no other studies identified which study pre-hospital PEWS in the paediatric population as a predictor of hospital admission.

In comparison, a retrospective analysis of adult ambulance NEWS in England by Burch et al (2008) found that patients with a NEWS classified as 'low risk' were more likely to be discharged, with a positive association between increasing NEWS and disposition (discharged, ward admission, ICU admission, death in ED, $p<0.001$) . PEWS in the Emergency Department has been more extensively studied, with mixed outcomes. It is confounded by the wide variety of PEWS systems studied and the

heterogeneity of the presenting problems in the paediatric population. In 2016, Lillitos examined 1,921 children presenting to the ED and found an AUROC for predicting hospitalisation of 0.690, not dissimilar to the 0.617 found in this study. As the cut off PEWS threshold increases, sensitivity decreases and specificity increases, with this study reporting an optimum cut off of ≥3 for a specificity of 93% and sensitivity of 32%. When examining 10 different PEWS systems in a prospective cohort of 17,943 children, Seiger reported AUROC ranging between 0.56-0.68 for predicting hospital admission. Bradman has performed two studies into the use of PEWS in the emergency department. One looked at 424 patients and found that higher PEWS scores were associated with a higher likelihood of admission, again with a low sensitivity. In 2014, Bradman compared triage nurse, PEWS and paediatric risk assessment score on predicting admission and reported that PEWS ≥4 had a 15% sensitivity and 98% specificity for admission. Triage nurses were found to have a higher predictive accuracy than the other measures studied.

The study also found no association between PEWS Scotland in the paediatric ambulance population and hospital length of stay. A study of 761 children in Oslo reported that children with a PEWS ≥3 had an average stay of three days in comparison to those with a PEWS 0-2 who had an two day average length of stay ($p<0.001$). This study took observations in the ward or emergency department rather than the pre-hospital setting. In addition, all the patients had been referred by a general practitioner which limits comparability with UK studies. In a small, single centre study of 73 children with bronchiolitis, PEWS correlates with length of stay ($r=0.43$, CI 0.22-0.60), and children with a PEWS >3 have a statistically significantly longer hospital stay ($p<0.001$).

Even in a cohort of patients arriving at hospital by ambulance, just under 30% require hospital admission. This overall figure hides a variation in admission rates across the paediatric age group, with hospital admission more common in younger children. These findings highlight multiple factors, apart from illness and physiological upset that influence hospital admission in children and young people. Bradman found that of paediatric patients presenting to their ED in Australia over a one week period in May 2010, 80% were discharged, although no information was given regarding how the patient arrived in the department, which is reflected by the national data which

provides a 72% discharge rate. Data from Addenbrookes hospital in the UK reports an 88% discharge rate over a 12 month period in 2013. An analysis of 887 emergency paediatric admissions to five Yorkshire hospitals showed that the majority of patients admitted had a minor illness and 61% stayed one night at most. Younger children are more likely to be admitted, with 25% of admissions representing children under 6 months of age. Around half of the same cohort completed questionnaires with parents providing feedback on their perceived need for admission. Themes were that admission provided observation and reassurance in a safe environment. The population in this study is an unselected group transferred by ambulance, where it is likely that parental/carer concern is high. It is likely that the decision to admit children from the Emergency Department is influenced by factors other than illness severity alone.

Limitations

This work has some limitations. The initial dataset for this study included 126,563 patients, but only 21,202 had a complete set of observations and known outcome data. Of those with a complete PEWS Scotland 29.9% were admitted, compared to 33.6% without a complete PEWS Scotland, $p<0.0001$. This suggests that the sample of data analysed may not represent that sample of patients transported by the Scottish Ambulance Service. In addition, as this population represents only the children transported by ambulance, it is not easy to generalise to the wider population of children presenting to the Emergency Department, or to other pre-hospital settings. Although it is impossible to tell the PEWS of the children with incomplete data sets, studies in the Emergency Department suggest that children with traumatic injuries are more likely to have incomplete vital sign documentation.

In addition, there are potential limitations to the use of PEWS Scotland and other PEWS in the pre-hospital environment. Factors such as the temperature and capillary refill will be affected by the environment, and the impact of distress on paediatric observations. Seiger's study into PEWS documentation in the Emergency Department found that oxygen saturation and blood pressure were the vital signs most likely to be omitted. Chapter 4 showed that an abbreviated PEWS score (qPEWS) performed as well as a full PEWS in predicting adverse outcome in the pre-hospital environment and the use of qPEWS may be a focus for future research in the pre-hospital

environment. One study, which was a single centre urban study undertaken in winter in a mixed adult and paediatric ED undertook a subgroup analysis. They found that PEWS is a good predictor of significant respiratory illness, of which there were a large proportion of in their study. Similarly, Chaiyakulsil examined 1,136 paediatric medical patients over one month in a tertiary centre in Japan, and whether their PEWS in the Emergency Department predicted disposition. They reported an AUROC of 0.71 (95% CI 0.66-0.75), suggesting the ED PEWS may be a better predictor of admission in subgroups of paediatric emergency presentations. This study did not analyse predictive value based on presenting complaint and this may be an area for future research.

Conclusions of Chapter 5

Overall, while PEWS Scotland is a useful indicator of severity of illness and potential adverse outcome in the pre-hospital paediatric population, these data show that it is not specific or sensitive enough to be used in isolation around the need for hospital admission. Future research may concentrate on the use of an abbreviated PEWS or use in specific medical complaints.

Chapter 6 Review of current literature and clinical practice

Chapters 1 to 5 summarise work previously published as part of this thesis. The work covers a period from 2012 through to 2020. The scientific literature has moved on, sometimes quite significantly, since I published these pieces of work. In this chapter I will review the current literature related to the previous published works and topics. The literature review was undertaken as a narrative literature review rather than a systematic review.

NEWS in the Emergency Department

The original publication on the use of NEWS in ED was in 2012. The field has continued to develop and progress over the last 9 years. NEWS has been updated with the publication of NEWS2 in 2017. A number of changes have been implemented with the change from NEWS to NEWS2, partly in response to concerns raised about the initial NEWS.

In summary there are a number of changes.

1. The recording of physiological parameters was reordered to align with the Resuscitation Council (UK) ABCDE sequence
2. The ranges for the boundaries of each parameter score are now shown on the NEWS chart
3. The NEWS chart has a dedicated section (SpO2 Scale 2) for use in patients with hypercapnic respiratory failure (usually due to COPD) who have clinically recommended oxygen saturation of 88–92%
4. The section of the chart for recording the rate of (L/min) and method/device for supplemental oxygen delivery has been improved
5. The importance of considering serious sepsis in patients with known or suspected infection, or at risk of infection, is emphasised. A NEW score of 5 or more is the key trigger threshold for urgent clinical review and action
6. The addition of ‘new confusion’ (which includes disorientation, delirium or any new alteration to mentation) to the AVPU score, which becomes ACVPU (where C represents confusion)

Uptake has been endorsed by NHS England and NHS Improvement for use in acute and ambulance settings,

Despite this, the use of NEWS in Emergency Departments remains controversial. This is in part due to the lack of high quality evidence showing that the use of NEWS in Emergency Departments improves patient outcomes.

Sepsis

Chapter 1 highlights the importance and epidemiological significance of sepsis as a disease process. The nonspecific presentation of sepsis and high mortality related to sepsis mean that use of NEWS has potential to identify physiological derangement in this patient group to facilitate early, targeted management.

A retrospective UK single centre study (Keep et al., 2016) used electronic records to evaluate 500 consecutive adult non trauma patients presenting to ED, in Manchester Triage Category 1-3. Of this group 50 (10.0%) fulfilled the definition of sepsis in use at that time (infection and SIRS criteria) and 27 (5.4%) had a final diagnosis of septic shock. This is a relatively high incidence, compared with other datasets which have an ED prevalence of about 1.5% for spies and 0.3% for septic shock. However these other datasets include all ED presentations, rather than focusing on adult non trauma in MTS 1-3 as was used in this study. The authors concluded that a NEWS of 3 or more may be a useful trigger for escalation of management. The PPV for this dataset, using the NEWS of 3 or more as a trigger, was 18.7% with 134/500 patients meeting this threshold and 25/27 patients with septic shock having a NEWS of 3 or more. This is a common concern about the use of NEWS that large numbers of patients will trigger the NEWS threshold, creating unnecessary review without clear evidence of patient benefit.

A single centre study in Liverpool (Goulden et al., 2018) examined the use of NEWS, qSOFA and SIRS for predicting adverse outcomes in an Emergency Department population. This was a retrospective cohort study amongst emergency admissions in whom sepsis was suspected and treated. Amongst 1818 patients the event rate for ICU admission was 3% and in-hospital mortality was 15%, which is similar to other cohorts. NEWS had an AUROC of 0.65 (95% CI 0.61 to 0.68) for in-hospital mortality

and AUROC 0.64 (95% CI 0.57 to 0.71) for ICU admission. Exploratory analysis in this group suggested an optimal Youden's index for a NEWS of 7.

Finally, in this section, is a systematic review of qSOFA and Hospital EWS for prognosis in suspected sepsis in ED patients (Sabir, 2020). This review identified 13 studies, including those listed above and elsewhere in this section, of relevance to this question. These studies included a total of 403,865 patients with outcomes of mortality reported on.

The authors identified in heterogeneity in the evidence – definitions of sepsis, scoring thresholds and outcomes of interest, which precluded a formal meta-analysis, and instead a descriptive narrative synthesis was presented.

The AUROC for in-hospital mortality for NEWS varied from 0.65 to 0.88 and for qSOFA from 0.62 to 0.79. Partial data on ICU admission from four studies showed AUROC for NEWS from 0.70 to 0.79 and for qSOFA from 0.63 to 0.68.

NEWS with a threshold of 5 or greater had a specificity of 90.2%, whereas qSOFA greater than or equal to 2 had a specificity of 98.7%. However NEWS trended to a better sensitivity than qSOFA for determining ICU admission and mortality.

Consequently, at the recommended thresholds for NEWS may be less likely to miss serious sepsis, which is necessary in an emergency setting, however, it may result in more overtriage than qSOFA.

Other condition specific use of NEWS in ED

A single centre study from Norway (Bilben et al, 2016) examined the use of NEWS in the acutely dyspnoeic patient in the ED. A prospective observational study was undertaken over a period of 6 months. Data was available for 246 patients presenting with acute dysnoea. NEWS was calculated at t0 (ED arrival), t1 (2-4 hours later) and t2 (24 hours). Of note, this was the original version of NEWS published in 2012 that was used in this study, rather than the updated 2017 version that accounted for some of the issues with use of NEWS in patients with chronic respiratory disease. In this study, NEWS at t0 (ED arrival) was correlated ($p<0.001$) with level of care required whilst in-hospital. An AUROC of 0.809 is given for NEWS as a predictor of

90 day survival. Multivariate analysis was performed for 90 day survival, and showed NEWS remained an independent predictor of 90 day survival, when controlled for age and COPD diagnosis.

Secondary analysis of a dataset (Sbiti-Rohr et al, 2016) was undertaken examining NEWS using data from a multicentre, randomised controlled trial of procalcitonin guided antibiotic therapy in patients with community acquired pneumonia (the ProHOSP study). Data was available for 925 patients with confirmed community acquired pneumonia including initial physiological measurements. For 30 day mortality prediction, NEWS showed only low discrimination (AUROC 0.65) with inferior performance compared with PSI and CURB-65. For prediction of ICU admission, NEWS showed moderate discrimination (AUROC 0.73). Addition of NEWS, improved the prognostic accuracy of CURB-65 (AUROCC from 0.64 to 0.73, p=0.015).

During the COVID pandemic, the PRIEST study (Thomas et al, 2021) examined the use of a number of different tools including NEWS for prognostication of ED patients with COVID. PRIEST was a mixed prospective and retrospective observational cohort study in 70 EDs across the UK. Data were collected from patients attending ED with suspected COVID-19 and used presenting data to determine the results of assessment with the WHO algorithm, National Early Warning Score version 2 (NEWS2), CURB-65, CRB-65, Pandemic Modified Early Warning Score (PMEWS) and the swine flu adult hospital pathway (SFAHP). The primary outcome was death or receipt of respiratory, cardiovascular or renal support.

Data were analysed for 20 891 adults, of whom 4611 (22.1%) died or received organ support (primary outcome), with 2058 (9.9%) receiving organ support and 2553 (12.2%) dying without organ support (secondary outcomes). C-statistics for the primary outcome were: CURB-65 0.75; CRB-65 0.70; PMEWS 0.77; NEWS2 (score) 0.77; NEWS2 (rule) 0.69; SFAHP (6-point rule) 0.70; SFAHP (7-point rule) 0.68; WHO algorithm 0.61. All triage tools showed worse prediction for receipt of organ support and better prediction for death without organ support. At the recommended threshold, PMEWS and the WHO criteria showed good sensitivity (0.97 and 0.95, respectively) at the expense of specificity (0.30 and 0.27, respectively). The NEWS2 score showed similar sensitivity (0.96) and specificity (0.28) when a lower threshold than recommended was used.

These studies show that NEWS can identify patients at higher risk of adverse outcome, amongst subgroups of ED patients. However this does introduce another layer of complexity in management of patients in ED if NEWS is only used in patients with a specific presenting complaint or provisional diagnosis. From a practical point of view, if NEWS is to be used in ED, then it should be used across the whole ED patient population.

All patients in ED

A prospective study (Alam et al., 2015) evaluated NEWS in a single centre European Emergency Department population over a six week period. A convenience sample of 300 patients were eligible with complete data available for 274 patients. They examined NEWS at ED admission (t0), 1 hour after admission (t1) and at ED departure (t2). Complete data was available for 274 patients at t0, 247 patients at t1 and 133 patients at t2. Most patients (80.3%) were medical admissions rather than surgical or trauma. They found that increasing NEWS was associated with hospital admission at all three time points. The AUROCs (95% CI) for NEWS for admission at T0, T1, T2 was respectively 0.664 (0.599–0.728), 0.687 (0.620–0.754), 0.697 (0.609–0.786). Length of stay was significantly correlated with NEWS, at all of the measured time points, p value for x^2 was <0.001. Spearman Rank Correlation was significant ($p < 0.0001$). Median length of stay more than doubled for a score >7 compared with a score of 0–4. A total of 10 patients were admitted to ICU, an event rate of 3.6% (10/274). ICU admission significantly correlated with NEWS >7 at time points T0 (Fisher's exact test; $p = 0.003$), T1 ($p < 0.001$) and at T2 ($p = 0.046$).

Further data from Finland (Kivipuro et al., 2016) prospectively looked at all ED patients over a one month period in a single centre study. At total of 1354 patients were included in the analysis. NEWS was associated with in-hospital mortality (OR 1.26, 95% CI 1.11-1.42; AUROC 0.75, 0.64–0.86, p < 0.001) and 30-day mortality (OR 1.27, 1.17-1.39; AUROC 0.78, 0.71–0.84, p < 0.001) irrespective of age and comorbidity. 64 patients (4.7%) had a subsequent ICU admission with median ED-NEWSs of 7. This median NEWS was significantly higher (p < 0.001) than NEWS for patients not admitted to ICU.

More recently, a study from Australia (Spencer et al., 2019) used a prospective convenience sample of 2000 patients presenting to a single urban ED to validate thirteen EWS, including NEWS. The outcomes of interest were ICU admission within 48 hours and 7 or 28 day in hospital mortality. Analysis was undertaken on 690 patients. NEWS was predictive of 48 hour mortality (AUROC 0.95 95%CI -.92 to 0.99), ICU admission within 48 hours (AUROC 0.69 95% CI 0.55 to 0.82) and 28 day in-hospital mortality (AUROC 0.82 (95%CI 0.74 to 0.89).

The organisation of health systems strongly influences ED population characteristics and outcomes, and this may be part of the explanation of the variation in performance of NEWS in different healthcare systems.

Overall these studies support the original findings that NEWS measured in the ED is a useful indicator of severity of disease process and an increase NEWS is associated with adverse outcomes (critical care admission and/or death). However there are no specific studies that take this work onto examine whether this finding can be translated into improved outcomes for patients in an ED setting.

Wider in hospital setting

Most studies on NEWS look at their use as part of the wider system of related to in hospital use rather than ED. A systematic review (Alam et al., 2016) of NEWS use in an in-hospital setting concluded that EWS are a simple and easy to use tool at the bedside, which may be of help in recognising patients with potential for acute deterioration. Coupled with an outreach service, it may be used to timely initiate adequate treatment upon recognition, which may influence the clinical outcomes positively. However the lack of prospective multicentre randomised mean that no positive conclusion can be drawn.

A further systematic review (Gerry et al., 2020), looking at the use of EWS in adult hospital patients. Overall this group found 23 studies of relevance developing an EWS, and 84 studies validating an existing EWS. This systematic review contains many of the studies described in Chapter 6. The conclusion was that most of these studies had poor methodology across all aspects of study design and analysis. Statistical issues were identified including handling of missing data along with the approaches to regression modelling. Few studies assessed calibration, with no study

assessing clinical utility using net benefit approaches. Essential details were missing from many studies, such as sample size, number of events, population characteristics, and details of statistical methods. Several studies failed to report the full model, preventing (independent) external validation or implementation of the model in practice.

The authors conclude with a number of key recommendations for future research which are summarised in Table 6-1.

These recommendations are summed up in the TRIPOD (transparent reporting of a multivariate prediction model for individual prognosis or diagnosis). Whilst this systematic review and subsequent recommendations are presented in the context of in-hospital patients, the principles apply to single value EWS in the emergency and pre-hospital care setting.

Table 6-1. Key recommendations from Gerry at al 2020 systematic review

Subject	Recommendation
Population	Population demographics, source of data, number of patients with and without event of interest, number of observations sets with and without event of interest
Sample size	Sample size should be large enough to robustly answer the question. For model development this should include a formal sample size calculation. For external validation, this should include at least 100 event patients.
Missing data	Description of missing data. Multiple imputation for accounting for missing data in analysis
Outcome measures	Outcome measures must be clinically meaningful, and a time horizon in which deterioration can be reasonably expected to occur. This is likely to be a few days at most.
Statistical methods	If a regression modelling approach is used, then should allow for non-linear predictor outcome relation (e.g. fractional polynomials and avoid categorisation of predictors prior to analysis. Predictor interaction terms and competing risk approaches should be considered if appropriate. New models need to be fully described to allow independent evaluation and implementation.
Validation	New models must be validated. Split sample validation should be avoided and bootstrapping is the preferred method.
Model performance	Assess both calibration and discrimination of EWS. Decision curve analysis should be used to assess clinical utility.

Non NEWS or enhanced NEWS scoring systems in ED

One of the benefits of the use of NEWS throughout the UK is the ability to compare data from different centres, and also to reduce confusion amongst staff moving between hospitals.

However the Emergency Department has unique circumstances around unselected patients, time pressure and lack of diagnostic clarity that may make a case for the use of a different type of early warning score in adults. EWS developed on the basis of predicting illness severity are often used to prioritise patients on the basis of urgency. Illness severity and urgency may not be interchangeable. Severe illness places patients at risk of adverse outcome, but treatment is only urgent if adverse outcome can be prevented by time-sensitive treatment.

A study from Sheffield (Challen et al., 2015) aimed to develop a score to identify patients in need of urgent treatment, on the basis of potential to benefit from time-sensitive intervention, and to compare this with a severity score identifying patients at high risk of death. Key variables were derived in an Emergency Department population to predict need for time critical intervention as well as 7 day mortality. Three variables (Pulse, systolic blood pressure and GCS) were predictive of a need for time critical intervention with moderate discrimination. Seven different variables (age, respiratory rate, diastolic blood pressure, oxygen saturations, temperature, GCS and pre-existing respiratory disease) were predictive of 7 day mortality. This highlights the issue of what function we want an early warning score to do in the Emergency Department – identify patients at risk of adverse outcome or identify patients that will benefit from urgent intervention.

There has also been work incorporating NEWS into other systems, particularly around identifying those patients that are likely to need hospital admission from ED. A multicentre, retrospective, cross-sectional study of triage records for all unscheduled adult attendances over 2 years (Cameron et al., 2014) described a composite clinical score (Glasgow Admission Prediction Score) based on 6 variables available at ED triage, one of which is NEWS. Clinical variables that had significant associations with admission on logistic regression were entered into a mixed-effects multiple logistic model. This provided weightings for the score, which was then

simplified and tested on a separate validation group by receiving operator characteristic (ROC) analysis and goodness-of-fit tests. 215 231 presentations were used for model derivation and 107 615 for validation. Variables in the final model showing clinically and statistically significant associations with admission were: triage category, age, National Early Warning Score (NEWS), arrival by ambulance, referral source and admission within the last year. The resulting 6-variable score showed excellent admission/discharge discrimination (area under ROC curve 0.8774, 95% CI 0.8752 to 0.8796).

The study from Goulden at al discussed in Chapter 2 examined the utility of NEWS v qSOFA for an ED population, rather than a pre-hospital setting. However in their population of 1818 ED patients their AUROC for NEWS was 0.65 (95% CI 0.61 to 0.68) for in-hospital mortality and AUROC 0.64 (95% CI 0.57 to 0.71) for ICU admission. For qSOFA the AUROC for in hospital mortality was 0.62 (95% CI 0.59 to 0.66) and for ICU admission the AUROC was 0.59 (0.52 to 0.67. There was no statistical difference between AUROC for either outcome.

This group also explored the composite outcome of in hospital death or ICU admission. For NEWS the AUROC was 0.65 (0.62 to 0.69) and for qSOFA the AUROC was 0.62 (0.59 to 0.66) with no significant difference between these AUROC.

A recent study (Lee et al., 2020) has produced an updated version of NEWS that is specifically centred around a single score calculated on arrival in ED, the Triage Early Warning Score (TREWS). This is a single centre study using data from all ED presentations over a seven year period, giving a dataset of 81,520 patients. This was split into a derivation group of 54,347 and a validation group of 27,173. Univariate and multivariate analysis identified some key changes to variables, compared with standard use. Crucially their outcome measure was mortality within 24 hours. In the TREWS model, oxygen saturation is no longer included and age and gender are added. The weightings and categorisations also change compare with NEWS. For example, a respiratory rate of less than 8 scores as a 3 in both NEWS and TREWS whereas a respiratory rate of 22 scores as a 0 in TREWS and a 1 in NEWS. In the derivation group, the AUROC of the TREWS for in-hospital mortality within 24 h was 0.906 (95% CI, 0.903–0.908), and those of the NEWS was 0.878 (95% CI, 0.875–0.881.

The AUROC differences between the TREWS and NEWS was 0.028 (95% CI, 0.022–0.033; $p < .001$).

This study is based on data from a single centre and a Korean healthcare system, which has significant differences to the UK health care system. It also has the disadvantage of being a system set up for a single location (ED) and therefore loses the advantage of NEWS that is a common language to use throughout the healthcare system. This study does show that electronic data capture of physiological variables can be used in an Emergency Department setting to gather a large amount of data, and potentially this can be used to improve the EWS that are used in the Emergency Department.

There is consensus amongst more recent literature that NEWS/NEWS2 is a potentially useful tool in the Emergency Department setting and has clinical validity in identifying patients at higher risk of adverse outcome. There is some variation as to what value of NEWS2 should act as a trigger for a different course of action for ED clinicians, and no clear consensus what that action should be. Again there are no studies addressing whether different patient pathways or staff action in response to an elevated pre-hospital NEWS improves patients outcomes. The benefit for NEWS remains that it is designed to be used across a whole healthcare system, rather than switching between different EWS in different parts of a health institution or wider healthcare system.

Overall despite the evidence that has been published to date, there is a need for prospective randomised clinical trials of NEWS use to be clear whether it confers benefit on patient outcomes for Emergency Department patients. There is also a need to clarify whether NEWS is the best tool to use in the Emergency Department setting.

NEWS in the Pre-hospital setting

Subsequent to the data from Chapter 2, which was originally published in 2013, there has been limited further evidence published about NEWS use in the pre-hospital setting.

A systematic review (Williams et al, 2016) examined the ability of EWS to detect critical illness in the pre-hospital setting. This group looked at a number of different EWS used in the pre-hospital setting. Our study detailed in Chapter 2 was the only study cited that reported on the use of NEWS. Their conclusion that overall the level of evidence was low, with no randomised controlled trial data available. Notwithstanding this, EWS appeared useful in predicting clinically important outcomes, but significant heterogeneity between different EWS suggest that these positive promising findings may not be generalizable.

Subsequent to the systematic review, data from the London Ambulance Service (Shaw et al, 2016) examined the use of NEWS in a prehospital setting. In a retrospective cohort, 287 patients who were treated by the ambulance service and subsequently transported to hospital, had a NEWS calculated based on their initial physiological observations. Disposition from ED was categorised into 4 groups – discharged from ED, admitted to a ward, admission to ICU or death. Prehospital NEWS-based ambulance service clinical observations were significantly associated with discharge disposition groups ($p<0.001$), with scores escalating in line with increasing severity of outcome. Patients who died or were admitted to ICU had higher scores than those admitted to a ward or discharged from ED (mean NEWS 7.2 and 7.5 vs 2.6 and 1.7, respectively), and in turn those who were admitted to a ward had higher pre-hospital NEWS than those who were discharged (2.6 vs 1.7).

Data from Japan (Endo et al, 2019) retrospectively analysed a cohort of patients transported to hospital over a one year period. NES was calculated based on physiological data recorded by ambulance staff. Disposition was categorised into four groups – discharged from ED, admitted to a ward, admitted to ICU or death in ED. Data from 2847 patients was available for analysis. Prehospital NEWS's AUROC (95% confidence interval) for admission to a ward/the ICU or death in ED was 0.733(0.715–0.751), admission to the ICU or death in ED was 0.807 (0.780–0.833), and death in ED was 0.900 (0.868– 0.933). After adjusting for age, gender and trauma, odds ratio (95% confidence interval) for admission to the ICU or death in ED of high-risk NEWS category (7) was 13.8 (8.9–21.6) and middle category (5 or 6) was 4.2 (2.5–7.1), each compared to low-risk category (<5).

Most recently, a group in Spain has published data related to the use of pre-hospital EWS. In their first publication (Martin-Rodriquez et al, 2019) a cohort of patients was defined from 349 consecutive patients brought by ambulance to two EDs over a 3 month period. The pre-hospital records for these patients were then reviewed and a six different EWS were tested against the outcome of mortality at 48 hours including NEWS2. All six performed well with the AUROC for NEWS of 0.896 (95% CI 0.82-0.95). NEWS2 and ViEWS were the best performers with no statistical difference between AUROC for the NEWS 2 and ViEWS, however the AUROC for NEWS2 and ViEWS was statistically different than the other four EWS tested.

This group subsequently published a larger, prospective multi-centre study (Martin-Rodriguez et al, 2020). Data were collected over a 14 month period for 2335 patients attended by the Spanish national EMS. The NEWS2 was calculated from observations taken by pre-hospital clinical staff at first contact. The NEWS2 was calculated from these values and examined with respect to the hospital mortality. The AUROC for one day mortality was 0.86 (95% CI: 0.78 to 0.93), within two days 0.88 (95% CI:0.84 to 0.92), within seven days 0.84 (95% CI: 0.79 to 0.87) and 30 day mortality was 0.81 (95% CI: 0.77 to 0.84). The authors suggest NEWS of 9 or more as a threshold for higher mortality in their study.

These studies support the hypothesis and data contained in Chapter 2 that a single NEWS undertaken by ambulance clinicians is predictive of adverse in-hospital outcome. There is broad agreement across different healthcare systems that NEWS/NEWS2 is a potentially useful tool. There is some variation as to what value of NEWS2 should act as a trigger for a different course of action for pre-hospital clinicians, and what that action should be. Again there are no studies addressing whether different patient pathways or staff action in response to an elevated pre-hospital NEWS improves patients outcomes.

PEWS in the Pre-hospital setting

As described in Chapter 3 and 4, there are a number of studies around the use of PEWS in the Emergency Department and in-hospital environment. To date, there are a small number of recent articles examining the use of PEWS in a pre-hospital setting.

A number of variations of PEWS have been developed, using ordinal scores to quantify severity of illness in a paediatric population. It is outwith the scope of this review, which is focussed on PEWS, to review all these scores. However some studies of note are worthy of discussion.

The largest study to date in the UK is the Paediatric Admission Guidance in the Emergency Department (PAGE) study (Rowland, 2020). This was an observational cohort study with internal and external validation of a predictive tool. This was a multicentre study in the UK using the primary outcome measure of admission to hospital from ED. Data were available for 36365 participants with 15 328 participants in the final analysis cohort (21 045 observations) and 17 710 participants were included in the validation cohort (23 262 observations). There were 14 variables entered into the regression analysis. Of the 13 that remained in the final model, 10 were present in all 500 bootstraps. The resulting Paediatric Admission Guidance in the Emergency Department (PAGE) score demonstrated good internal validity. The C-index (area under the ROC) was 0.779 (95% CI 0.772 to 0.786).

Of note from this study final variables included physiology variables (heart rate, respiratory rate, temperature, oxygen saturation, breathing, behaviour and work of breathing) and demographic or healthcare systems variables (nurse judgement, multimorbidity, ambulance use, advised by medical professional to attend). This is consistent with our work on PEWS and hospital admission which identified that a purely physiological score (PEWS) was not a useful predictor of the need for hospital admission.

In the UK (Broughton and Maconochie, 2019) published data looking at young children in the 0-2 age group. A retrospective single centre study undertaken over a 12 month period was conducted, using a randomised sample of 300 Emergency Department patients. The ambulance PEWS was used to assess against the outcome of interest – ED disposition. Complete data was available for 169 patients, with disposition to home (59.2%), GP (17.8%) and hospital admission (10.7%). The remaining 12.4% had a number of low frequency dispositions. An elevated pre-hospital PEWS was specific for need for hospital admission from ED. PEWS had poor sensitivity for hospital admission and a low PEWS was not a useful tool for predicting those patients not requiring hospital admission.

More recently a group in Denmark (Neilsen et al, 2021) published data examining vital sign measurement in paediatric patients transported by emergency ambulance. They used a similar methodology to the studies outlined in Chapter 2 and 3 by using regional, electronic data collected by the ambulance service. Data was available for 25 039 patients over a 12 year period. The proportion of patients with the first observed vital signs outside the normal age-specific range was as follows: 33.6% for heart rate, 15.3% for Glasgow Coma Score, 17.4% for respiratory rate and 37.4% for oxygen saturation regardless of oxygen treatment. This group is undertaking prospective work to evaluate the validity of PEWS in their healthcare system and also whether actions mandated dependent on PEWS can alter patient outcomes.

These data are in keeping with the data presented in Chapter 4 around the level of recording of vital signs in paediatric patients in ambulances.

A systematic review of PEWS (Lambert et al 2017) appraised the available evidence on PEWS for use in the acute paediatric healthcare setting, specifically around detection of clinical deterioration and timely response to clinical deterioration. The review found 90 papers of interest, however all related to paediatric inpatient hospital settings with no pre-hospital data included.

Chapter 7 Summary

Summary of theses

This thesis set out to examine the use of early warning scores, and specifically NEWS and PEWS(Scotland), in the Emergency Department and pre-hospital setting. The work set out in this thesis shows that, in both ED and PHC, a single early warning score is associated with adverse outcomes for patients. In adults, this association is shown in the heterogeneous group of all emergency presentations as well as a specific condition (sepsis). In children and young people, a single pre-hospital PEWS is predictive of adverse outcome, but PEWS is not a useful tool to predict the need for hospital admission. There may be scope to streamline the current parameters included in PEWS to improve data capture, without sacrificing accuracy.

Impact of work

The published papers presented in Chapters 1 and 2 have been incorporated into development of NEWS2 published by RCP London in 2017. The published papers are also referenced in the NICE guidance "Sepsis: recognition, diagnosis and early management" published in 2016 and updated in 2017. The data from Chapter 2 was undertaken in conjunction with SAS, and has been useful in supporting the corporate decision to ensure that NEWS is not used as a tool to drive decisions around non conveyance.

The work outlined in Chapter 3, 4 and 5 was undertaken in conjunction with the SAS. There was a realisation that the data held by SAS could be used to examine whether the use of PEWS in the pre-hospital environment was a valid tool to identify children at risk of adverse outcome. This was an important question at an operational level and, at the time of the work, there was no research to directly answer that question. Following peer reviewed publication of the findings from Chapter 3 and in consultation with the relevant stakeholders, SAS moved to update their electronic PRF to alert paramedic crews if a child or young person has a

PEWS equal to or greater than 5. There is currently no mandated action following this alert.

To date (August 2021) the six papers in this thesis have accumulated 312 citations in peer reviewed journals. This provides objective evidence that this work is relevant in the field and is adding to the accumulated knowledge in area of the use of early warning scores in an emergency setting.

Future research

Through the work contained in this thesis and presentation of the findings at meetings, I am contact with a collaborative group of pre-hospital clinicians and researchers in Denmark. We recognised the need to examine whether the use of PEWS impacts outcome. We have designed a step wedge, randomised controlled trial of PEWS. In the intervention arm, an elevated PEWS will mandate crews to pre-alert the receiving ED to a potentially unwell patient arriving. Outcomes of interest are mortality, ICU admission along with qualitative work around staff perception of the introduction of mandated pre-alerts.

I am also aware of a group in England and Wales taking forward a similar themed study which as well as assessing the validity of PEWS as a predictor of outcome amongst pre-hospital paediatric patients, will examine whether identification of elevated PEWS impacts on patient pathways and outcomes.

More widely, a number of different studies have shown that clinical or physiological scoring systems can be combined with biomarkers to develop a prognostic tool that is superior to scoring systems alone. There is scope to look at the use of early warning systems in combination with point of care biomarkers in a number of different scenarios.

Overall, very few of described studies including NEWS and NEWS2, fit the criteria described by Gerry et al in their systematic review and the TRIPOD criteria for development of EWS. There is an opportunity with electronic capture of data on a large scale, to rework NEWS and PEWS in a more methodologically sound way to ensure it is a valid tool. Only after that, can we address the issue of whether introduction of NEWS and PEWS as part of a complex healthcare intervention delivers benefit to patients.

Reflection

As with any project, there are a number of elements of the work presented in this thesis that I would alter, with the benefit of hindsight. Whilst I would argue that the methodology has improved over time, there are weaknesses in my work. The principle amongst these is the handling of missing data. The approach to missing data has been basic, in that we have used a complete case analysis approach and compared characteristics of groups for missing data versus complete data. This approach was to clarify if the data were missing at random (MAR), rather than missing not at random (MNAR). A more statistically robust method would either have been to use logistic regression imputation or, ideally, multiple imputation as the way to address the missing values.

Chapters 3 to 5 are partly based on the use of routine datasets from the Scottish Ambulance Service. Having access to national data was the only way to effectively look at PEWS, given the thankfully relatively low event rate of adverse outcomes in children and young people.

Working with large datasets (>100,000 patients) presents unique challenges and I am indebted to the statistical and database guidance I received from Dr Harry Staines. With large datasets, statistical significance is easily achieved for many comparisons and the question of clinically important difference becomes more important.

A set of reporting guidelines to use when reporting on multivariate prediction model (TRIPOD) was published in 2015. Although the later elements of this thesis incorporate aspects of these guidelines, in retrospect I wish that I had incorporated the TRIPOD guidelines more fully.

Epilogue

A benefit of the approach of using published work, and the passage of time, is that the impact of the work on clinical practice is clearer. Having my work referenced in the development of NEWS2 and guidance produced by the National

Institute of Clinical Excellence gives me some external validation about the relevance and robustness of the work I have undertaken. Similarly seeing direct impact of my work with PEWS in pre-hospital paediatric patients on the national guidance and processes delivered by the Scottish Ambulance Service.

There has been personal satisfaction in “completing the circle” in writing this thesis. My first work in early warning scores was almost 20 years ago whilst working as an anaesthetic trainee. Completing a retrospective project about the potential use of early warning scores for our ICU admissions led me to present that work and then become interested in conducting more research. It feels appropriate that my MD subject returns to the same topic area.

Whilst there are elements of the work that I would do differently, I feel overall that the process has been positive. As well as significantly improving my understanding of many aspects of the subject matter, the act of reflecting on the whole project has improved my understanding of the process of undertaking research projects. It is now clearer to me that successful research in emergency care is due to a combination of a clear idea, adequate time and resource allocation and a collaborative approach.

Glossary

Triage- (French, lit: “sort”) the process of establishing priority of treatment of patients according to severity of illness or injury.

Emergency Medical Service (EMS) – global term used to describe local equivalent of a UK ambulance service

References

Agulnik A, Mora Robles LN, Forbes PW, Soberanis Vasquez DJ, Mack R, Antillon-Klussmann F, Kleinman M, Rodriguez-Galindo C. Improved outcomes after successful implementation of a pediatric early warning system (PEWS) in a resource-limited pediatric oncology hospital. Cancer. 2017 Aug 1;123(15):2965-2974. doi: 10.1002/cncr.30664. Epub 2017 Apr 25.

Alam, N., Vegting, I., Houben, E., van Berkel, B., Vaughan, L., Kramer, M. and Nanayakkara, P., 2015. Exploring the performance of the National Early Warning Score (NEWS) in a European emergency department. *Resuscitation*, 90, pp.111-115.

Askim, Å., Moser, F., Gustad, L., Stene, H., Gundersen, M., Åsvold, B., Dale, J., Bjørnsen, L., Damås, J. and Solligård, E., 2017. Poor performance of quick-SOFA (qSOFA) score in predicting severe sepsis and mortality – a prospective study of patients admitted with infection to the emergency department. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*, 25(1).

Bellomo, R., Goldsmith, D., Uchino, S., Buckmaster, J., Hart, G., Opdam, H., Silvester, W., Doolan, L. and Gutteridge, G., 2004. Prospective controlled trial of effect of medical emergency team on postoperative morbidity and mortality rates. *Critical Care Medicine*, 32(4), pp.916-921.

Bilben, B., Grandal, L., and Søvik, S., 2016. National Early Warning Score (NEWS) as an emergency department predictor of disease severity and 90-day survival in the acutely dyspneic patient – a prospective observational study. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*, 24 (1).

Bion, J., Jaeschke, R., Thompson, B., Levy, M. and Dellinger, R., 2008. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Intensive Care Medicine*, 34(6), pp.1163-1164.

Bird, C. and Michie, C., 2008. Measuring blood pressure in children. *BMJ*, 336(7657), pp.1321-1321.

Bradman, K. and Maconochie, I., 2008. Can paediatric early warning score be used as a triage tool in paediatric accident and emergency?. *European Journal of Emergency Medicine*, 15(6), pp.359-360.

Bradman, K., Borland, M. and Pascoe, E., 2012. Predicting patient disposition in a paediatric emergency department. *Journal of Paediatrics and Child Health*, 50(10), pp.E39-E44.

Breslin, K., Marx, J., Hoffman, H., McBeth, R. and Pavuluri, P., 2014. Pediatric Early Warning Score at Time of Emergency Department Disposition Is Associated With Level of Care. *Pediatric Emergency Care*, 30(2), pp.97-103.

Buist, M., 2002. Effects of a medical emergency team on reduction of incidence of and mortality from unexpected cardiac arrests in hospital: preliminary study. *BMJ*, 324(7334), pp.387-390.

Burch, V., Tarr, G. and Morroni, C., 2008. Modified early warning score predicts the need for hospital admission and inhospital mortality. *Emergency Medicine Journal*, 25(10), pp.674-678.
Chapman, S., Wray, J., Oulton, K. and Peters, M., 2016. Systematic review of paediatric track and trigger systems for hospitalised children. *Resuscitation*, 109, pp.87-109.

Cameron, A., Rodgers, K., Ireland, A., Jamdar, R. and McKay, G., 2014. A simple tool to predict admission at the time of triage. *Emergency Medicine Journal*, 32(3), pp.174-179.

Chaiyakulsil, C. and Pandee, U., 2015. Validation of pediatric early warning score in pediatric emergency department. *Pediatrics International*, 57(4), pp.694-698.

Chapman, S., Wray, J., Oulton, K., Pagel, C., Ray, S. and Peters, M., 2017. 'The Score Matters': wide variations in predictive performance of 18 paediatric track and trigger systems. *Archives of Disease in Childhood*, 102(6), pp.487-495.

Challen, K., Bradburn, M. and Goodacre, S., 2015. Development and validation of a score to identify in the Emergency Department patients who may benefit from a time-critical intervention: a cohort study. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*, 23(1).

Churpek, M., Snyder, A., Han, X., Sokol, S., Pettit, N., Howell, M. and Edelson, D., 2017. Quick Sepsis-related Organ Failure Assessment, Systemic Inflammatory Response Syndrome, and Early Warning Scores for Detecting Clinical Deterioration in Infected Patients outside the Intensive Care Unit. *American Journal of Respiratory and Critical Care Medicine*, 195(7), pp.906-911.

Clements, F., Beattie, J., Beattie, J., McIntyre, Maley, A. and Wagstaff, A., 2008. Development and implementation of a paediatric early warning scoring system into a sick childrens hospital. *Resuscitation*, 77, p.S32.

Dacey, M., Mirza, E., Wilcox, V., Doherty, M., Mello, J., Boyer, A., Gates, J., Brothers, T. and Baute, R., 2007. The effect of a rapid response team on major clinical outcome measures in a community hospital. *Critical Care Medicine*, 35(9), pp.2076-2082.

Endo, T., Yoshida, T., Shinozaki, T., Motohashi, T., Hsu, H., Fukuda, S., Tsukuda, J., Naito, T., Morisawa, K., Shimozawa, N., Taira, Y. and Fujitani, S., 2020. Efficacy of prehospital National Early Warning Score to predict outpatient disposition at an emergency department of a Japanese tertiary hospital: a retrospective study. *BMJ Open*, 10(6), p.e034602.

Fleischmann, C., Scherag, A., Adhikari, N., Hartog, C., Tsaganos, T., Schlattmann, P., Angus, D. and Reinhart, K., 2015. Global burden of sepsis: a systematic review. *Critical Care*, 19(Suppl 1), p.P21.

Fleming, S., Gill, P., Jones, C., Taylor, J., Van den Bruel, A., Heneghan, C. and Thompson, M., 2014. Validity and reliability of measurement of capillary refill time in children: a systematic review. *Archives of Disease in Childhood*, 100(3), pp.239-249.

Goulden, R., Hoyle, M., Monis, J., Railton, D., Riley, V., Martin, P., Martina, R. and Nsutebu, E., 2018. qSOFA, SIRS and NEWS for predicting inhospital mortality and ICU admission in emergency admissions treated as sepsis. *Emergency Medicine Journal*, 35(6), pp.345-349.

Griffiths, J. and Kidney, E., 2011. Current use of early warning scores in UK emergency departments. *Emergency Medicine Journal*, 29(1), pp.65-66.

Groarke, J., Gallagher, J., Stack, J., Aftab, A., Dwyer, C., McGovern, R. and Courtney, G., 2008. Use of an admission early warning score to predict patient morbidity and mortality and treatment success. *Emergency Medicine Journal*, 25(12), pp.803-806.

Hillman, K., Bristow, P., Chey, T., Daffurn, K., Jacques, T., Norman, S., Bishop, G., and Simmons, G., 2002. Duration of life-threatening antecedents prior to intensive care admission. *Intensive Care Medicine*, 28 (11), 1629–1634.

Hoffmann F, Schmalhofer M, Lehner M, Zimatschek S, Grote V, Reiter K. Comparison of the AVPU Scale and the Pediatric GCS in Pre-hospital Setting. Prehosp Emerg Care. 2016 Jul-Aug; 20(4):493-8

Kause, J., Smith, G., Prytherch, D., Parr, M., Flabouris, A., and Hillman, K., 2004. A comparison of Antecedents to Cardiac Arrests, Deaths and Emergency Intensive care Admissions in Australia and New Zealand, and the United Kingdom—the ACADEMIA study. *Resuscitation*, 62 (3), 275–282.

Keep, J., Messmer, A., Sladden, R., Burrell, N., Pinate, R., Tunnicliff, M. and Glucksman, E., 2015. National early warning score at Emergency Department triage may allow earlier identification of patients with severe sepsis and septic shock: a retrospective observational study. *Emergency Medicine Journal*, 33(1), pp.37-41.

Kivipuro, M., Tirkkonen, J., Kontula, T., Solin, J., Kalliomäki, J., Pauniaho, S., Huhtala, H., Yli-Hankala, A. and Hoppu, S., 2018. National early warning score (NEWS) in a Finnish multidisciplinary emergency department and direct vs. late admission to intensive care. *Resuscitation*, 128, pp.164-169.

Lambert, V., Matthews, A., MacDonell, R. and Fitzsimons, J., 2017. Paediatric early warning systems for detecting and responding to clinical deterioration in children: a systematic review. *BMJ Open*, 7(3), p.e014497.

Lee, S.B., Kim, D.H., Kim, T., Kang, C., Lee, S.H., Jeong, J.H., Kim, S.C., Park, Y.J., and Lim, D., 2020. Emergency Department Triage Early Warning Score (TREWS) predicts in-hospital mortality in the emergency department. *The American Journal of Emergency Medicine*, 38 (2), 203–210.

Levy, M., Fink, M., Marshall, J., Abraham, E., Angus, D., Cook, D., Cohen, J., Opal, S., Vincent, J. and Ramsay, G., 2003. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Critical Care Medicine*, 31(4), pp.1250-1256.

Lillitos, P., Hadley, G. and Maconochie, I., 2015. Can paediatric early warning scores (PEWS) be used to guide the need for hospital admission and predict significant illness in children presenting to the emergency department? An assessment of PEWS diagnostic accuracy using sensitivity and specificity. *Emergency Medicine Journal*, 33(5), pp.329-337.

Loeff ISVD, Campbell J. 2017. G425 Paediatric early warning scores on admission correlate to length of stay and hdu admission in children with bronchiolitis presenting to Colchester general hospital *Archives of Disease in Childhood,* 10, A167.

Martín-Rodríguez, F., Castro-Villamor, M., del Pozo Vegas, C., Martín-Conty, J., Mayo-Iscar, A., Delgado Benito, J., del Brio Ibañez, P., Arnillas-

Gómez, P., Escudero-Cuadrillero, C. and López-Izquierdo, R., 2019. Analysis of the early warning score to detect critical or high-risk patients in the prehospital setting. *Internal and Emergency Medicine*, 14(4), pp.581-589.

Martín-Rodríguez, F., López-Izquierdo, R., Del Pozo Vegas, C., Sánchez-Soberón, I., Delgado-Benito, J. F., Martín-Conty, J. L., & Castro-Villamor, M. A. (2020). Can the prehospital National Early Warning Score 2 identify patients at risk of in-hospital early mortality? A prospective, multicenter cohort study. *Heart & lung : the journal of critical care*, *49*(5), 585–591. https://doi.org/10.1016/j.hrtlng.2020.02.047

Nielsen, V., Kløjgård, T., Bruun, H., Søvsø, M. and Christensen, E., 2020. Progression of vital signs during ambulance transport categorised by a paediatric triage model: a population-based historical cohort study. *BMJ Open*, 10(11), p.e042401.

Parshuram, C., Dryden-Palmer, K., Farrell, C., Gottesman, R., Gray, M., Hutchison, J., Helfaer, M., Hunt, E., Joffe, A., Lacroix, J., Moga, M., Nadkarni, V., Ninis, N., Parkin, P., Wensley, D., Willan, A. and Tomlinson, G., 2018. Effect of a Pediatric Early Warning System on All-Cause Mortality in Hospitalized Pediatric Patients. *JAMA*, 319(10), p.1002.

Rees, J., Mann C. 2004. Use of the patient at risk scores in the emergency department: a preliminary study. *Emergency Medicine Journal*, 21(6), pp.698-699.

Roland, D. and Jahn, H., 2012. Are early warning scores too early for paramedic practice?. *Journal of Paramedic Practice*, 4(1), pp.16-21.

Roland, D., Oliver, A., Edwards, E., Mason, B. and Powell, C., 2013. Use of paediatric early warning systems in Great Britain: has there been a change of practice in the last 7 years?. *Archives of Disease in Childhood*, 99(1), pp.26-29.

Royal College of Paediatrics and Child Health. 2014. Why children die: death in infants, children and young people in the UK: Part D

Royal College of Physicians. 2012. Standardising the assessment of acute illness severity in the NHS. Report of a working party. London

Royal College of Physicians. 2017. *National Early Warning Score (NEWS) 2: Standardising the assessment of acute-illness severity in the NHS*. Updated report of a working party. London: RCP.

https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2 (Accessed 28th July 2021)

Sabir, L., Ramlakhan, S., Goodacre, S., 2021. Comparison of qSOFA and Hospital Early Warning Scores for prognosis in suspected sepsis in emergency department patients: a systematic review. *British Medical Journal*. doi: 10.1136/emermed-2020-210416

Seiger, N., Maconochie, I., Oostenbrink, R. and Moll, H., 2013. Validity of Different Pediatric Early Warning Scores in the Emergency Department. *PEDIATRICS*, 132(4), pp.e841-e850.

Shankar-Hari, M. and Rubenfeld, G., 2016. Understanding Long-Term Outcomes Following Sepsis: Implications and Challenges. *Current Infectious Disease Reports*, 18(11).

Shaw, J., Fothergill, R., Clark, S. and Moore, F., 2017. Can the prehospital National Early Warning Score identify patients most at risk from subsequent deterioration?. *Emergency Medicine Journal*, 34(8), pp.533-537.

Singer, M., Deutschman, C., Seymour, C., Shankar-Hari, M., Annane, D., Bauer, M., Bellomo, R., Bernard, G., Chiche, J., Coopersmith, C., Hotchkiss, R., Levy, M., Marshall, J., Martin, G., Opal, S., Rubenfeld, G., van der Poll, T., Vincent, J. and Angus, D., 2016. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*, 315(8), p.801.

Smith, G., Prytherch, D., Meredith, P., Schmidt, P. and Featherstone, P., 2013. The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. *Resuscitation*, 84(4), pp.465-470.

Solevåg, A., Eggen, E., Schröder, J. and Nakstad, B., 2013. Use of a Modified Pediatric Early Warning Score in a Department of Pediatric and Adolescent Medicine. *PLoS ONE*, 8(8), p.e72534.

Spencer, W., Smith, J., Date, P., de Tonnerre, E. and Taylor, D., 2019. Determination of the best early warning scores to predict clinical outcomes of patients in emergency department. *Emergency Medicine Journal*, pp.emermed-2019-208622.

Thomas, B., Goodacre, S., Lee, E., Sutton, L., Bursnall, M., Loban, A., Waterhouse, S., Simmonds, R., Biggs, K., Marincowitz, C., Schutter, J., Connelly, S., Sheldon, E., Hall, J., Young, E., Bentley, A., Challen, K., Fitzsimmons, C., Harris, T., Lecky, F., Lee, A., Maconochie, I. and Walter, D., 2021. Prognostic accuracy of emergency department triage tools for

adults with suspected COVID-19: the PRIEST observational cohort study. *Emergency Medicine Journal*, 38(8), pp.587-593.

Vorwerk, C., Loryman, B., Coats, T., Stephenson, J., Gray, L., Reddy, G., Florence, L. and Butler, N., 2009. Prediction of mortality in adult emergency department patients with sepsis. *Emergency Medicine Journal*, 26(4), pp.254-258.

Williams, T., Tohira, H., Finn, J., Perkins, G. and Ho, K., 2016. The ability of early warning scores (EWS) to detect critical illness in the prehospital setting: A systematic review. *Resuscitation*, 102, pp.35-43.