TITLE PAGE

Title

National Early Warning Score accurately discriminates the risk of serious adverse events in patients with liver disease

Short title (max 45 characters incl. spaces)

National Early Warning Score in liver disease

Names of Authors

1. Theresa J Hydes[1]

2. Paul Meredith[2]

3. Paul E Schmidt[2,3]

4. Gary B Smith[2,4]

5. David R Prytherch[2,5]

6. Richard J Aspinall[1]

Affiliations

[1] Department of Gastroenterology & Hepatology

Portsmouth Hospitals NHS Trust

Queen Alexandra Hospital

Portsmouth

PO6 3LY

United Kingdom

[2]Clinical Outcomes Research Group

Research and Innovation

Portsmouth Hospitals NHS Trust

Queen Alexandra Hospital

Portsmouth

PO6 3LY

United Kingdom

[3]Acute Medicine

Portsmouth Hospitals NHS Trust

Queen Alexandra Hospital

Portsmouth

PO6 3LY

United Kingdom

[4]Faculty of Health and Social Sciences

Bournemouth University

Christchurch Road

Bournemouth

BH1 3LT

United Kingdom

[5]Centre for Healthcare Modelling and Informatics

University of Portsmouth

Buckingham Building, Lion Terrace

Portsmouth

PO1 3HE

United Kingdom

Grant support

None

List of abbreviations

ACLF: acute-on chronic liver failure

APACHE: Acute Physiology and Chronic Health Evaluation

ARLD: alcohol-related liver disease

AUROC: area under receiver operating characteristics curve

AVPU: Alert-Verbal-Painful-Unresponsive scale

CCS: Clinical Classifications Software

CI: confidence interval

CLD: chronic liver disease

CLIF-SOFA: Chronic Liver Failure Sequential Organ Failure Assessment

DNACPR: Do Not Attempt Cardiopulmonary Resuscitation

EWS: early warning score

FCE: finished consultant episode

ICD-10: International Classification of Diseases 10

ICU: intensive care unit

MELD: Model for End Stage Liver Disease

NCEPOD: National Confidential Enquiry into Patient Outcome and Death

NEWS: National Early Warning Score

PAS: Patient Administration System

SAPS: Simplified Acute Physiology Score

SHMI: Summary Hospital-level Mortality Indicator

SIH: Systemic Inflammation Hypothesis

SIRS: systemic inflammatory response syndrome

SOFA: Sequential Organ Failure Assessment

TIPSS: transjugular intrahepatic portosystemic shunt

UK: United Kingdom

UKELD: United Kingdom End Stage Liver Disease Score

US: United States

Corresponding Author

Richard J Aspinall MBChB, PhD

Consultant Hepatologist

Department of Gastroenterology and Hepatology

Portsmouth Hospitals NHS Trust

Queen Alexandra Hospital

Portsmouth

PO6 3LY

United Kingdom

Email: r.j.aspinall@doctors.org.uk

Tel: 02392 286255

Fax: 02392 286822

Disclosures

VitalPAC™ is a collaborative development of The Learning Clinic Ltd (TLC) and Portsmouth Hospitals NHS Trust (PHT). At the time of the study PHT had a royalty agreement with TLC to pay for the use of PHT intellectual property within the VitalPAC™ product. Drs Schmidt, Aspinall and Meredith are employed by PHT. Professors Smith and Prytherch were employees of PHT until 31/03/2011 and 31/07/2016, respectively. Dr Schmidt, and the wives of Professors Smith and Prytherch were shareholders in TLC at the time of the study. Professors Smith and Prytherch, and Dr Schmidt, were unpaid research advisors to TLC until May 2016. Professors Smith and Prytherch have received reimbursement of travel expenses from TLC for attending symposia in the UK.

Vitalpac is a trading name of The Learning Clinic Limited. Vitalpac is part of System C Healthcare (www.systemc.com).

T.Hydes: None to declare

Author Contributions

Theresa J Hydes: study concept and design, analysis and interpretation of data, drafting of the manuscript

Paul Meredith: study concept and design, analysis and interpretation of data, technical support

Paul E Schmidt: study concept and design, analysis and interpretation of data

Gary B Smith: study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content

David R Prytherch: study concept and design, acquisition of data, analysis and interpretation of data, statistical analysis

Richard J Aspinall: study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content

Abstract:

Background & Aims: The National Early Warning Score (NEWS) is used to identify deteriorating adult hospital inpatients. However, it includes physiological parameters frequently altered in patients with cirrhosis. We aimed to assess the performance of the NEWS in acute and chronic liver diseases.

Methods: We collected vital signs, recorded in real time, from completed consecutive admissions of patients 16 years or older to a large acute-care hospital in Southern England, from January 1, 2010 through October 31, 2014. Using ICD-10 codes, we categorized patients as having primary liver disease, secondary liver disease, or none. For patients with liver disease, 2 analysis groups were developed: the first based on clinical group (such as acute or chronic, alcohol-induced, or associated with portal hypertension) and the second based on summary liver-related hospital-level mortality indicator diagnoses. For each, we compared the abilities of the NEWS and 34 other early warning scores to discriminate 24-hr mortality, cardiac arrest, or unanticipated admission to the intensive care unit using area under the receiver operating characteristics (AUROC) curve and early warning score efficiency curve analyses.

Results: The NEWS identified patients with primary, non-primary, and no diagnoses of liver disease with AUROC values of 0.873 (95% CI, 0.860–0.886), 0.898 (95% CI, 0.891–0.905), and 0.879 (95% CI, 0.877–0.881), respectively. High AUROC values were also obtained for all clinical subgroups; the NEWS identified patients with alcohol-related liver disease with an AUROC value of 0.927 (95% CI, 0.912–0.941). The NEWS identified patients with liver diseases with higher AUROC values than other early warning scoring systems.

Conclusion: The NEWS accurately discriminates patients at risk of death, admission to the intensive care unit, or cardiac arrest within a 24-hr period for a range of liver-related diagnoses. Its widespread use provides a ready-made, easy to use option for identifying patients with liver disease who require early assessment and intervention, without the need to modify parameters, weightings or escalation criteria.

KEY WORDS: liver failure, sepsis, portal hypertension, cirrhosis, alcohol

Word Count (max 4100 references, table & figure legends): 4099

Number of figures & tables: Figures 3, Tables 3, Supplementary Tables 9

INTRODUCTION

Hospitalized patients with chronic liver disease (CLD) can rapidly deteriorate, particularly when acute decompensation is accompanied by extrahepatic organ dysfunction, a situation associated with high mortality.[1] Early recognition of clinical deterioration is vital if effective, goal-directed therapies are to be employed before complications develop.[2]

Clinical early warning scores (EWS) can identify patients at high risk of mortality[3] and are deployed in many hospitals in the USA and Europe.[4] Many different EWS are available (**Supplementary Table 1**) and to reduce variation in the United Kingdom (UK), a National EWS (NEWS) was launched by the Royal College of Physicians for use in all adults except pregnant women (**Supplementary Table 2**).[5] NEWS allocates weighted points, based on derangement of vital signs from defined normal ranges. The sum of allocated points directs changes in the level of care e.g. more frequent monitoring, involvement of senior staff, calling a rapid response team.

NEWS is calculated using: pulse, respiratory rate, systolic blood pressure, AVPU (Alert-Verbal-Painful-Unresponsive) scale, temperature, peripheral oxygen saturations (S_pO_2) and use of supplemental oxygen. NEWS was validated in 35,585 unselected medical patients, achieving an area under the receiver operating characteristics (AUROC) curve [95% confidence interval (CI)] of 0.894 [0.887-0.902], 0.857 [0.847-0.868] and 0.722 [0.685-0.759] for discriminating risk of death, unanticipated intensive care unit (ICU) admission and cardiac arrest, within 24 hours, respectively.[6]

The introduction of NEWS was timely, coinciding with a National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report on treating patients with alcohol-related liver disease (ARLD) in UK hospitals, which identified widespread deficiencies in management.[7] These included poor recognition of deterioration and failure to escalate care. Opportunities were missed to manage sepsis, hypovolaemia, renal failure and variceal haemorrhage effectively. While current predictive models estimate medium and long-term prognosis in patients with liver disease, none are validated for short-term outcomes in a ward setting. There is an urgent need for tools to identify liver patients at risk of deterioration, which can be deployed outside the ICU.

However, a potential concern is that many patients with liver disease have chronic physiological derangements affecting NEWS parameters.[8] Patients with cirrhosis often have low systemic vascular resistance, hypotension or resting tachycardia.[9,10] Pyrexial response may be blunted in decompensated cirrhosis and respiratory rate increased in encephalopathy.[2]

These changes raise the possibility that NEWS may perform suboptimally in cirrhosis and other hepatic conditions. Indeed, no EWS has been specifically evaluated in liver patients. Therefore, the aims of our study were to determine whether NEWS accurately discriminates the risk of early in-hospital death, cardiac arrest or ICU admission in hospitalized patients with liver disease and to compare its performance against all other EWS.

PATIENTS AND METHODS

The Isle of Wight, Portsmouth and SE Hampshire research ethics committee approved our study (ref. 08/02/1394).

Setting

The study was performed in a large acute hospital in Southern England, serving 650,000 people.

Patient group

We analysed a database of electronically captured vital signs recorded in real-time from completed consecutive admissions (episodes) of patients aged ≥ 16 years between 01/01/2010 and 31/10/14. Electronic NEWS recordings were in hospital-wide use excluding the emergency department and ICU. Patients discharged before midnight on the day of admission and those admitted directly to ICU were excluded.

Identification and classification of patients with liver disease

Patient admissions were categorized according to International Classification of Diseases (ICD-10) codes for any finished consultant episode (FCE). Data were extracted from the hospital's Patient Administration System (PAS). If care was transferred to another consultant or specialty during the same admission, a new FCE and further set of ICD-10 codes were recorded. Groups included (1) patients with primary diagnosis of liver disease, (2) those with non-primary liver diagnosis (co-morbidity) and (3) patients not allocated any liver disease codes (control group). Where patients had more than one FCE during admission, the final

liver primary diagnosis or top-ranking liver secondary diagnosis (if no primary liver code) prior to discharge was used. Therefore each admission could only belong to one group.

ICD-10 codes were divided into four subgroups to examine NEWS performance according to whether liver disease was acute or chronic, alcohol-induced or associated with portal hypertension (**Supplementary Table 3)**. Clinical subgroups included: (A) acute alcohol-induced liver injury, (B) other acute injury, (C) CLD without cirrhosis, (D) cirrhosis. Liver-related ICD-10 codes were identified separately using Summary Hospital-level Mortality Indicator (SHMI) definitions employed routinely in the UK's National Health Service.[11] Three previously defined SHMI groups were selected: (1) Alcohol-related liver disease (SHMI group 93), (2) Other liver disease (SHMI group 94), and (3) Hepatitis, viral infection, other infections (SHMI group 6, Clinical Classification System (CCS) group 6), which includes viral hepatitis, autoimmune and drug-induced liver disease (**Supplementary Table 4).**[11] Division between SHMI groups 93 and 94 may be relevant as ethanol can effect cardiovascular physiology independent of liver disease. Patients were defined as having no liver disease if none of their episodes of care during, or prior to this study, contained any liver ICD-10 codes (primary or secondary diagnosis) identified by the three SHMI groups or four clinical subgroups.

Outcomes

The primary outcome was any of the following events occurring within 24 hours of an observation set: in-hospital mortality, unanticipated ICU admission, or cardiac arrest.

Data collection

Nurses recorded data required for NEWS at the bedside using electronic devices running VitalPAC™ software.[12] Vital sign sets with implausible physiological values were excluded, as were events for which no observations were recorded within the preceding 24 hours. Reasons for this included end of life care or an outcome following admission to ICU. We excluded observations recorded after a primary outcome had occurred.

Comparison of NEWS with other EWS

To compare the performance of NEWS[6] with 34 other published EWS in patients with liver disease, we applied each EWS to our data set.

Statistics

Data manipulation was performed using MicroSoft® Visual Fox-Pro 9.0. The ability of NEWS to discriminate outcomes was assessed using AUROC on IBM SPSSv22. Data were analysed regarding (a) percentage of observations that would trigger medical review if escalation occurred at or above a given NEWS value and (b) percentage of observations that were followed by death, cardiac arrest or ICU admission within 24 hours at, or above this value. EWS efficiency curves were constructed using this data.[13] All observation sets were treated independently.

RESULTS

Study population

Categorising patient episodes using the four clinical subgroups, 773 patients (1197 episodes) were discharged with a primary diagnosis of liver disease and 2525 (3953 episodes) with non-primary (co-morbid) diagnosis. In the same period, if patient episodes were categorised using the three SHMI groups, 1216 patients (2016 episodes) were discharged with a primary diagnosis of liver disease and 4957 (6459 episodes) with a non-primary (co-morbid) diagnosis. After excluding episodes with no observations recorded 24 hours prior to an adverse event, the final dataset where episodes were categorised using the four clinical subgroups, comprised 722 patients (1112 episodes) with a primary liver diagnosis, and 2339 patients (3658 episodes) with a non-primary liver diagnosis **(Table 1)**. Similarly, after the same exclusions, the final dataset where patient episodes were categorised using the three SHMI groups comprised 1136 patients (1894 episodes) with a primary liver diagnosis, and 4486 patients (5840 episodes) with a non-primary liver diagnosis **(Supplementary Table 5)**.

From these datasets we examined NEWS' performance in liver disorders using over 3.5 million vital sign sets. As described in the Methods, we included all observations for analysis. We identified 39,619 sets from patients allocated a liver ICD-10 code as primary diagnosis and 105,092 from those with a non-primary liver diagnosis defined by the four clinical subgroups; in addition to 3,525,420 sets from those never allocated a liver ICD-10 code (control group) **(Table 1)**. Of these 2.53% (1001 / 39,619), 1.94% (2035 / 105,092), and 0.87% (30,522 / 3,525,420) observations were followed by an adverse event within 24 hours respectively **(Table 1)**. Using the SHMI classification, we identified 57,836 sets from patients allocated a liver primary diagnosis and 205,194 from those with a non-primary liver diagnosis

(Supplementary Table 5). Overall 2.19% (1269 / 57,836) and 1.91% (3917 / 205,194) of these observations were followed by an event within 24 hours.

NEWS performance in primary and non-primary liver disease vs. patients without liver disease

NEWS performed equally well in patients with primary diagnoses of liver disease with AUROC values [CI] of 0.873 [0.860–0.886] compared to 0.879 [0.877-0.881] for patients without liver disease. NEWS achieved even higher levels of efficiency in patients with a non-primary diagnosis of liver disease, AUROC 0.898 [0.891–0.905] (**Table 2, Figure. 1**).

NEWS performance in four clinical subgroups of liver disease

NEWS performed as well in patients with non-alcohol related acute liver injury (AUROC [CI] 0.906 [0.879–0.933]) and CLD (AUROC [CI] 0.865 [0.835–0.894]) as it did in patients without liver disease (AUROC [CI] 0.879 [0.877-0.881]) (**Table 2**). Compared to those without liver disease, NEWS performed significantly higher in acute alcohol-induced liver injury (AUROC [CI] 0.927 [0.912–0.941]) and slightly lower in cirrhosis (AUROC [CI] 0.824 [0.797–0.850]) (**Table 2, Figure 2a**). In patients with non-primary diagnoses of liver disease, NEWS performed better for several groups (all liver diagnoses combined, AUROC [CI] 0.898 [0.891–0.905]; acute alcohol-induced liver injury, AUROC [CI] 0.929 [0.909–0.949], and CLD, AUROC [CI] 0.905 [0.894–0.917]) than in patients without liver disease **(Table 2, Figure 2b)**.

NEWS performance in subgroups of liver disease according to SHMI classification

NEWS performed equally well in patients with primary (AUROC [CI] 0.886 [0.875-0.896]) and non-primary (AUROC [CI] 0.880 [0.874-0.885]) liver disease defined using SHMI classification for all liver groups **(Table 3).** NEWS performed better in ARLD than other SHMI liver diagnoses, both as primary (AUROC [CI] 0.902 [0.889-0.916]) and non-primary diagnosis (AUROC [CI] 0.915 [0.903-0.928]) (**Figure 3a and 3b**). Admission numbers for SHMI group 6, CCS 6 were too small for meaningful interpretation.

Performance of other EWS in patients with and without a primary diagnosis of liver disease

NEWS performed better than the other 34 EWS evaluated for patients with a primary or non-primary liver diagnosis (**Supplementary Table 6**). On dividing patients into clinical subgroups, NEWS performed better than the 34 EWS for those with primary or secondary diagnosis of acute alcohol-related injury (group A) and patients with secondary diagnosis of CLD (group C) (**Supplemental Tables 7 and 8**). While NEWS also appeared to perform better in all other liver cohorts, there was no significant difference between NEWS and other high performing scores. NEWS performed better than the 34 EWS for alcohol and non-alcohol related liver disease groups according to the SHMI classification (**Supplemental Table 9**).

DISCUSSION

In the UK, the Royal College of Physicians recommended that NEWS is deployed to standardize assessment of acute-illness severity in hospitals. Our study was designed to test the hypothesis that NEWS might not accurately predict serious events in patients with liver disease due to pre-existing altered physiology associated with the underlying condition. This

hypothesis was disproven and we were encouraged to find NEWS remained a highly accurate discriminator of adverse events in liver disorders, with its performance being highest in ARLD. Sensitivity and specificity was slightly reduced in patients with cirrhosis but remained clinically relevant. In a direct comparison with 34 other EWS systems, NEWS was the most discriminating in patients with primary or non-primary diagnostic codes for liver disease.

As described in the Systemic Inflammation Hypothesis (SIH), patients with advanced liver disease are imperiled by progressive interactions between circulatory disturbance and systemic inflammation.[14] These can abruptly worsen, leading to acute-on-chronic liver failure (ACLF), multiple organ dysfunction and death.[15] To allow effective interventions, physicians need to be promptly alerted to deterioration. Unfortunately many doctors fail to recognize deteriorating patients with liver disease.[7]

In our study, NEWS was validated as an accurate discriminator of short-term (< 24 hour) deterioration of inpatients with liver disease. The recent increase in hospital admissions secondary to cirrhosis in the UK[16] and 43% increase in cirrhosis-associated deaths per year in the USA make these findings pertinent.[17] NEWS' reliance on routine vital signs facilitates serial monitoring, a potential advantage over many predictive scores. Its widespread adoption provides opportunities for standardization of care and the potential benefits.

The availability of other predictors of short-term mortality for ward-based patients with CLD is limited. Model for End Stage Liver Disease (MELD)[18,19] and UK End Stage Liver Disease (UKELD) scores[20] are more accurate in predicting medium-term mortality. Child-Pugh score is limited by two subjective parameters and a ceiling effect.[21] These scoring systems, along

with the Glasgow alcoholic hepatitis score[22] and Maddrey's discriminant function[23] are reliant on laboratory parameters and less easily applied at the bedside for frequent monitoring.

Clinical, hematological and biochemical criteria can predict short-term mortality using the Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE) II and Simplified Acute Physiology (SAPS) II scores, but these have only been validated in ICU settings.[24] These prognostic models appear most accurate 48 hours after ICU admission and may not perform optimally on general wards.[25,26] The adapted Chronic Liver Failure (CLIF)-SOFA score and CLIF-Consortium Organ Failure score for ACLF (CLIF-C ACLF) were validated as predictors of 28-day transplant-free mortality.[1,27] Despite outperforming MELD and Child-Pugh, the predictive value of CLIF-C ACLF is lowest at day one of diagnosis and may not reveal the earliest point of deterioration.[27] Thus, none of the existing liver-specific scores have been validated as predictors of short-term (< 24 hour) mortality in a ward environment.

NEWS incorporates several parameters that can be deranged in the systemic inflammatory response syndrome (SIRS). This may be relevant to our finding that NEWS performs especially well in ARLD patients, who are particularly susceptible to sepsis.[28] Alcohol misuse can lead to an altered intestinal microbiome, increased translocation of bacteria and elevated endotoxin levels.[29,30] These events can worsen the liver injury itself, particularly alcoholic hepatitis.[31,32]

A recent multi-centre study demonstrated strong associations between SIRS, multi-organ failure and death in patients with alcoholic hepatitis, independent of infection.[33] Furthermore, alcohol-related cirrhosis may be associated with higher portal pressures and a more

hyperdynamic circulation.[34,35] Similarly, low arterial pressures and increased intrahepatic resistance correlate with mortality in alcohol-related ACLF.[36]

While the efficiency of NEWS was slightly reduced in cirrhosis compared to other subgroups, its ability to identify acute deterioration remained high. Importantly, AUROC values for NEWS in this group were higher than other EWS systems.

The strength of this study lies in its access to a large electronic dataset of four years of hospital-wide vital signs captured at the point of care. Exclusion rate was small (~6%), reflecting a valid cross-section of inpatients. Potential weaknesses include reliance on ICD-10 coding which may limit the accurate placement of patients into clinical subgroups. In addition, this study was not designed to demonstrate whether introducing NEWS improved clinical care and saved lives in patients with liver diseases. This would be difficult to demonstrate, as NEWS is merely a clinical tool to identify patients at risk of deterioration.

NEWS forms only one part of the 'Chain of Prevention',[37] which requires staff education, timely vital signs monitoring, escalation of care and appropriate clinical responses. No EWS could be expected to improve outcomes if other components of the chain are not optimised. Additionally, metrics that might indicate NEWS-mediated improvements in care (e.g. microbiology cultures, fluid resuscitation, ICU outreach referrals) are affected by factors with no bearing on the performance of EWS. Furthermore, some metrics, e.g. number of ICU outreach referrals, might be difficult to interpret. For instance, would a reduction in the number of critical care referrals be a good or bad indicator? One could argue that increased referral to ICU implies a more pre-emptive approach to critical illness, whereas another might argue that fewer calls result from improved ward care.

Other potential weaknesses of our study include its retrospective nature and the fact that we obtained date/time of death (or discharge) from the hospital's PAS computer system. Some events may have been recorded later than they occurred, potentially underestimating the number of observations followed by an event within 24 hours. For simplicity, we used all observations for analysis. It would have been possible to randomly choose one observation

per episode, either by randomly choosing one, or to select a random time and take the nearest NEWS value. However, we have previously demonstrated that whichever of these approaches is taken, the ranking of competing early warning systems (EWSs) is essentially unchanged.[37] Our analysis aimed to rank performance of different EWSs and so we used the computationally simplest.

This work could be extended by identifying whether changes in NEWS over time are more accurate predictors of deterioration, particularly in patients judged to be activating NEWS despite appearing clinically stable. It might also be possible to combine bedside observations with laboratory markers to develop a scoring system with additional medium term predictive qualities.

Many clinicians would agree that shock or severe sepsis are easily recognized, yet many doctors fail to recognize deteriorating patients with liver disease and other conditions.[7,38,39] An assessment using NEWS is easily performed by inexperienced and experienced staff alike. It provides an aggregate score based upon the, sometimes subtle, physiologic disturbance of several vital signs and may permit earlier risk stratification than when detailed clinical examination and initial laboratory test results are required. However, this current study was not designed to determine if there was such a measurable benefit from using NEWS.

In conclusion, we have demonstrated that NEWS accurately discriminates risk of death, ICU admission or cardiac arrest within 24 hours in patients with liver-related diagnoses. Its widespread use in hospitals provides an easy-to-use assessment without needing to modify parameters, weightings or escalation criteria. This could be particularly valuable for identifying patients with decompensated liver disease at risk of deterioration.

REFERENCES

1. Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology*. 2013;144(7):1426-1437, 1437-9.

2. Wong F, Bernardi M, Balk R, et al. Sepsis in cirrhosis: report on the 7th meeting of the International Ascites Club. *Gut*. 2005;54(5):718-725.
3. Smith GB, Prytherch DR, Schmidt PE, Featherstone PI. Review and performance evaluation of aggregate weighted “track and trigger” systems. *Resuscitation*. 2008;77(2):170-179.
4. Smith MEB, Chiovaro JC, O’Neil M, et al. Early Warning System Scores for Clinical Deterioration in Hospitalized Patients: A Systematic Review. *Ann Am Thorac Soc*. 2014;11(9):1454-1465.
5. Royal College of Physicians London. *National Early Warning Score (NEWS): Standardising the Assessment of Acute-Illness Severity in the NHS. Report of a Working Party*.; 2012.
6. Smith GB, Prytherch DR, Meredith P, Schmidt PE, Featherstone PI. 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*. 2013;84(4):465-470.
7. National Confidential Enquiry into Patient Outcome and Death. *National Confidential Enquiry into Patient Outcome and Death. Measuring the Units: A Review of Patients Who Died with Alcohol-Related Liver Disease.* London; 2013. http://www.ncepod.org.uk/2013arld.html.
8. Fernández J, Gustot T. Management of bacterial infections in cirrhosis. *J Hepatol*. 2012;56 Suppl 1:S1-12.
9. Kowalski H, Abelman W. The cardiac output at rest in laennec’s cirrhosis. 1953;32:1025-1033.
10. Iwakiri Y, Groszmann RJ. The hyperdynamic circulation of chronic liver diseases: from the patient to the molecule. *Hepatology*. 2006;43(2 Suppl 1):S121-31.

11. Clinical Indicators Team. *Indicator Specification: Summary Hospital-Level Mortality Indicator*.; 2015.
12. Smith GB, Prytherch DR, Schmidt P, et al. Hospital-wide physiological surveillance-a new approach to the early identification and management of the sick patient. *Resuscitation*. 2006;71(1):19-28.
13. Prytherch DR, Smith GB, Schmidt PE, Featherstone PI. ViEWS--Towards a national early warning score for detecting adult inpatient deterioration. *Resuscitation*. 2010;81(8):932-937.
14. Bernardi M, Moreau R, Angeli P, Schnabl B, Arroyo V. Mechanisms of decompensation and organ failure in cirrhosis: From peripheral arterial vasodilation to systemic inflammation hypothesis. *J Hepatol*. 2015;63(5):1272-1284.
15. Clària J, Stauber RE, Coenraad MJ, et al. Systemic inflammation in decompensated cirrhosis: Characterization and role in acute-on-chronic liver failure. *Hepatology*. 2016;64(4):1249-1264.
16. Thomson SJ, Westlake S, Rahman TM, et al. Chronic liver disease--an increasing problem: a study of hospital admission and mortality rates in England, 1979-2005, with particular reference to alcoholic liver disease. *Alcohol Alcohol*. 43(4):416-422.
17. Murray CJL, Atkinson C, Bhalla K, et al. The State of US Health, 1990-2010. *JAMA*. 2013;310(6):591.
18. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology*. 2000;31(4):864-871.
19. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology*. 2001;33(2):464-470.
20. Barber K, Madden S, Allen J, Collett D, Neuberger J, Gimson A. Elective liver

transplant list mortality: development of a United Kingdom end-stage liver disease score. *Transplantation*. 2011;92(4):469-476.

21. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973;60(8):646-649.
22. Forrest EH, Evans CDJ, Stewart S, et al. Analysis of factors predictive of mortality in alcoholic hepatitis and derivation and validation of the Glasgow alcoholic hepatitis score. *Gut*. 2005;54(8):1174-1179.
23. Maddrey WC, Boitnott JK, Bedine MS, Weber FL, Mezey E, White RI. Corticosteroid therapy of alcoholic hepatitis. *Gastroenterology*. 1978;75(2):193-199.
24. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22(7):707-710.
25. Thomson SJ, Moran C, Cowan ML, et al. Outcomes of critically ill patients with cirrhosis admitted to intensive care: an important perspective from the non-transplant setting. *Aliment Pharmacol Ther*. 2010;32(2):233-243.
26. Cholongitas E, Betrosian A, Senzolo M, et al. Prognostic models in cirrhotics admitted to intensive care units better predict outcome when assessed at 48 h after admission. *J Gastroenterol Hepatol*. 2008;23(8 Pt 1):1223-1227.
27. Jalan R, Saliba F, Pavesi M, et al. Development and Validation of a Prognostic Score to Predict Mortality in Patients with Acute on Chronic Liver Failure. *J Hepatol*. 2014;61(5):1038-1047.
28. Gustot T, Fernandez J, Szabo G, et al. Sepsis in alcohol-related liver disease. *J Hepatol*. 2017. doi:10.1016/j.jhep.2017.06.013.
29. Yan AW, Fouts DE, Brandl J, et al. Enteric dysbiosis associated with a mouse model

of alcoholic liver disease. *Hepatology*. 2011;53(1):96-105.

30. Bode JC, Bode C, Heidelbach R, Dürr HK, Martini GA. Jejunal microflora in patients with chronic alcohol abuse. *Hepatogastroenterology*. 1984;31(1):30-34.
31. Adachi Y, Moore LE, Bradford BU, Gao W, Thurman RG. Antibiotics prevent liver injury in rats following long-term exposure to ethanol. *Gastroenterology*. 1995;108(1):218-224.
32. Uesugi T, Froh M, Arteel GE, Bradford BU, Thurman RG. Toll-like receptor 4 is involved in the mechanism of early alcohol-induced liver injury in mice. *Hepatology*. 2001;34(1):101-108.
33. Michelena J, Altamirano J, Abraldes JG, et al. Systemic inflammatory response and serum lipopolysaccharide levels predict multiple organ failure and death in alcoholic hepatitis. *Hepatology*. 2015;62(3):762-772.
34. Nagula S, Jain D, Groszmann RJ, Garcia-Tsao G. Histological-hemodynamic correlation in cirrhosis-a histological classification of the severity of cirrhosis. *J Hepatol*. 2006;44(1):111-117.
35. Perelló A, Escorsell A, Bru C, et al. Wedged hepatic venous pressure adequately reflects portal pressure in hepatitis C virus-related cirrhosis. *Hepatology*. 1999;30(6):1393-1397.
36. Mehta G, Mookerjee RP, Sharma V, Jalan R. Systemic inflammation is associated with increased intrahepatic resistance and mortality in alcohol-related acute-on-chronic liver failure. *Liver Int*. 2015;35(3):724-734.
37. Smith GB. In-hospital cardiac arrest: Is it time for an in-hospital “chain of prevention”? *Resuscitation*. 2010;81(9):1209-1211.
38. *National Confidential Enquiry into Patient Outcome and Death. An Acute Problem? A Report of the National Confidential Enquiry into Patient Outcome and Death*.; 2005.

http://www.ncepod.org.uk/2005report/NCEPOD_Report_2005.pdf. (accessed 14th November 2017)

39. *National Confidential Enquiry into Patient Outcome and Death. Just Say Sepsis! A Review of the Process of Care Received by Patients with Sepsis. A Report by the National Confidential Enquiry into Patient Outcome and Death.*; 2015 http://www.ncepod.org.uk/2015sepsis.html (accessed 14th November 2017)

TABLES

Table 1: Demographic, observation and event data regarding patient admissions with primary or non-primary diagnosis of liver disease defined by four clinical subgroups

Table 2: NEWS performance in liver disease according to four clinical subgroups

Table 3: NEWS performance in liver disease according to SHMI classification

FIGURE LEGENDS

Figure 1. Calling efficiency curves of NEWS for combined outcome of cardiac arrest, unanticipated ICU admission or death occurring within 24 hours: comparison between patients with a primary or non-primary liver code vs. patients without liver disease

Figure 2. Calling efficiency curves of NEWS for combined outcome of cardiac arrest, unanticipated ICU admission or death occurring within 24 hours: comparison between ICD-10 defined clinical subgroups of liver disease assigned to **a)** primary diagnosis**,** and **b)** non-primary diagnosis

Figure 3. Calling efficiency curves of NEWS for combined outcome of cardiac arrest, unanticipated ICU admission or death occurring within 24 hours: comparison between SHMI

defined subgroups of liver disease assigned to **a)** primary diagnosis**,** and **b)** non-primary diagnosis

Figure 1

Figure 1

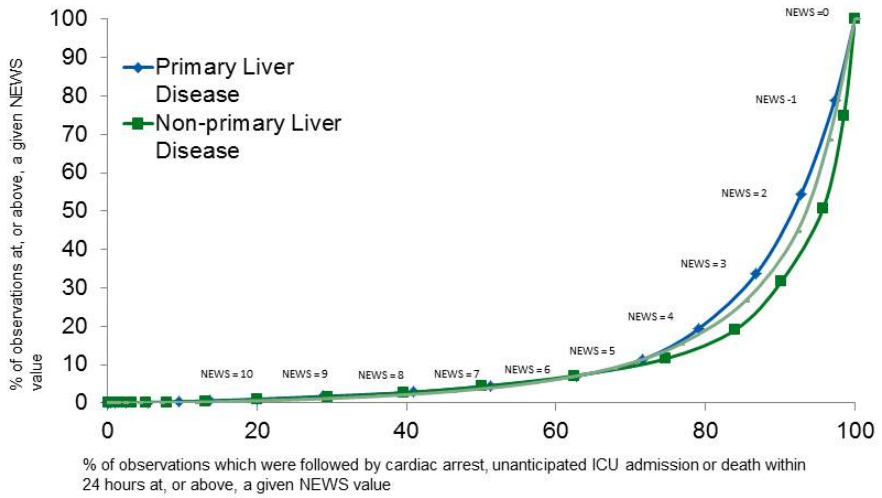

Figure shows the efficiency curves for patients with a primary liver code, a non-primary liver code and patients without either a primary or non-primary diagnosis of liver disease, as defined by the four clinical subgroups of liver disease. For each NEWS value the percentage of the total number of observations at, or above, that NEWS value is platted against the percentage of the total number of observations that were followed by cardiac arrest, unanticipated ICU admission or death within 24 hours at, or above, a given NEWS.

Figure 2

Figure 2a

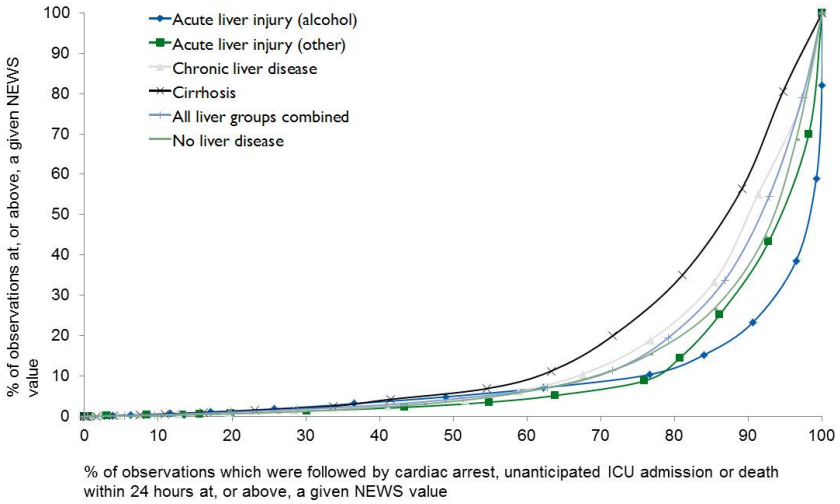

Figure shows the efficiency curves for patients allocated a primary diagnosis of acute liver injury due to alcohol, acute liver injury due to other causes, chronic liver disease, cirrhosis, any of the four clinical liver subgroups and patients without any primary or non-primary diagnosis of liver disease. For each NEWS value the percentage of the total number of observations at, or above, that NEWS value is platted against the percentage of the total number of observations that were followed by cardiac arrest, unanticipated ICU admission or death within 24 hours at, or above, a given NEWS.

Figure 2b

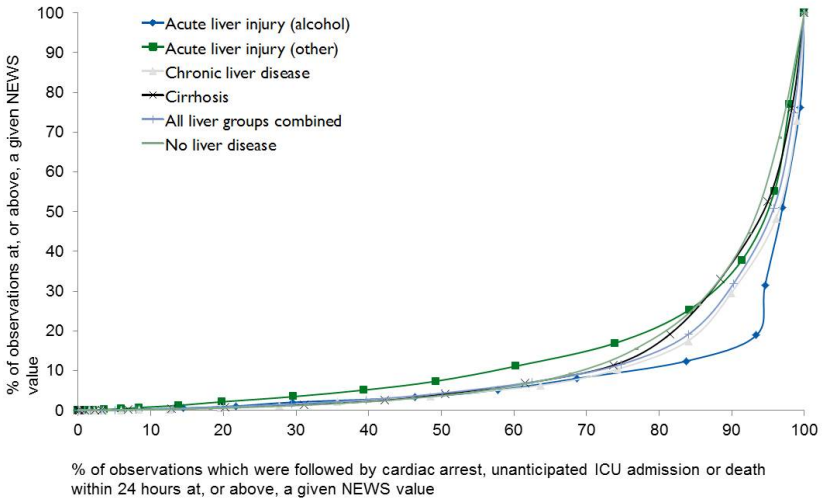

Figure shows the efficiency curves for patients allocated a non-primary diagnosis of acute liver injury due to alcohol, acute liver injury due to other causes, chronic liver disease, cirrhosis, any of the four clinical liver subgroups and patients without any primary or non-primary diagnosis of liver disease. For each NEWS value the percentage of the total number of observations at, or above, that NEWS value is platted against the percentage of the total number of observations that were followed by cardiac arrest, unanticipated ICU admission or death within 24 hours at, or above, a given NEWS.

Figure 3

Figure 3a

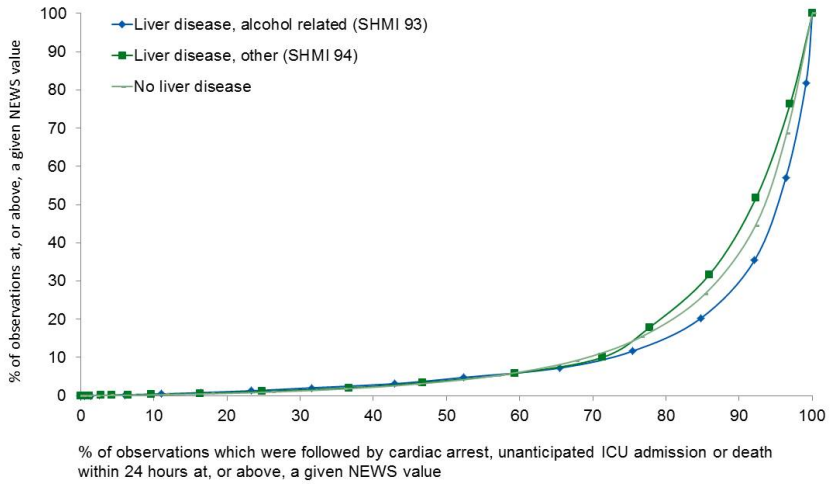

Figure shows the efficiency curves for patients allocated a primary diagnosis of alcohol related liver disease (SHMI 93), liver disease due to other causes (SHMI 94) and patients without any primary or non-primary diagnosis of liver disease. For each NEWS value the percentage of the total number of observations at, or above, that NEWS value is platted against the percentage of the total number of observations that were followed by cardiac arrest, unanticipated ICU admission or death within 24 hours at, or above, a given NEWS.

Figure 3b

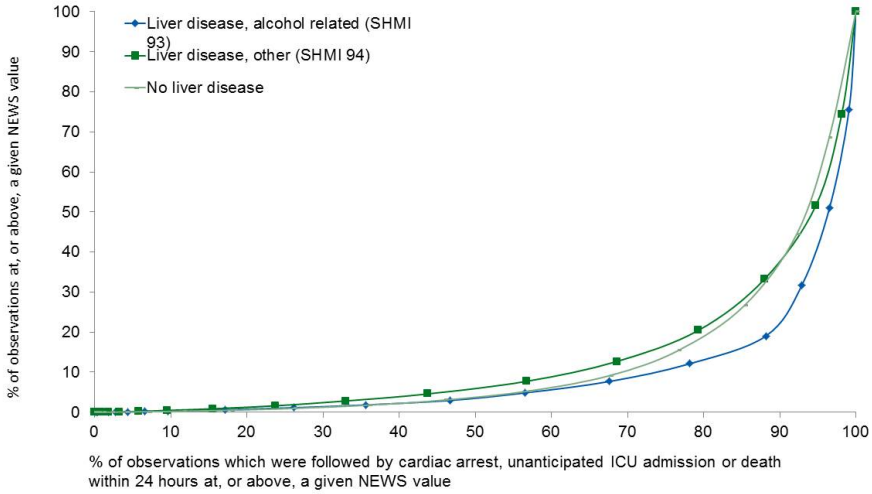

Figure shows the efficiency curves for patients allocated a non-primary diagnosis of alcohol related liver disease (SHMI 93), liver disease due to other causes (SHMI 94) and patients without any primary or non-primary diagnosis of liver disease. For each NEWS value the percentage of the total number of observations at, or above, that NEWS value is platted against the percentage of the total number of observations that were followed by cardiac arrest, unanticipated ICU admission or death within 24 hours at, or above, a given NEWS.

Supplementary Table 1: Early warning scoring systems

System number	Reference
1	Morgan RJM, Williams F, Wright M. An early warning scoring system for detecting developing critical illness. Clin Intensive Care. 1997;8:100
2	Wright MM, Stenhouse CW, Morgan RJ. Early detection of patients at risk (PART). Anaesthesia. 2000;55(4):391-2
3	Subbe CP, Kruger M, Rutherford P, Gemmel L. Validation of a modified Early Warning Score in medical admissions. QJM. 2001;94(10):521-6
4	Subbe CP, Kruger M, Rutherford P, Gemmel L. Validation of a modified Early Warning Score in medical admissions. QJM. 2001;94(10):521-6
5	Fox N. Critical care outreach team sees fall in cardiac arrests. *Nurs Times* 2001;97:34-5.
6	Riley B. Critical care outreach: rationale and development. *BJA CEPD Rev* 2001;1:146-9.
7	Cooper N. Patient at risk! Clin Med (Lond). 2001;1(4):309-11
8	Subbe CP, Hibbs R, Williams E, Rutherford P, Gemmel L. ASSIST: a screening tool for the critically ill patients on general medical wards. Intensive Care Med. 2002;28:21
9	Wasson C, Greer R, Dawson S, Slater R. An assessment of the temperature component of the early warning score. Br J Anaesth. 2002;89:367
10	Odell M, Forster A, Rudman K, Bass F. The critical care outreach service and the early warning system on surgical wards. Nurs Crit Care. 2002;7(3):132-5
11	Carberry M. Implementing the modified early warning system: our experiences. Nurs Crit Care. 2002;7(5):220-6
12	Rees JE. Early warning scores. Update Anaesth 2003;17:30-3
13	Rees JE, Mann C. Use of the patient at risk scores in the emergency department: a preliminary study. Emerg Med J. 2004;21(6):698-9
14	Priestley G, Watson W, Rashidian A, Mozley C, Russell D, Wilson J, Cope J, Hart D, Kay D, Cowley K, Pateraki J. Introducing Critical Care Outreach: a ward-randomised trial of phased introduction in a general hospital. Intensive Care Med. 2004;30(7):1398-404
15	Ryan H, Cadman C, Hann L. Setting standards for assessment of ward patients at risk of deterioration. Br J Nurs. 2004;13(20):1186-90
16	Allen K. Recognising and managing adult patients who are critically sick. Nurs Times. 2004 Aug 31-Sep 6;100(35):34-7.

17	Goldhill DR. Preventing surgical deaths: critical care and intensive care outreach services in the postoperative period. Br J Anaesth. 2005;95(1):88-94.
18	Chatterjee MT, Moon JC, Murphy R, McCrea D. The "OBS" chart: an evidence based approach to re-design of the patient observation chart in a district general hospital setting. Postgrad Med J. 2005 Oct;81(960):663-6
19	Heaps N, Thorley K, Langley S. Critical care outreach: creating a safe culture. Br J Nurs. 2005 Dec 8-2006 Jan 11;14(22):1208-11
20	Andrews T, Waterman H. Packaging: a grounded theory of how to report physiological deterioration effectively. J Adv Nurs. 2005;52:473–81.
21	Bakir A, Duckitt R, Buxton-Thomas R. A simple physiological scoring system for medical in-patients derived by modeling hospital mortality data. Poster presentation Intensive Care Society State of the Art Meeting 2005. London: Intensive Care Society
22	Smith GB, Prytherch DR, Schmidt P, Featherstone PI, Knight D, Clements G, Mohammed MA. Hospital-wide physiological surveillance-a new approach to the early identification and management of the sick patient. Resuscitation. 2006;71(1):19-28.