Top tips in Acute Geriatrics

Dr Linda Dykes
Consultant EM & GPwSI in Acute Community COTE
Bangor, North Wales

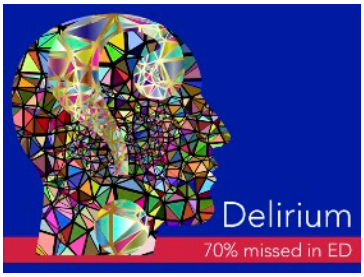
@DrLindaDykes

Admissions from care homes

https://www.nursingtimes.net/news/community-news/over-40-of-emergency-admissions-from-care-homes-avoidable-25-07-2019/

UTI diagnosis in older people

1. Public Health England Guidelines
2. https://www.ncbi.nlm.nih.gov/pubmed/19054190/
3. https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2748454

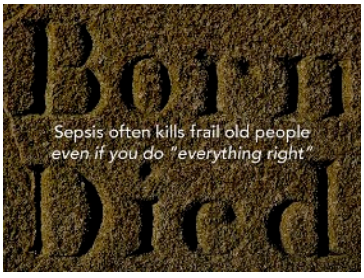


Delirium: associated mortality, 4AT and SQiD

https://bmcgeriatr.biomedcentral.com/articles/10.1186/s12877-017-0661-7
https://www.the4at.com
Example of ED delirium screening from Bradford.

Frailty, initial treatment response & movement

https://academic.oup.com/ageing/article/46/6/920/2926042

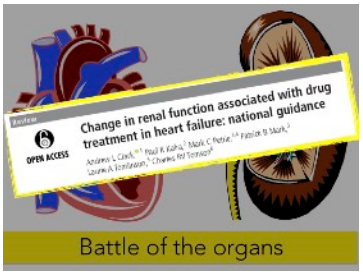


THAT LETTER in the Lancet on 26/10/19!

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)32483-3/fulltext

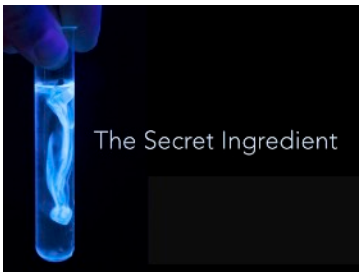
Sick day rules - hazards of stopping low dose aspirin

https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.117.028321



Renal function and heart failure: UK Guidelines 2019

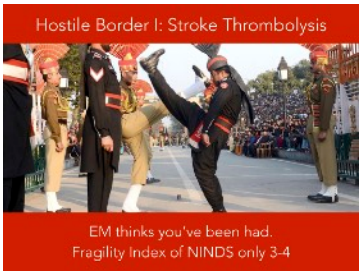
https://heart.bmj.com/content/heartjnl/105/12/904.full.pdf



The Secret Ingredient - the quest for safe discharge from the ED

https://www.ncbi.nlm.nih.gov/pubmed/31504931

https://www.ncbi.nlm.nih.gov/pubmed/28974330



Stroke thrombolysis: the fragility index of the NINDS trial

https://emcrit.org/pulmcrit/fragility-index-ninds/

NNT/NNH

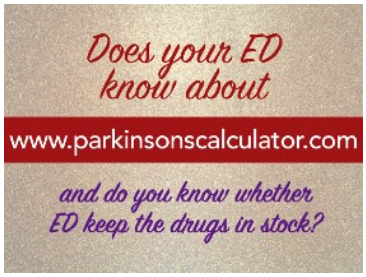
www.thennt.com

Calculating the anticholinergic burden

www.acbcalc.com

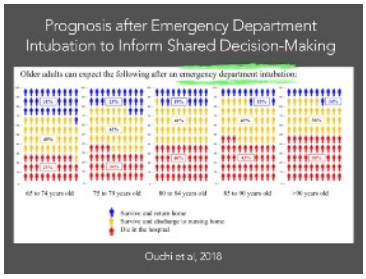
Rationalising medication - Scottish guidelines

https://www.therapeutics.scot.nhs.uk/wp-content/uploads/2018/04/Polypharmacy-Guidance-2018.pdf



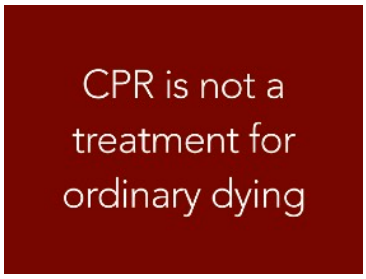
Parkinsons resources for Emergency Departments: OPTIMAL

http://www.parkinsonscalculator.com



Prognosis after Emergency Department intubation (Ouchi et al)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6320691/



#HaveTheConversation

www.lindadykes.org/havetheconversation

Thank you for coming to my talk at AGM 2019!

- I'd welcome any feedback - email me at lindaDykes@wales.nhs.uk - I'd particularly like to know if anything you have heard today has changed your practice.
- I'm also on Twitter - @DrLindaDykes - and my direct messages are open.

Resuscitation 106 (2016) 49–52

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

Combined use of the National Early Warning Score and D-dimer levels to predict 30-day and 365-day mortality in medical patients☆

Christian H. Nickel[a,*], John Kellett[b], Tim Cooksley[c], Roland Bingisser[a], Daniel P. Henriksen[d], Mikkel Brabrand[b,d]

[a] Emergency Department, University Hospital Basel, Switzerland
[b] Department of Emergency Medicine, Hospital of South West Jutland, Esbjerg, Denmark
[c] Department of Acute Medicine, University Hospital of South Manchester, United Kingdom
[d] Department of Emergency Medicine, Odense University Hospital, Denmark

ARTICLE INFO

Article history:
Received 30 March 2016
Received in revised form 11 May 2016
Accepted 12 June 2016

Keywords:
Early warning scores
D-dimer
predictive scores
Risk stratification
Emergency department
Mortality

ABSTRACT

Aim: To investigate the combined use of NEWS and D-dimer levels to predict the 30-day and 365-day mortality rates of a cohort of Danish patients with complete follow-up.
Methods: Post-hoc retrospective observational study of acutely admitted medical patients aged 18 years or older who had D-dimer measured within 6 h after arrival to two medical admission units in Denmark.
Results: The final study population consisted of 1201 patients with a median age of 65.0 years (range 18.0–107.0 years), and 44.7% were of male sex. Four patients (0.3%) died within 24 h of admission, 69 (5.7%) within 30 days and 198 (16.5%) within 365 days. On admission, 576 (48%) patients had a NEWS ≥ 3 – of these 441 had a D-dimer ≥ 0.50 mg L^{-1}: 55 (12.5%) of these patients died within 30 days, compared with 5 (3.7%) of the 135 patients with a D-dimer < 0.50 mg L^{-1} (odds ratio 3.7, 95%CI 1.4–10.8). Nine of the 625 patients with a NEWS on admission <3 died within 30 days and all of these patients had a D-dimer ≥ 0.50 mg L^{-1}. None of the 218 patients with a D-dimer < 0.50 mg L^{-1} died within 30 days of admission.
Conclusion: The combination of NEWS score < 3 and D-dimer levels below 0.50 mg L^{-1} appears to identify patients of low risk of mortality within 30 days and, therefore, may prove to be a powerful risk assessment tool for acutely ill medical patients.

Introduction

Large increases in emergency admissions are raising concerns about whether all admissions are necessary. Obvious justifications for hospital admission are severe pain, breathlessness, bleeding, impaired mental and/or functional capacity, and grossly abnormal vital signs. However, hospital admissions are also related to numerous additional factors such as local social issues (e.g. unemployment rates), and the way emergency departments, hospitals, emergency ambulance services and general practice are structured.[1] Moreover, patients with nonspecific complaints such as generalized weakness present frequently to acute care settings and are at risk of adverse health outcomes.[2]

When the need for hospital admission is being assessed the paramount concern is determining the imminent risk of death. If there was a fast reliable system that determined that risk many patients could be safely returned to primary care or out-patient follow-up clinics. The UK's National Early Warning Score (NEWS)[3] was primarily designed to predict death within 24 h: after this time its discrimination falls, so that a low score cannot be used to justify discharging a patient from hospital. Elevated D-Dimer levels are associated with increased mortality rates in healthy adults, independent of other risk factors.[4] In addition to their use in ruling out thromboembolic disease, D-dimers have been used to predict the morbidity and mortality of medical or surgical intensive care unit (ICU) patients,[5,6] and for risk stratification of patients with nonspecific complaints.[7]

In this study we report the combined use of NEWS and D-dimer levels to predict the 30-day and 365-day mortality rates of a cohort

☆ A Spanish translated version of the summary of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2016.06.012.

* Corresponding author at: Emergency Department, University Hospital Basel, Petersgraben 2, CH-4031 Basel, Switzerland.
E-mail addresses: christian.nickel@usb.ch, replynickel@gmail.com (C.H. Nickel).

http://dx.doi.org/10.1016/j.resuscitation.2016.06.012
0300-9572/

of 1201 Danish patients for which the Danish nationwide registries provided 100% follow-up.

Methods

This is a post-hoc retrospective observational study of acutely admitted medical patients to two medical admission units in Denmark who had D-dimer levels measured at admission. These cohorts were originally used to develop a risk stratification tool for all-cause 7-day mortality,[8] and assess sepsis patients.[9]

Settings

The Hospital of South West Jutland (HSWJ) is a 450-bed regional teaching hospital. Odense University Hospital (OUH) is a 900-bed tertiary university hospital serving as a tertiary referral center for the region of Southern Denmark (1.2 million inhabitants). At both locations, medical patients are admitted through a medical admission unit (MAU) from the emergency department, outpatient clinics, general practitioners (GP), the out-of-hours GP service and emergency medical services.

Demographic information and vital signs were collected on admission and entered into a research database and blood tests were extracted from the hospital databases. After discharged survival status were extracted from the Danish Civil Registration System,[10] ensuring complete follow-up. All previous contacts with the Danish health care system were extracted from the National Patient Register[11] and used to calculate the Charlson co-morbidity index.[12]

Patients

The study included all Danish residents 18 years or older who had D-dimer measured within 6 h after arrival and were then admitted to the HSWJ MAU from 2 October 2008 to 19 February 2009 and 23 February to 26 May 2010 and to OUH MAU from 1 September 2010 to 31 August 2011. A total of 526 patients were recruited from HSW and 675 from OUH. Patients from OUH had a 30 day mortality more than twice those from HSW (7.7% versus 3.2%, Odds ratio 2.5 (95% CI 1.4–4.6)).

D-Dimer measurement

D-dimer levels for all patients were measured on the day of enrollment by using a highly sensitive quantitative D-dimer test (cutoff level, 0.50 mg L^{-1}). In both study centers, a Latex agglutination test (STA Liatest D-Dimer (Diagnostica Stago, Asnieres-sur-Seine, France) with a detection rate ranging from 0.27 μg mL^{-1} up to 20 μg mL^{-1} was used. Citrate plasma for D-Dimer estimation was obtained by centrifuging at 3500 rpm for 10 min.

Ethics

According to Danish law, approval of observational cohort studies by an ethics committee is not required. The study was approved by the Danish Data Protection Agency and the Danish National Board of Health. The study will be reported in accordance with the STROBE guidelines.[13]

Statistics

Calculations were performed using Epi-Info version 6.0 and 7.0 (Center for Disease Control and Prevention, USA), logistic regression analysis using Logistic software,[14] and Kaplan–Meier survival curves by Online Application for the Survival Analysis software (OASIS) available at http://sbi.postech.ac.kr/oasis/surv/.[15] The p value for statistical significance was 0.05 and was tested using Student's t-test and Chi square analysis that applied Yates continuity correction. Kaplan–Meier survival curves were compared by the log-rank test. c statistics were calculated according to the method of Hanley and McNeil.[16]

Results

The final study population of 1201 patients was aged 62.7 SD 18.8 years (median 65.0 years, range 18.0–107.0 years), had a length of hospital stay of 4.0 SD 5.6 days and 44.7% were of male sex.

Four patients (0.3%) died within 24 h of admission, 69 (5.7%) within 30 days and 198 (16.5%) within 365 days. Apart from gender and temperature there were significant differences between survivors and non-survivors 30 days after admission (Table 1).

On admission 576 (48%) patients had a NEWS ≥ 3 – of these 441 had a D-dimer ≥ 0.50 mg L^{-1} and 55 (12.5%) died within 30 days, compared with 5 (3.7%) of the 135 patients with a D-dimer < 0.50 mg L^{-1} (odds ratio 3.7, 95%CI 1.4–10.8). In contrast, 9 of the 625 patients with a NEWS on admission <3 died within 30 days and all of these patients had a D-dimer ≥ 0.50 mg L^{-1} – none of the 218 patients with a low D-dimer died (risk difference 2.2%, 95%CI 0.8–3.6%, Chi-square 3.46, Fisher exact p 0.03) (Fig. 1).

Table 1
Differences between continuous and categorical variables of 30 day survivors and non-survivors: n = patient number; NEWS = National Early Warning Score.

	Alive 30 days after admission (n 1132)	Died within 30 days of admission (n 69)	Odds ratio (95% CI)	Chi-square	p
Heart rate (bpm)	89.9 SD 21.2	95.7 SD 25.7			0.03
Systolic BP (mmHg)	141.2 SD 25.7	126.5 SD 28.6			<0.0001
Diastolic BP (mmHg)	80.7 SD 15.4	74.3 SD 19.6			0.0009
Respiratory rate (bpm)	19.7 SD 6.7	25.5 SD 8.2			<0.0001
Temperature (°C)	37.2 SD 1.0	37.2 SD 1.0			0.97
FiO2	0.25 SD 0.10	0.38 SD 0.19			<0.0001
Oxygen saturation (%)	95.4 SD 4.5%	91.8 SD 7.6%			<0.0001
Age (years)	61.7 SD 18.7	78.6 SD 12.2			<0.0001
D-dimer (mg L^{-1})	2.00 SD 3.25	4.64 SD 6.93			<0.0001
Length of hospital stay (days)	3.8 SD 5.6	6.1 SD 5.9			0.001
NEWS	3.1 SD 3.1	6.8 SD 3.6			<0.0001
Charlson Index	1.15 SD 1.17	1.75 SD 1.14			<0.0001
Male sex	506	31	1.01 (0.60–1.70)	0.01	0.93
On oxygen	269	42	4.99 (2.92–8.54)	44.75	<0.0001
Altered alertness	23	12	10.15 (4.47–22.82)	48.94	<0.0001
D-dimer ≥ 0.50 mg L^{-1}	784	64	5.68 (2.16–16.31)	16.19	<0.0001
NEWS ≥ 3	516	60	7.96 (3.75–17.48)	42.96	<0.0001
Age > 65	563	60	6.74 (3.17–14.80)	34.62	<0.0001
Charlson Index ≥ 1	668	56	2.99 (1.56–5.85)	12.42	0.0004

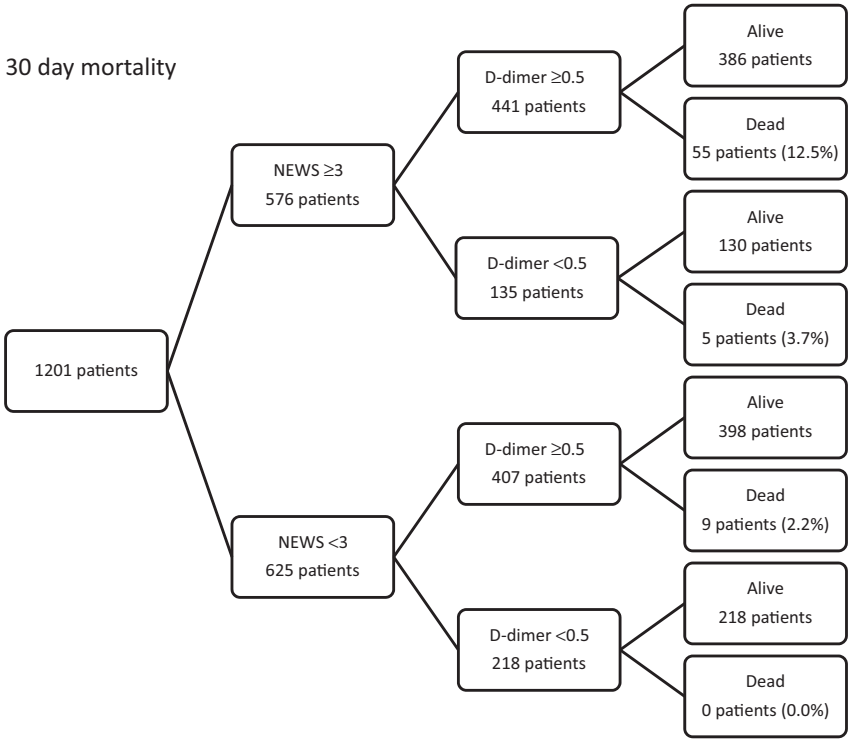


Fig. 1. Flow chart of 1201 patients after 30 days according to D-dimer level (<0.5, ≥0.5 μg mL^{-1}) and NEWS score

All of the four patients who died within 24 h of admission had an admission NEWS ≥ 3 and a D-dimer ≥ 0.50 mg L^{-1}.

Logistic regression showed that age above the median of 65 years, any alteration in alertness, a NEWS ≥ 3 and D-dimer ≥ 0.50 mg L^{-1} were all independent predictors of 30-day mortality (see Supplemental data). A simple predictive model that awarded one point to each variable had a *c* statistic of 0.82 SE 0.03 and Hosmer–Lemeshow goodness of fit statistic *p* 0.59.

Kaplan–Meier curves showed that for patients with both high and low NEWS on admission elevated D-dimer greatly reduced their chance of survival at 365 days after admission: for patients with an admission NEWS <3 the survival of patients with a low D-dimer was significantly better than those with an elevated D-dimer (Chi-square 13.2, *p* 0.0003), as it was for patients with an admission NEWS ≥ 3 (Chi-square 22.7, $p < 0.0001$) (Fig. 2). By 365 days after admission 141 (32%) of the 441 patients with an high admission NEWS and an elevated D-dimer had died compared with 14 (10%) of the 135 patients with a high NEWS and a low D-dimer (odds ratio 4.1, 95%CI 2.2–7.7): 39 (9.6%) of the 407 patients with a low NEWS and a high D-dimer had died compared with 4 (1.8%) of the 218 patients with a low NEWS and a low D-dimer (odds ratio 5.7, 95% CI 1.91–19.0).

The nine patients with a NEWS ≥ 3 and an elevated D-dimer who died within 30 days of admission had a diagnosis at discharge of vascular disease (2 patients), renal disease (2 patients), hepatorenal syndrome, thromboembolic disease, pneumonia, chronic obstructive lung disease and cancer. Nearly 60% of 198 patients who died within 365 days had one of the following principle diagnoses when discharged: pneumonia (37 patients), chronic obstructive lung disease (19 patients), thromboembolic disease (14 patients), respiratory failure (12 patients), cardiac disease (12 patients), cancer (11 patients) and infections (8 patients). Only 18 patients with a low D-dimer died within 365 days of admission: the discharge diagnoses of the four patients admitted with a low NEWS who died were cancer, osteopenia, and two undiagnosed.

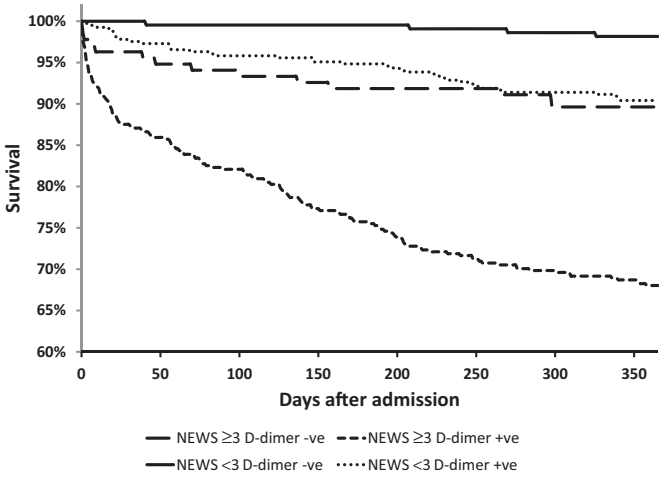


Fig. 2. Kaplan–Meier survival curves for 365-day survival of 1201 acute medical patients grouped by cutoffs of D-Dimer (<0.5, ≥0.5 μg mL^{-1}) and NEWS score.

Discussion

This retrospective study suggests that the combination of NEWS and D-dimer scores is, potentially, a powerful tool in the risk assessment of acutely ill patients. Its main strength is the 100% certain follow-up provided by the Danish Civil Registration System. The cut-off for NEWS was chosen to ensure that no patient with altered alertness was included. Nearly a fifth (18%) of patients had a low NEWS and low D-Dimer levels. Although none of these patients died within 30 days of admission, statistically this could have been as high as 0.8%. Nevertheless, only five of these patients died within a year.

We do not know the mechanism by which low D-dimer levels predict survival, and further studies are required to establish the optimal D-dimer "cut-off" value for mortality prediction. Although the value of D-dimer for the diagnosis of thrombo-embolic disease

varies with age, we found no variation in the number of young and old patients who died within a year at D-dimer levels below 0.50 mg L^{-1} (see Supplemental figure).

We found D-dimer levels to be a highly sensitive but poorly specific predictor of death, and when combined with a low NEWS made an excellent "rule out" test for imminent mortality. In our patient population no patients with a D-dimer < 0.50 mg L^{-1} and a NEWS < 3 died within 30 days, and the negative predictive value for death at 365 days after admission was 0.98. However, our results should be viewed with caution. It is entirely possible that many deaths were prevented by treatment given after hospital admission. Moreover, this was a non-funded post-hoc retrospective biased study that combined different cohorts of patients from two different hospitals, which had significantly different mortality rates. The original cohorts were used to develop a risk stratification tool for all-cause 7-day mortality and assess sepsis patients, and we only studied those patients on whom D-dimer had been measured. The patients, therefore, might not be representative of other cohorts of unselected acutely ill patients either presenting to emergency departments and/or admitted to hospital.

Conclusions

The combination of NEWS and D-dimer levels may prove to be of value in helping to stratify low risk patients that can be managed in an ambulatory or outpatient setting.

Conflict of interest statement

This is to certify that this study was performed entirely by the authors and received no financial support from anyone. John Kellett is a major shareholder, director and chief medical officer of Tapa Healthcare DAC.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2016.06.012.

References

1. O'Cathain A, Knowles E, Maheswaran R, et al. A system-wide approach to explaining variation in potentially avoidable emergency admissions: national ecological study. BMJ Qual Saf 2014;23:47–55, http://dx.doi.org/10.1136/bmjqs-2013-002003.
2. Nemec M, Koller MT, Nickel CH, et al. Patients presenting to the emergency department with non-specific complaints: the Basel Non-specific Complaints (BANC) study. Acad Emerg Med 2010;17:284–92, http://dx.doi.org/10.1111/j.1553-2712.2009.00658.x.
3. Physicians RCo. National EarlyWarning Score (NEWS): standardising the assessment of acute illness severity in the NHS. In: Report of a working party. RCP; 2012.
4. Di Castelnuovo A, de Curtis A, Costanzo S, et al. Association of D-dimer levels with all-cause mortality in a healthy adult population: findings from the MOLI-SANI study. Haematologica 2013;98:1476–80, http://dx.doi.org/10.3324/haematol.2012.083410.
5. Shitrit D, Izbicki G, Shitrit AB, et al. Prognostic value of a new quantitative D-dimer test in critically ill patients 24 and 48 h following admission to the intensive care unit. Blood Coagul Fibrinolysis 2004;15:15–9.
6. Shorr AF, Trotta RF, Alkins SA, Hanzel GS, Diehl LF. D-dimer assay predicts mortality in critically ill patients without disseminated intravascular coagulation or venous thromboembolic disease. Intensive Care Med 1999;25:207–10.
7. Nickel CH, Kuster T, Keil C, Messmer AS, Geigy N, Bingisser R. Risk stratification using D-dimers in patients presenting to the emergency department with nonspecific complaints. Eur J Internal Med 2016, http://dx.doi.org/10.1016/j.ejim.2016.03.006.
8. Brabrand M, Lassen AT, Knudsen T, Hallas J. Seven-day mortality can be predicted in medical patients by blood pressure, age, respiratory rate, loss of independence, and peripheral oxygen saturation (the PARIS score): a prospective cohort study with external validation. PLoS ONE 2015;10:e0122480, http://dx.doi.org/10.1371/journal.pone.0122480.
9. Henriksen DP, Laursen CB, Jensen TG, Hallas J, Pedersen C, Lassen AT. Incidence rate of community-acquired sepsis among hospitalized acute medical patients-a population-based survey. Crit Care Med 2015;43:13–21, http://dx.doi.org/10.1097/ccm.0000000000000611.
10. Pedersen CB. The Danish civil registration system. Scand J Public Health 2011;39(Suppl.):22–5, http://dx.doi.org/10.1177/1403494810387965.
11. Lynge E, Sandegaard JL, Rebolj M. The Danish national patient register. Scand J Public Health 2011;39(Suppl.):30–3, http://dx.doi.org/10.1177/1403494811401482.
12. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
13. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Epidemiology 2007;18:805–35, http://dx.doi.org/10.1097/EDE.0b013e3181577511.
14. GED. LOGISTIC: a logistic regression program for the IBM PC. Am Stat 1988;42.
15. Yang JS, Nam HJ, Seo M, et al. OASIS: online application for the survival analysis of lifespan assays performed in aging research. PLoS ONE 2011;6:e23525, http://dx.doi.org/10.1371/journal.pone.0023525.
16. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology 1983;148:839–43, http://dx.doi.org/10.1148/radiology.148.3.6878708.

European Journal of Internal Medicine 31 (2016) 20–24

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Risk stratification using D-dimers in patients presenting to the emergency department with nonspecific complaints

C.H. Nickel [a,*], T. Kuster [a], C. Keil [a], A.S. Messmer [a], N. Geigy [b], R. Bingisser [a]

[a] Emergency Department, University Hospital, Basel, Switzerland
[b] Emergency Department, Kantonsspital Baselland, Liestal, Switzerland

ARTICLE INFO

Article history:
Received 27 May 2015
Received in revised form 4 March 2016
Accepted 7 March 2016
Available online 1 April 2016

Keywords:
Nonspecific complaints
D-dimer
Geriatric
TRIAGE
Mortality

ABSTRACT

Background: Patients with nonspecific complaints (NSC) such as generalized weakness present frequently to acute care settings. These patients are at risk of adverse health outcomes. The aim of our study was to test the hypothesis whether D-dimers are predictive for 30-day mortality in patients with NSCs.
Methods: Delayed type cross-sectional diagnostic study with a 30-day follow-up period, registered with ClinicalTrials.gov (NCT00920491). This study took place in 2 EDs in Northwestern Switzerland. Patients were enrolled in the study if they were over 18 years of age, gave informed consent, and if they presented with NSCs such as generalized weakness. D-dimer levels were determined at ED presentation.
Results: The final study population consisted of 524 patients. Median age was 82 years (IQR = 75 to 87 years); 40.5% were men. There were 489 survivors and 35 non-survivors at 30-day follow-up. Twenty-one (60%) of the non-survivors were males. D-dimer levels were significantly higher in non-survivors than in survivors ($p < 0.001$). Univariate Cox regression models for D-dimer resulted in a C-index of 0.77 for prediction of mortality. A model including sex, age, Katz ADL and D-dimer in a multivariate Cox regression lead to a C-Index of 0.80.
Conclusion: D-dimer testing might be an effective risk stratification tool in patients with NSC by helping to identify patients at low risk of short-term mortality with a sensitivity of 0.97 and a negative likelihood ratio of 0.121. The use of D-dimers for risk stratification in patients with NSC should be confirmed with prospective studies.

1. Introduction

Acute care settings are increasingly faced with older patients with non-specific complaints (NSCs), such as "generalized weakness" [1]. Across different acute care settings worldwide, NSCs are among the top five presenting complaints [2–4]. According to previous reports, most patients with NSCs are older and have an underlying acute medical problem or are at risk of developing adverse health outcomes [5,4]. The spectrum of underlying diagnoses and outcomes is very similar across studies and covers almost all ICD-10 categories [2,3,6–9]. In contrast to specific complaints, diagnostic accuracy is low in the first hours of work-up [10]. Therefore, risk-stratification tools are urgently needed.

D-dimer, a small protein resulting from the plasmin-mediated degradation of cross-linked fibrin clots, is an indicator for coagulation and fibrinolysis, and thus can support the detection of thrombotic activity [11]. D-dimer is widely used to rule out venous thromboembolism (VTE) and pulmonary embolism (PE) [12–14]. D-dimer levels not only elevate in illnesses directly related to the coagulation process, but might also potentially predict adverse outcomes in a variety of clinical settings, e.g., cancer, cardiac disease, acute ischemic stroke or hemorrhage, community acquired pneumonia, and sepsis [15–26]. Previous studies have shown that D-dimer levels may be used for the prediction of morbidity and mortality, both in medical or surgical intensive care unit (ICU) patients [27,28]. Moreover, D-dimer levels had predictive power similar to clinical scoring systems, such as the Simplified Acute Physiology Score (SAPS), the Acute Physiology and Chronic Health Evaluation (APACHE) II score and the Sequential Organ Failure Assessment (SOFA) score [26–28]. Surprisingly, elevated D-Dimer levels were found to be associated with mortality in healthy adults, independent of any other existing risk factors [29].

As D-dimer levels increase with age, cut-off values varied significantly between the cited studies; and several studies proposed the adoption of age-dependent reference intervals in clinical practice in the setting of pulmonary embolism [12,13,30–33].

It was our hypothesis that D-dimer levels in patients presenting to the Emergency Department (ED) with NSCs are predictive for 30-day

* Corresponding author at: Department of Emergency Medicine, University Hospital Basel, Petersgraben 2, CH-4031 Basel, Switzerland. Tel.: +41 61 556 5315; fax: +41 61 265 58 31.
E-mail address: christian.nickel@usb.ch (C.H. Nickel).

http://dx.doi.org/10.1016/j.ejim.2016.03.006
0953-6205/

mortality. Furthermore, we aimed to test whether age-adjusted cut-off values improve prognostic performance.

2. Methods

2.1. Study design

This study is based on data acquired in the third Basel Nonspecific Complaints study, which is a prospective observational study with a consecutive sample with a 30-day follow-up period (delayed type cross-sectional diagnostic study) [34]. The study protocol conforms to the Helsinki Declaration, and was approved by the local ethics board. Written informed consent was obtained from each participating patient. The study is registered with ClinicalTrials.gov (NCT00920491).

2.2. Study setting and population

This BANC (part III of a IV-part study) took place in three EDs in Northwestern Switzerland. For this analysis, patients were included from May 27, 2009, and July 26th 2011 from two (out of three) EDs with admission rates ranging from 12,000 to 45,000 patients per year. This study took place in the ED of the University Hospital of Basel, Switzerland (a tertiary care university hospital) and the Kantonsspital Liestal (a regional hospital), both of which were able to provide consecutive enrolment. All consecutive non-trauma patients presenting with Emergency Severity Index (ESI) scores of 2 or 3 were prospectively screened for eligibility. The ESI is a reliable and valid triage tool that was used to exclude all patients in immediate life-threatening condition (ESI level 1). Patients with an ESI score of 4 or 5 were excluded as well, because a full work-up was not necessary and there is very low risk of death in this patient group [35].

2.3. Inclusion criteria

Patients were prospectively enrolled in the study if they were over 18 years of age, gave informed consent, and if they presented with NSCs such as “generalized weakness”. NSCs were defined as all complaints that are not part of the set of specific complaints (e.g chest pain, dyspnea, and headache) or signs (hemodynamic instability) or where an initial working diagnosis cannot be established. This definition was chosen because an active definition would require a countless enumeration of possible NSCs [4].

2.4. Exclusion criteria

Excluded from the study were patients with specific complaints such as chest pain, clinical instability, or any clinical presentation that led directly to a working hypothesis (e.g., anemic pallor), as well as referrals from other hospitals. Patients presenting with hemodynamic instability, specific electrocardiogram (ECG) changes (e.g., 3rd degree heart block) or recent external laboratory results were not eligible. Furthermore, palliative patients such as patients with known terminal cancer or patients who were deemed likely to die within the follow-up period of 30 days were not eligible [4].

2.5. Study protocol

Patients' complaints, demographic data, use of medications, and physical examination information were documented in a standardized data collection form [36]. Activities of daily living as assessed by the Katz ADL index [36], previously shown to be predictive of 30-day-mortality in patients with NSC, were obtained by bedside patient interviews [37,38]. Furthermore, the Charlson Comorbidity Index [39], a prospectively applicable method for classifying comorbid conditions, which was recently shown to be an independent predictor of short- and long-term mortality in acutely ill hospitalized elderly adults, was recorded [40].

A blood sample including D-dimers was taken from each individual and a wide array of blood testing was performed. D-dimer levels were determined at ED presentation. Diagnostic tests or imaging studies were performed at the discretion of the treating emergency physician (EP). Questionnaires from the patient's primary care physicians and hospital discharge reports were used to obtain written follow-up data after 30 days.

All included patients were reviewed by 2 independent outcome assessors according to inclusion and exclusion criteria before the outcome ascertainment. Outcome ascertainment occurred after termination of the 30-day follow-up period. Furthermore, the most likely cause of death was determined independently by the outcome assessors.

2.6. D-dimer level assessment

D-dimer levels were measured using a viscosity-based detection method on the STA-R system (Diagnostica Stago S.A.S., Asnières sur Seine Cedex, France) with a detection rate ranging from 0.27 μg/ml up to 20 μg/ml. Citrate plasma for D-dimer estimation was obtained by centrifuging at 3500 rpm for 10 min. A cutoff, set at 0.5 μg/mL (500 ng/ml), was used. In addition to the conventional cutoff, an age adjusted cutoff was used by multiplying the patient's age by 10 ng/ml [33]. The laboratory personnel performing the assay were not made aware of the purpose of the study.

2.7. Statistical analysis

Descriptive statistics are expressed as counts and percentages or as medians with interquartile ranges (IQR). Differences were tested using the Kruskall–Wallis test, the chi-squared or the exact Fisher test, where appropriate. D-dimer values were log10-transformed to achieve approximate normality.

To predict 30-day mortality using various predictors over the time course, uni- and multivariable Cox-Regressions were performed. Sex, age, Charlson Comorbidity Index, and the Katz ADL were considered in addition to D-dimer. For all models, the proportional hazard assumption was tested and all tests were non-significant. The predictive value of each model was assessed by the model likelihood ratio (LR) chi-square statistic. The effect measure of all regression models were evaluated using bootstrap-corrected C-indices. For illustrative purposes, Kaplan–Meier survival curves are presented. Furthermore, sensitivity, specificity, positive likelihood ratio and negative likelihood ratio for both cutoffs (0.5 μg/mL, age-adjusted) were calculated. A p-value <0.05 is considered significant. All analyses were performed using R version 3.0.1 (http://www.r-project.org).

D-dimer values below the detection limit (0.27 μg/mL) were replaced by half the lower detection limit ($n = 59$); values above the detection limit by 20 μg/mL ($n = 3$); and values larger 4 μg/mL ($n = 2$) by a D-Dimer value of 20 μg/mL, as both patients belong to the group of 30-day survivors (conservative way).

3. Results

The study population consisted of 612 patients with NSCs. Nineteen patients were excluded from the study by the outcome assessors due to protocol violations (specific complaints ($n = 8$), vital signs out of predefined limits ($n = 8$), trauma patients ($n = 2$), unknown ($n = 1$), missing data ($n = 1$), as well as 69 others with missing D-dimer levels. This resulted in a final study population of 524 patients in whom D-dimer levels could be determined. Baseline characteristics are presented in Table 1. Median age was 82 years (IQR = 75 to 87 years); 40.5% were men. Survival, age, sex, and ADL did not differ between the patients who had D-dimers assessed and the patients without D-dimer testing. Referral to the ED occurred mostly by ambulance (260, 53.2%), but also

by family physicians (134, 27.4%); self-referral (59, 12.1%); and proxies (36, 7.36%).

There were 489 survivors and 35 non-survivors at 30-day follow-up. Twenty-one (60%) of the non-survivors were males. Furthermore, the Katz ADL was lower (4 vs. 6) in non-survivors compared to survivors. Similarly, the Charlson Comorbidity Index was higher in non-survivors.

Comorbidities in our patients were chronic hypertension in 298 (57%) patients, coronary artery and/or valvular heart disease in 195 (37.2%) patients, diabetes in 96 (18.3%) patients, cancer in 74 (14.1%), lymphoma in 8 patients (1.5%), leukemia in 4 (0.8%) patients. Causes of death are shown in Table 4.

3.1. Outcome prediction

Of 35 non-survivors, 34 patients had a D-dimer level higher than 0.5 μg/mL. Thromboembolic events occurred in 6 patients: Five patients of all included patients suffered from pulmonary embolism (two of whom died), and one patient was diagnosed with deep venous thrombosis. Autopsies were available for 4 patients. One patient without elevated D-dimer died of sudden cardiac arrest within the follow up period (after 21 days). D-dimer levels were significantly higher in non-survivors than in survivors ($p < 0.001$; Table 1). A D-dimer below the regular cutoff (<0.5 μg/mL) was measured in 116 (22.1%) patients.

Table 2 shows univariate and multivariate Cox regression analyses and C-index of D-dimer. Univariate Cox regression models for D-dimer resulted in a C-index of 0.77. A model including sex, age, Katz ADL and D-Dimer in a multivariate Cox regression lead to a C-Index of 0.80. For (age-adjusted) performance criteria see Table 3.

Kaplan–Meier survival curves were calculated then stratified into two groups according to the D-dimer level, with a cut-off of 0.5 μg/mL (See Fig. 1.).

4. Discussion

In this prospective multicenter study, we found that patients presenting with NSCs with negative D-dimer levels are at low risk for 30-day mortality. Application of age-adjusted D-Dimer levels led to decreased sensitivity without substantially improving specificity, suggesting that D-dimer might serve as a "rule-out test" for mortality in our study population.

D-dimer is a useful biomarker in the detection of thrombotic and thrombolytic activity [11]. Due to its high sensitivity, it can be safely used to rule out VTE in patients with low and intermediate pretest probability [14,41]. A meta-analysis performed by Becattini et al. found an association between elevated D-dimer levels and short-term and three-month mortality in patients with acute PE, suggesting a potential use of D-dimer testing in the risk stratification of these patients [17]. Interestingly, two of our six patients with thrombo-embolic disease did not survive for 30 days.

In order to use D-dimer as a risk-stratification tool in clinical practice, an optimized cut-off must be determined. Several recent studies have described an age-dependent increase in D-Dimer levels, therefore implying the application of an age-adjusted cut-off, as described by Douma et al. (patient's age * 10 μg/L) [30,33]. The age-adjusted cut-off was highly effective for the exclusion of PE, and for increasing specificity without reducing sensitivity [12,13,31]. In our study, an age-adjusted D-dimer cut-off slightly improved specificity, but lowered negative likelihood — suggesting that age adjusted cutoffs are less useful in prediction of low mortality in patients with NSC.

Apart from PE, VTE and increasing age, D-dimer levels are also elevated by various causes, including infections, trauma, aortic dissection, cancer, and renal failure [15,16,42,43]. Furthermore, D-dimers were shown to be a predictor in patients with CAP and sepsis [22,24–26]. However, the added prognostic value of D-dimer testing as compared to a clinical score in CAP patients was limited [44].

The predictive power of D-dimer depicted in several additional yet unrelated clinical scenarios supports the main finding of our study, as non-survivors had significantly higher D-dimer levels compared to survivors in all studies cited [18–22,28,45].

Patients with NSCs such as "generalized weakness" account for up to 20% of all ED presentations in older ED patients [1]. These patients are at risk of undertriage, due to their ambiguous symptoms [5]. In addition, a previous study found that 59% of all patients with NSCs were diagnosed with acute morbidity, short-term mortality was 6% [4]. Although the diagnostic accuracy in patients with NSCs is low, prediction of adverse outcomes using clinician "gestalt" is possible to some degree [10,46]. However, for the purpose of safely identifying patients at risk of adverse outcome, additional risk stratification tools are needed. As opposed to other novel stress biomarkers [47], D-dimers are readily available and can be determined reliably, even with point of care devices, which make immediate decisions possible.

The results of this study may be meaningful to practicing physicians in several ways: They might be helpful in assisting the triage process of

Table 1
Baseline characteristics and D-dimer concentration for the whole study population, separated by survivors and non-survivors, values are n (%) unless otherwise indicated.

Variable	All patients N = 524	30-day survivors N = 489	Non-survivors N = 35	p-value	N
Age, median (IQR)	82 [75–87]	82 [74–87]	83 [79–88]	0.254	524
Sex, male	212 (40.5%)	191 (39.1%)	21 (60.0%)	0.024	524
Mode of admission:				0.576	489
Self-referral	59 (12.1%)	57 (12.5%)	2 (6.06%)		
By family doctor	134 (27.4%)	122 (26.8%)	12 (36.4%)		
By proxy	36 (7.36%)	34 (7.46%)	2 (6.06%)		
Ambulance	260 (53.2%)	243 (53.3%)	17 (51.5%)		
ESI category:				0.640	415
2	22 (5.30%)	20 (5.14%)	2 (7.69%)		
3	393 (94.7%)	369 (94.9%)	24 (92.3%)		
Katz ADL	6 [5-6]	6 [5-6]	4 [1-6]	<0.001	467
CCI	1.00 [0.00;3.00]	1.00 [0.00;3.00]	2.00 [1.00;4.50]	0.006	524
CCI (age-adjusted)	5.00 [4.00;7.00]	5.00 [4.00;7.00]	6.00 [5.00;8.00]	0.005	524
D-dimer (μg/ml)	1.17 (0.58;2.40)	1.08 (0.54;2.19)	3.41 (1.75;6.41)	<0.001	524

ESI = Emergency Severity Index; IQR = interquartile range. Mode of admission adds to 489 (missing data); ESI category adds up to 415 patients (109 patients were direct to bed, no triage level assigned). CCI = Charlson Comorbidity Index.

Table 2
Model statistics and univariate and multivariate cox models for prediction of death within 30 days after presentation.

Model	n	Events	Model Chi-square	DF	p-value	C-index
Age	524	35	2.94	1	0.09	0.55
Sex	524	35	5.70	1	0.02	0.59
ADL Katz Index	467	31	18.61	1	<0.001	0.68
CCI	524	35	9.91	1	0.0016	0.63
Log D-dimers	524	35	33.16	1	<0.001	0.78
Age + sex	524	35	10.79	2	0.0045	0.63
Age + sex + CCI	524	35	16.78	3	<0.001	0.67
Log D-dimers + Katz ADL	467	31	43.75	2	<0.001	0.80
Age + Sex + Katz ADL	467	31	25.27	3	<0.001	0.71
Log D-dimers + sex + age	524	35	40.50	3	<0.001	0.77
Log D-dimers + Katz ADL + Sex	467	31	47.48	3	<0.001	0.79
Log D-dimers + Katz ADL + Sex + CCI	467	31	49.28	4	<0.001	0.81

Katz ADL = activities of daily living, DF = degree of freedom, CCI = Charlson Comorbidity Index. The model chi-square, degree of freedom and the p-value correspond to the model likelihood ratio (LR) chi-square statistic.

Table 3
Sensitivity, specificity, and likelihood ratios for different D-dimer cut-offs.

D-dimers	0.5 μg/mL	Age-adjusted
Sensitivity	0.971	0.914
Specificity	0.235	0.395
Positive likelihood ratio	1.270	1.510
Negative likelihood ratio	0.121	0.217

patients with NSCs by identifying patients at low risk of short term mortality, when negative. This might be helpful for disposition decisions to lower levels of care, such as geriatric community hospitals, in case of low risk.

On the other hand, routinely obtaining D-dimers in a large population of patients with NSC could result in exposure to radiation and elevated costs due to subsequent imaging studies, as potentially unnecessary testing for thromboembolism may be triggered.

5. Limitations

Our cohort predominantly consisted of white, older patients of European ancestry with specific triage levels (ESI 2 and 3) admitted to two EDs in northwestern Switzerland. This limits the generalizability of our results. Further, only in a minority of patients cause of death was determined by autopsy, raising the possibility that pulmonary embolism could have been missed.

D-dimer levels could not be estimated in all participating patients, therefore a potential selection bias cannot be ruled out completely. However, the comparable outcomes between patients tested and not tested do not suggest bias, and the large patient sample size recruited consecutively from 2 centers also diminishes this possibility.

Table 4
Causes of death, D-dimer-levels (cutoff 0.5 μg/mL), ID — identification number, BANC III study = Basel non-specific complaints study, part III.

Patient ID	Cause of death	D-dimer-level [μg/mL]	Autopsy
38	Bronchial cancer	7.99	No
40	Glioblastoma multiforme	0.60	No
65	Sudden cardiac death, known coronary artery disease	0.30	No
73	Liver failure	1.96	No
91	Aortic valve stenosis	1.31	No
94	Heart failure	3.41	No
123	Bronchial cancer	0.99	No
155	Heart failure	5.75	No
157	Pneumonia	6.17	Yes
158	COPD	2.13	No
167	Pancreatic cancer	3.28	No
186	Sepsis due to diverticulitis	4.15	No
200	Heart failure	18.28	No
236	Heart failure	1.98	No
238	Heart failure	1.47	No
243	Pulmonary embolism	10.01	No
254	Pneumonia	9.92	No
260	Multi organ failure	1.27	Yes
261	Heart failure	2.80	No
271	Brain tumor of left hemisphere	0.95	No
383	Heart failure	1.53	No
385	Gastrointestinal bleeding	20	No
396	Heart failure	2.54	No
402	Pneumonia	4.68	Yes
403	Pneumonia	4.68	No
460	Heart failure	3.7	Yes
490	Pulmonary embolism	3.41	No
498	Pneumonia	3.32	Yes
507	Acute renal failure	7.33	No
534	Urosepsis	6.65	No
550	Pneumonia	0.68	No
563	Pneumonia	3.59	No
569	Pneumonia	10.26	No
587	Pneumonia	4.06	No
602	Anemia, intraabdominal bleeding	20.00	No

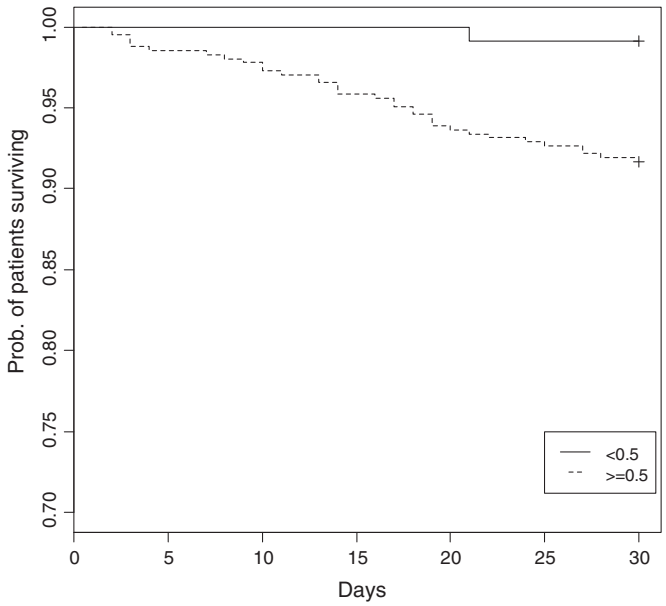


Fig. 1. Kaplan–Meier survival curves for 30-day survival in patients presenting to the ED with NSCs grouped by cutoffs of D-Dimer (<0.5, ≥0.5 μg/mL).

6. Conclusion

D-dimer testing might be an effective risk stratification tool in patients with NSC by helping to identify patients at low risk of short-term mortality. The application of age adjusted cut-off values for D-dimer tests in our patient sample slightly increased specificity at the cost of sensitivity. Further studies are needed in order to prove that physicians informed of the lower risk in these presentations behave differently and are able to take quicker decisions in these notoriously difficult presentations.

Conflict of interest

- Christian H Nickel: Speaker honoraria for thermofisher.
- Tobias Kuster: No disclosures.
- Christoph Keil: No disclosures.
- Anna S Messmer: No disclosures.
- Nicolas Geigy: No disclosures.
- Roland Bingisser: Honoraria by Astra, Sanofi, Philips, Bayer, Board memberships: Philips.

Acknowledgments

Thank you to Zack Anderson and Michael Koller MD for helpful discussions, Christian Müller (Eudox) for statistical analysis. This work was supported by scientific funds of the University Hospital Basel.

References

[1] Vanpee D, Swine C, Vandenbossche P, Gillet JB. Epidemiological profile of geriatric patients admitted to the emergency department of a university hospital localized in a rural area. Eur J Emerg Med 2001;8:301–4.
[2] Bhalla MC, Wilber ST, Stiffler KA, Ondrejka JE, Gerson LW. Weakness and fatigue in older ED patients in the United States. Am J Emerg Med 2014;32:1395–8.
[3] Safwenberg U, Terent A, Lind L. The Emergency Department presenting complaint as predictor of in-hospital fatality. Eur J Emerg Med 2007;14:324–31.
[4] Nemec M, Koller MT, Nickel CH, Maile S, Winterhalder C, Karrer C, et al. Patients presenting to the emergency department with non-specific complaints: the Basel Non-

specific Complaints (BANC) study. Acad Emerg Med Off J Soc Acad Emerg Med 2010; 17:284–92.
[5] Rutschmann OT, Chevalley T, Zumwald C, Luthy C, Vermeulen B, Sarasin FP. Pitfalls in the emergency department triage of frail elderly patients without specific complaints. Swiss Med Wkly 2005;135:145–50.
[6] Nickel CH, Nemec M, Bingisser R. Weakness as presenting symptom in the emergency department. Swiss Med Wkly 2009;139:271–2.
[7] Nickel CH, Malinovska A, Bingisser R. Should weakness be subsumed to nonspecific complaints? Correspondence in response to Bhalla et al. Am J Emerg Med 2015.
[8] Djarv T, Castren M, Martenson L, Kurland L. Decreased general condition in the emergency department: high in-hospital mortality and a broad range of discharge diagnoses. Eur J Emerg Med 2015;22:241–6.
[9] Karakoumis J, Nickel CH, Kirsch M, Rohacek M, Geigy N, Müller B, et al. Emergency presentations with nonspecific complaints-the burden of morbidity and the spectrum of underlying disease: nonspecific complaints and underlying disease. Medicine (Baltimore) 2015;94:e840.
[10] Peng A, Rohacek M, Ackermann S, Ilsemann-Karakoumis J, Ghanim L, Messmer AS, et al. The proportion of correct diagnoses is low in emergency patients with nonspecific complaints presenting to the emergency department. Swiss Med Wkly 2015; 145:w14121.
[11] Bates SM. D-dimer assays in diagnosis and management of thrombotic and bleeding disorders. Semin Thromb Hemost 2012;38:673–82.
[12] Polo Friz H, Pasciuti L, Meloni DF, Crippa M, Villa G, Molteno M, et al. A higher d-dimer threshold safely rules-out pulmonary embolism in very elderly emergency department patients. Thromb Res 2014;133:380–3.
[13] Penaloza A, Roy PM, Kline J, Verschuren F, LE Gal G, Quentin-Georget S, et al. Performance of age-adjusted D-dimer cut-off to rule out pulmonary embolism. J Thromb Haemost 2012;10:1291–6.
[14] Clinical policy: critical issues in the evaluation and management of adult patients presenting with suspected lower-extremity deep venous thrombosisAnn Emerg Med 2003;42:124–35.
[15] Lippi G, Bonfanti L, Saccenti C, Cervellin G. Causes of elevated D-dimer in patients admitted to a large urban emergency department. Eur J Intern Med 2014;25:45–8.
[16] Kabrhel C, Mark Courtney D, Camargo Jr CA, Plewa MC, Nordenholz KE, Moore CL, et al. Factors associated with positive D-dimer results in patients evaluated for pulmonary embolism. Acad Emerg Med 2010;17:589–97.
[17] Becattini C, Lignani A, Masotti L, Forte MB, Agnelli G. D-dimer for risk stratification in patients with acute pulmonary embolism. J Thromb Thrombolysis 2012;33:48–57.
[18] Chiu CC, Li YN, Lin LJ, Hsiao CT, Hsiao KY, Chen IC. Serum D-dimer as a predictor of mortality in patients with acute spontaneous intracerebral hemorrhage. J Clin Neurosci 2012;19:810–3.
[19] Szymanski FM, Karpinski G, Filipiak KJ, Platek AE, Hrynkiewicz-Szymanska A, Kotkowski M, Opolski G, et al. Usefulness of the D-dimer concentration as a predictor of mortality in patients with out-of-hospital cardiac arrest. Am J Cardiol 2013; 112:467–71.
[20] Zorlu A, Yilmaz MB, Yucel H, Bektasoglu G, Refiker Ege M, Tandogan I. Increased d-dimer levels predict cardiovascular mortality in patients with systolic heart failure. J Thromb Thrombolysis 2012;33:322–8.
[21] Yang XY, Gao S, Ding J, Chen Y, Zhou XS, Wang JE. Plasma d-dimer predicts short-term poor outcome after acute ischemic stroke. PLoS One 2014;9:e89756.
[22] Rodelo JR1, De la Rosa G, Valencia ML, Ospina S, Arango CM, Gómez CI, et al. D-dimer is a significant prognostic factor in patients with suspected infection and sepsis. Am J Emerg Med 2012;30:1991–9.
[23] Arslan S, Ugurlu S, Bulut G, Akkurt I. The association between plasma D-dimer levels and community-acquired pneumonia. Clinics (Sao Paulo) 2010;65:593–7.
[24] Querol-Ribelles JM1, Tenias JM, Grau E, Querol-Borras JM, Climent JL, Gomez E, et al. Plasma d-dimer levels correlate with outcomes in patients with community-acquired pneumonia. Chest 2004;126:1087–92.
[25] Chalmers JD, Singanayagam A, Scally C, Hill AT. Admission D-dimer can identify low-risk patients with community-acquired pneumonia. Ann Emerg Med 2009;53: 633–8.
[26] Salluh JI1, Rabello LS, Rosolem MM, Soares M, Bozza FA, Verdean JC, et al. The impact of coagulation parameters on the outcomes of patients with severe community-acquired pneumonia requiring intensive care unit admission. J Crit Care 2011;26: 496–501.
[27] Shitrit D, Izbicki G, Shitrit AB, Kramer MR, Rudensky B, Sulkes J, et al. Prognostic value of a new quantitative D-dimer test in critically ill patients 24 and 48 h following admission to the intensive care unit. Blood Coagul Fibrinolysis 2004;15:15–9.
[28] Shorr AF, Trotta RF, Alkins SA, Hanzel GS, Diehl LF. D-dimer assay predicts mortality in critically ill patients without disseminated intravascular coagulation or venous thromboembolic disease. Intensive Care Med 1999;25:207–10.
[29] Di Castelnuovo A, de Curtis A, Costanzo S, Persichillo M, Olivieri M, Zito F, et al. Association of D-dimer levels with all-cause mortality in a healthy adult population: findings from the MOLI-SANI study. Haematologica 2013;98:1476–80.
[30] Haase C, Joergensen M, Ellervik C, Joergensen MK, Bathum L. Age- and sex-dependent reference intervals for D-dimer: evidence for a marked increase by age. Thromb Res 2013;132:676–80.
[31] Righini M, Van Es J, Den Exter PL, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. JAMA 2014;311:1117–24.
[32] Righini M, Van Es J, Den Exter PL, Roy PM, Verschuren F, Ghuysen A,. Effects of age on the performance of common diagnostic tests for pulmonary embolism. Am J Med 2000;109:357–61.
[33] Douma RA, le Gal G, Sohne M, Righini M, Kamphuisen PW, Perrier A, et al. Potential of an age adjusted D-dimer cut-off value to improve the exclusion of pulmonary embolism in older patients: a retrospective analysis of three large cohorts. BMJ 2010; 340:c1475.
[34] Knottnerus JA, Muris JW. Assessment of the accuracy of diagnostic tests: the cross-sectional study. J Clin Epidemiol 2003;56:1118–28.
[35] Grossmann FF, Nickel CH, Christ M, Schneider K, Spirig R, Bingisser R. Transporting clinical tools to new settings: cultural adaptation and validation of the Emergency Severity Index in German. Ann Emerg Med U S Inc 2011:257–64.
[36] Katz S, Akpom CA. 12. index of ADL. Med Care 1976;14:116–8.
[37] Nickel CH, Messmer AS, Geigy N, Misch F, Mueller B, Dusemund F, et al. Stress markers predict mortality in patients with nonspecific complaints presenting to the emergency department and may be a useful risk stratification tool to support disposition planning. Acad Emerg Med Off J Soc Acad Emerg Med 2013;20:670–9.
[38] Nickel CH, Ruedinger J, Misch F, Blume K, Maile S, Schulte J, et al. Copeptin and peroxiredoxin-4 independently predict mortality in patients with nonspecific complaints presenting to the emergency department. Acad Emerg Med Off J Soc Acad Emerg Med 2011;18:851–9.
[39] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
[40] Frenkel WJ, Jongerius EJ, Mandjes-van Uitert MJ, van Munster BC, de Rooij SE. Validation of the Charlson Comorbidity Index in acutely hospitalized elderly adults: a prospective cohort study. J Am Geriatr Soc 2014;62:342–6.
[41] Clinical policy: Critical issues in the evaluation and management of adult patients presenting with suspected pulmonary embolismAnn Emerg Med 2003;41:257–70.
[42] Lindner G, Funk GC, Pfortmueller CA, Leichtle AB, Fiedler GM, Schwarz C, et al. D-dimer to rule out pulmonary embolism in renal insufficiency. Am J Med 2014;127: 343–7.
[43] Diercks DB, Promes SB, Schuur JD, Shah K, Valente JH, Cantrill SV. Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients With Suspected Acute Nontraumatic Thoracic Aortic Dissection. Ann Emerg Med;65:32–42.e12.
[44] Snijders D, Schoorl M, Bartels PC, van der Werf TS, Boersma WG. D-dimer levels in assessing severity and clinical outcome in patients with community-acquired pneumonia. A secondary analysis of a randomised clinical trial. Eur J Intern Med 2012;23:436–41.
[45] Kollef MH, Eisenberg PR, Shannon W. A rapid assay for the detection of circulating D-dimer is associated with clinical outcomes among critically ill patients. Crit Care Med 1998;26:1054–60.
[46] Beglinger B, Rohacek M, Ackermann S, Hertwig R, Karakoumis-Ilsemann J, Boutellier S, et al. Physician's first clinical impression of emergency department patients with nonspecific complaints is associated with morbidity and mortality. Medicine (Baltimore) 2015;94:e374.
[47] Nickel CH, Messmer AS, Ghanim L, Ilsemann-Karakoumis J, Giersdorf S, Hertel S, et al. Adrenomedullin for risk stratification of emergency patients with nonspecific complaints: an interventional multicenter pilot study. Medicine (Baltimore) 2016; 95:e2395.

QJM: An International Journal of Medicine, 2019, 1–7

doi: 10.1093/qjmed/hcz226
Advance Access Publication Date: 28 August 2019
Original Article

ORIGINAL ARTICLE

Normal gait, albumin and d-dimer levels identify low risk emergency department patients: a prospective observational cohort study with 365-day 100% follow-up

L. Lyngholm[1], C.H. Nickel[2], J. Kellett [1], S. Chang[3,4], T. Cooksley[5] and M. Brabrand [1,6]

From the [1]Department of Emergency Medicine, Hospital of South West Jutland, Esbjerg, Denmark, [2]Emergency Department, University Hospital Basel, Basel, Switzerland, [3]Unit for Thrombosis Research, Department of Regional Health Research, University of Southern Denmark, Esbjerg, Denmark, [4]Department of Clinical Biochemistry, Hospital of South West Jutland, Esbjerg, Denmark, [5]Department of Acute Medicine, University Hospital of South Manchester, Manchester, UK and [6]Department of Emergency Medicine, Odense University Hospital, Odense, Denmark

Address correspondence to Dr J. Kellett, Ballinaclough, Nenagh, County Tipperary E45 Y722, Ireland. email: jgkellett@eircom.net

Summary

Background: If survival could be reliably predicted many patients could be safely managed outside of hospital in an ambulatory care setting.
Aim: Comparison of common laboratory findings, co-morbidities, mobility and vital signs as predictors of mortality of acutely ill emergency department (ED) attendees.
Design: Prospective observational study.
Methods: Secondary analysis of 1334 consenting acutely ill patients attending a Danish ED.
Results: 67 (5%) out of 1334 patients died within 100 days. After logistic regression seven predictors of 100 days mortality remained significant: an albumin level ≤34 gm/l, D-dimer level >0.51 mg/l, an Asadollahi score (based on admission laboratory data and age) ≥12, a platelet count <159 X 1000/ml, impaired mobility on presentation, a respiratory rate ≥30 bpm and a Charlson co-morbidity index ≥3. Only 5 of the 442 without any of these variables died within 365 days. Only one of the 517 patients with a stable independent gait and normal d-dimer and albumin levels died within 100 days, none died within 30 days of assessment and 12 died within 365 days. Of the remaining 817 patients 66 (8%) died within 100 days.
Conclusion: These findings suggest that normal gait, albumin and d-dimer levels are the most parsimonious way of identifying low risk ED patients.

Introduction

If it were possible to reliably predict survival many patients could be safely managed outside of hospital in an ambulatory care setting.[1] However, the great concern in any emergency department (ED) or acute hospital service is an unanticipated death after discharge. Although breathlessness and nonspecific symptoms such as weakness and fatigue are associated with

Received: 5 July 2019; Revised (in revised form): 12 August 2019

mortality,[2] severity of illness, functional status and co-morbid conditions are the three factors generally recognized as the major determinants of mortality.[3] Vital signs, either alone or aggregated into early warning scores, capture one aspect of disease severity[4] and impaired mobility can reflect reduced functional status.[5] The Charlson index assigns weighted scores to 17 co-morbidities[6] and it can be quickly, easily and inexpensively determined from administrative data.[7] In addition a number of predictive scores based on laboratory data,[8] such as the Asadollahi score calculated from the complete blood counts, blood glucose, urea and electrolytes,[9] and individual values such serum albumin[10] and C-reactive protein (CRP)[11] have all been proposed as predictors of outcome.

D-dimer levels are routinely used to rule out venous thrombo-embolic disease.[12] However, elevated d-dimers levels have also been used to predict morbidity and all-cause mortality in both medical and surgical patients in intensive care units[13,14] and in ED patients with nonspecific complaints.[15] Furthermore, high d-dimer levels have been associated with increased mortality in healthy adults independently of other risk factors,[16] and in a retrospective study of Danish ED patients we found that none of the patients with a d-dimer <0.50 mg/l and a National Early Warning Score (NEWS) ≤ 2 died within 30 days.[17]

A prospective study has confirmed that ED patients with low d-dimer levels are unlikely to die.[18] This paper reports a secondary analysis of this study's data, which further examines the relationship between d-dimer levels and other variables usually available in ED patients and their subsequent risk of mortality up to 365 days after assessment. These variables included breathlessness, fatigue, mobility, co-morbid conditions, vital signs and common routinely ordered laboratory values.

Materials and methods

Study design

Prospective observational cohort study performed on adult patients attending an ED according to the STROBE guidelines.[19] This is a secondary analysis of a previously published study that reported normal d-dimer levels identified patients at low risk of 30-day mortality.[18]

Setting

The Hospital of South West Jutland, a 450-bed regional teaching hospital in the region of Southern Denmark that serves approximately 220 000 inhabitants. Medical patients are referred to the ED by general practitioners (GP), outpatient clinics, out-of-hours GP service and emergency medical services.

Participants

All patients aged 18 years or older who required any blood sample on a clinical indication on arrival to the ED were eligible for inclusion in the study. Participants were required to give written informed consent before enrollment. Patients incapable of giving informed consent, e.g. language barriers or lacking mental capacity were excluded. Therefore, all patients included in the study were alert and had a normal mental status. Patients who did not have a blood sample available were excluded. Patients could only be included in the study once.

Screening and inclusion

Three trained research assistants performed the screening and inclusion process. All medical patients presenting to the ED were screened for eligibility between the 24 April 2017 and 19 August 2017 7 days a week, except for those admitted between 10 pm and 1 am at which time it was not possible to obtain an accurate d-dimer measurement. All eligible patients were offered the information required to provide informed consent and asked to participate.

Data collection

Presenting symptoms and signs

Each patient was asked if breathlessness or fatigue were amongst their presenting complaints. Impaired mobility on presentation (IMOP), a known predictor of mortality,[5] was defined as lack of a stable independent gait when first assessed.[20] Therefore, all patients who had an unstable gait, needed help to walk or were bedbound were deemed not to have a stable independent gait.

Co-morbid conditions

Each patient's Charlson co-morbidity index was determined from administrative data.

Vital signs

Vital signs were routinely collected upon presentation to the ED and entered into the hospital database by the regular staff. NEWS was calculated retrospectively from the hospital database.[21]

D-dimer levels

D-dimers were measured in all consenting patients included in the study. Plasma d-dimer was quantitatively measured using a latex agglutination test [STA Liatest d-dimer (Diagnostica Stago, Asnieres-sur-Seine, France)]. Citrate plasma for d-dimer estimation was obtained by centrifuging at 3500 rpm for 10 min.

As d-dimer levels can be ordered up to 10 h after the blood sample is initially collected, we were able to include patients who arrived at night. Therefore, patients who arrived between 10 pm and 1am could not be included.

Other laboratory results

All laboratory investigations ordered by the patients' physicians in the emergency room were analysed. The commonest investigations ordered were complete blood counts, blood glucose, urea and electrolytes from which the Asadollahi score could be calculated and serum albumin and CRP levels.

Outcome. Mortality within 365 days of ED attendance was extracted from the Danish Civil Registration System for all patients, which ensured 100% follow-up.[22]

Blinding. All clinicians providing direct care to patients were unaware of the ongoing study: the treating physician was only given the d-dimer result if it had been ordered as part of the routine care of the patient. This was done in order to avoid unnecessary investigations and treatment of thromboembolic disease that had not been suspected. All results were registered in a confidential research database which could only be accessed by the study investigators after the study was completed.

Ethics

The study design was approved by the Danish Regional Committee of Health Research Ethics (Identifier: S-20170005) and the Danish Data Protection Agency (Identifier: Region Syddanmark 2452). The study protocol was registered at ClinicalTrials.gov 3 April 2017, before enrollment of patients (ClinicalTrials.gov, Identifier: NCT03108807).

Statistical methods

Calculations were performed using Epi-Info version 6.0 (Center for Disease Control and Prevention, USA). Numeric variables were compared using Student's *t*-test and categorical variables were compared using Chi square analysis that applied Yates continuity correction. The *P*-values for statistical significance was 0.05. Continuous variables were converted into categorical variables using the value with the highest Chi-square number as the 'cut off'.

Significant predictors of mortality on univariate analysis that were not significant on multivariate analysis using logistic regression were eliminated. Predictive logistic regression models were then built using Logistic software[23]: 100-day survival as selected as the outcome for these models in order to have a sufficient number of events (i.e. at least 10 events per variable).[24] Survival analysis was performed using the Online Application for the Survival Analysis software (OASIS) available at http://sbi.postech.ac.kr/oasis/surv/.[25] Kaplan–Meier survival curves were compared by the log-rank test. Receiver operating characteristic (ROC) curves were constructed and the area under the curves compared according to the method of Hanley and McNeil.[26]

Results

Participants

During the study period 1697 acutely ill patients attended the hospital ED, required at least one blood sample to be performed and consented to be included in the study. Of these 1334 (79%) patients (the final study population) had a complete set of vital signs recorded and the following laboratory investigations performed: hemoglobin, white cell count, neutrophil count, platelet count, serum sodium, urea, creatinine, CRP, albumin and d-dimer levels. Eight hundred and ninety of these patients (66.7%) were admitted to hospital for a length of stay 4.7 SD 8.5 days: 67 (5%) patients died within 100 days of ED assessment, 11 patients died while in hospital (mean length of stay 11.8 SD 7.3 days).

Identification of mortality predictors by univariate analysis

There were significant differences between the values of survivors and those who died within 100 days for all the continuous variables tested except for diastolic blood pressure, heart rate, temperature, platelet count and blood sugar levels (Table 1). All of the 27 categorical variables tested also showed significant unadjusted odds ratios for death within in 100 days apart from breathlessness on presentation and abnormal temperatures (Table 2).

Elimination of mortality predictors by multivariate analysis

Odds ratio adjustment by logistic regression identified 7 clinically significant predictors of 100 day mortality: an albumin level $\leq$34 gm/l, d-dimer level >0.51 mg/l, an Asadollahi score $\geq$12, a platelet count <159 X 1000/ml, IMOP, a respiratory rate $\geq$30 breaths per minute and a Charlson index $\geq$3. The sum of the adjusted odds to the nearest integer of each of these variables was used to make a weighted predictive score, which had a c statistic for death within 100 days of 0.882 SE 0.027 (Table 3).

Predictive model development

All the possible combinations of albumin levels, d-dimer levels, the Asadollahi score, IMOP, respiratory rate and the Charlson Index were tested in models that used two, three, four, five or all six of these variables. In 23 models only one patient with a score of zero died within 100 days and no patients died within 30 days: all these models contained d-dimer levels and IMOP as variables (Table 4).

The model that identified the largest number of patients with the lowest 100-day mortality only contained the three variables of an albumin level <35 gm/l, a d-dimer level >0.51 mg/l and IMOP. The addition of each predictor variable increased the 100 days mortality exponentially, and Kaplan–Meier survival curves for patients with zero, one, two and three of the model's predictor variables were all significantly different (Figure 1).

Causes of death

Only 5 patients died within 7 days of presenting to the ED, and all were admitted to hospital: one with a score of two points died within 24 h with the non-specific ICD10 code of Z03.4 (i.e. *Encounter for medical observation for suspected diseases and conditions ruled out*) recorded at ED departure. Over the next 6 days four more patients died with the following ICD10 codes recorded on ED departure: pneumonia (J15.9) in one patient with one predictive score point, ileus (K56.7) in one patient with two points and of two patients with three points one was coded as bradycardia (R00.1) and the other as respiratory arrest (R09.2). The ICD10 codes on ED departure of all the patients who died within 100 days of ED presentation are provided as Supplementary Material.

365-day follow-up

After 1 year follow-up 12 of the 517 (2.3%) patients with normal mobility, albumin and d-dimer levels died, compared with 131 (16%) of the remaining 817 patients. Only 5 of the 425 (1.1%) patients with normal mobility, albumin and d-dimer levels, an Asadollah score <12, a platelet count <159 X1000/ml, a respiratory rate <30 breaths per minute and a Charlson index <3 died within a year, compared with 138 (15%) of the remaining 909 patients.

Discussion

Principle findings

This study found that a significant proportion of patients attending an ED (39% of all patients) had a stable independent gait and normal d-dimer and albumin levels. These patients had a less than 0.2% change of dying within 100 days, none died within 30 days of assessment and 12 (2.3%) died within a year. Of the remaining 817 patients 66 (8.1%) died within 100 days, 32 (3.9%) within 30 days and 131 (16%) within a year.

Table 1. Continuous variables tested

Variable	Died within 100 days ($n = 67$)	Survived 100 days ($n = 1267$)	P
Age (years)	73.9 SD 12.7	62.6 SD 18.3	0.0000001
Systolic blood pressure (mmHg)	133 SD 25	139 SD 24	0.03
Diastolic blood pressure (mmHg)	77 SD 16	81 SD 14	0.06
Heart rate (beats per minute)	87 SD 24	83 SD 20	0.07
Respiratory rate (breaths per min)	21 SD 7	18 SD 4	0.0000001
Oxygen saturation (%)	95 SD 5	97 SD 3	0.0000001
Temperature (°C)	37.1 SD 0.8	37.0 SD 0.7	0.79
Glasgow Coma Scale	15.0 SD 0.2	15.0 SD 0.3	0.69
D-Dimer (mg/l)	3.3 SD 3.5	0.9 SD 1.6	0.0000001
NEWS	3.3 SD 2.8	1.6 SD 2.0	0.0000001
Length of hospital stay (days)	6.6 SD 6.3	3.0 SD 7.3	0.00007
Urea (mmol/l)	10.3 SD 7.1	6.6 SD 4.8	0.0000001
Hemoglobin (mmol/l)	7.3 SD 1.4	8.2 SD 1.2	0.0000001
White Blood Cell count (X 1000/ml)	11.1 SD 5.7	9.1 SD 4.2	0.0001
Platelet count (X1000/ml)	242 SD 142	248 SD 86	0.61
Sodium (mmol/l)	135 SD 6	137 SD 4	0.00002
Blood sugar (mmol/l)	7.3 SD 2.3	7.1 SD 2.9	0.57
Albumin (gm/l)	34.2 SD 4.7	39.8 SD 4.1	0.0000001
C reactive protein (mg/l)	75 SD 77	32 SD 63	0.0000001
Creatinine (mmol/l)	121 SD 116	90 SD 72	0.001
Neutrophil count (X 1000/ml)	8.5 SD 4.6	6.3 SD 3.8	0.000004
Asadollahi score	10.7 SD 4.6	5.9 SD 4.5	0.0000001
C reactive protein / Albumin ratio	2.0 SD 2.2	0.8 SD 1.6	0.0000001

Table 2. Categorical variables tested

Variable	OR	95% CI	95% CI	Chi-square	P
D-Dimer >0.51 mg/l	11.43	4.95	27.77	54.17	<0.0000001
Respiratory rate ≥30 breaths per minute	11.10	4.74	25.63	50.83	<0.0000001
Albumin ≤34 gm/l	10.30	5.93	17.90	106.98	<0.0000001
Asdollahi score ≥12	6.18	3.60	10.62	59.17	<0.0000001
Oxygen saturation <90%	5.99	2.38	14.62	19.34	0.00001
CRP ≥45 mg/l	5.65	3.31	9.69	53.36	<0.0000001
Admission to hospital	5.37	2.19	14.00	17.64	0.00003
NEWS ≥5	4.94	2.77	8.78	37.94	<0.0000001
Length of hospital stay ≥6 days	4.82	2.81	8.28	41.67	<0.0000001
Hemoglobin <7.8 mmol/l	4.47	2.58	7.80	35.81	<0.0000001
Urea ≥8.4 mmol/l	4.39	2.58	7.49	37.13	<0.0000001
Sodium ≤130 mmol/l	4.37	2.14	8.81	20.48	0.000006
IMOP	4.35	2.46	7.74	32.10	<0.0000001
Neutrophil count ≥9.2 x1000/ml	4.16	2.41	7.17	32.64	<0.0000001
Charlson Index ≥3	4.14	2.43	7.05	34.05	<0.0000001
White blood cell count >12 x1000/ml	3.82	2.22	6.57	28.47	<0.0000001
Creatinine ≥110 mmol/l	3.59	2.07	6.21	24.78	0.000001
Platelets <159 X 1000/ml	3.55	1.94	6.47	20.11	0.00001
NEWS ≥3	3.31	1.95	5.62	23.34	0.000001
Age ≥70 years	3.08	1.75	5.49	17.57	0.00003
Fatigue	2.24	1.06	4.61	4.70	0.03
Blood sugar ≥6.9 mmol/l	2.17	1.28	3.67	9.03	0.003
Heart rate >102 beats per minute	2.12	1.15	3.85	6.24	0.01
Systolic blood pressure <126 mmHg	2.10	1.24	3.56	8.15	0.004
Breathlessness	1.83	0.99	3.36	3.75	0.053
Temperature >38°C	1.23	0.46	3.07	0.05	0.82
Temperature ≤36°C	0.36	0.02	2.51	0.52	0.47

NEWS = National Early Warning Score.

Strengths and weaknesses

This single-center study performed in a Danish ED, systematically assessed the association of mortality with d-dimer and impaired mobility along with the other variables commonly collected at an ED visit. A major strength of the study is that the Danish registries provided complete follow-up on all the patients. The main limitation is its small size. Nevertheless,

Table 3. Logistic regression—only variables with statistically significant adjusted odds ratios for 100 days mortality

Variables	Adjusted odds ratio (95% CI)	*P*	Model score
Albumin ≤34 gm/l	4.27 (2.43–7.52)	0.0000	4
D-dimer >0.51mg/l	4.45 (1.93–10.28)	0.0005	4
Asadollahi score ≥12	2.65 (1.49–4.71)	0.0009	3
IMOP	2.04 (1.13–3.69)	0.0188	2
Respiratory rate ≥30 breaths per minute	6.29 (2.60–15.21)	0.0000	6
Charlson index ≥3	1.83 (1.04–3.23)	0.0360	2
Platelets <159 X 1000 ml	2.20 (1.17–4.13)	0.0141	2
Hosmer–Lemeshow statistic: P 0.55			

IMOP = impaired mobility on presentation.

Table 4. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of the 23 models when zero points were present

Model	Sensitivity	Specificity	PPV	NPV	LR+	LR−ve	100-day mortality (%)	Proportion (%)	Total	No died
AL-DD-IM	0.9851	0.4071	0.0809	0.9981	1.66	0.04	0.19	38.76	517	1
AL-DD-IM-RR	0.9851	0.4032	0.0804	0.9980	1.65	0.04	0.20	38.38	512	1
DD-AS-IM	0.9851	0.3960	0.0795	0.9980	1.63	0.04	0.20	37.63	502	1
DD-IM-PT	0.9851	0.3923	0.0789	0.9980	1.62	0.03	0.20	37.33	498	1
DD-AS-IM-RR	0.9851	0.3921	0.079	0.9980	1.62	0.04	0.20	37.26	497	1
DD-IM-RR-PT	0.9851	0.3899	0.0787	0.9980	1.61	0.04	0.20	37.11	495	1
AL-DD-AS-IM	0.9851	0.3889	0.0787	0.9980	1.61	0.04	0.20	37.03	494	1
AL-DD-IM-PT	0.9851	0.3875	0.0784	0.9980	1.61	0.04	0.20	36.81	491	1
AL-DD-AS-IM-RR	0.9851	0.3850	0.0782	0.9980	1.6	0.04	0.20	36.66	489	1
AL-DD-IM-RR-PT	0.9851	0.3844	0.0780	0.9980	1.60	0.04	0.20	36.58	488	1
DD-AS-IM-PT	0.9851	0.3765	0.0771	0.9979	1.58	0.04	0.21	35.83	478	1
DD-AS-IM-RR-PT	0.9851	0.3741	0.0768	0.9979	1.57	0.04	0.21	35.61	475	1
AL-DD-AS-IM-PT	0.9851	0.3710	0.0765	0.9979	1.57	0.04	0.21	35.23	470	1
AL-DD-AS-IM-RR-PT	0.9851	0.3686	0.0762	0.9979	1.56	0.04	0.21	35.08	468	1
AL-DD-IM-RR-CH	0.9851	0.3589	0.0753	0.9978	1.54	0.04	0.22	34.18	456	1
DD-AS-IM-RR-CH	0.9851	0.3526	0.0746	0.9978	1.52	0.04	0.22	33.58	448	1
AL-DD-AS-IM-CH	0.9851	0.3494	0.0742	0.9977	1.51	0.04	0.23	33.28	444	1
AL-DD-AS-IM-RR-CH	0.9851	0.3478	0.0741	0.9977	1.51	0.04	0.23	33.13	442	1
DD-IM-CH-PT	0.9851	0.3481	0.074	0.9977	1.51	0.04	0.23	33.13	442	1
AL-DD-IM-RR-CH-PT	0.9851	0.3433	0.0735	0.9977	1.50	0.04	0.23	32.68	436	1
DD-AS-IM-RR-CH-PT	0.9851	0.3386	0.0730	0.9977	1.49	0.04	0.23	32.23	430	1
AL-DD-AS-IM-CH-PT	0.9851	0.3354	0.0727	0.9977	1.48	0.04	0.23	31.93	426	1
AL-DD-AS-IM-RR-CH-PT	0.9851	0.3346	0.0726	0.9976	1.48	0.04	0.24	31.86	425	1

Only one patient with a score of zero in any of these models died within 100 days.

LR+ve = positive likelihood ratio; LR−ve = negative likelihood ratio. AL = albumin ≤34 gm/l; DD = d-dimer >0.51 mg/l; IM = impaired mobility on presentation; AS = Asadollahi score ≥12; RR = respiratory rate ≥30 breaths per minute; CH = Charlson Index ≥3; PT = platelet count <159 X 1000 ml. Total = total number of patients with zero points. Proportion is the proportion of final study population of 1334 patients with a score of zero points.

there were just enough deaths after 100 days to allow multivariate analysis to identify and examine the seven significant predictors of mortality.[24] However some variables, especially those with values above and below a normal range associated with death, could not be adequately tested. For example, none of our patients presented with hypoglycemia, only five had a temperature below 35.5°C, only 21 with a heart rate below 50 beats per minute, only 6 had a respiratory rate below 12 breaths per minute.

The cohort contained only patients who required a blood sample on clinical indication. Patients needed to give their informed consent before enrollment which made it impossible for patients with altered mental status to participate. The other major limitation of this study is that the only outcome examined was death. No attempt was made to examine morbidity, quality of life, relief of pain, suffering or anxiety, or other outcomes that may be important to both patients and physicians. It is also important to note that every patient may have received some form of treatment, which might have prevented death.

Interpretation

These findings must be independently validated and compared against clinician 'gestalt'. In order to be of clinical value a score designed to identify patients at no risk of death must be as sensitive as possible (i.e. always negative in patients who do not die). It could be argued that the low mortality of the study cohort is attributable to life-saving interventions provided in the ED. Review of the diagnoses made in the ED in patients who died (Supplementary Material) makes this possibility unlikely: of the 67 patients who died within 100 days 14 (21%) had a non-specific diagnosis made in the ED, two had a complication of treatment and some of the specific diagnoses made were trivial and unlikely to have been related to subsequent mortality (e.g. olecranon bursitis, syncope, gastroenteritis etc.). It is of note that of the 6 patients who died within 100 days who were not admitted 4 had 2 or more predictive score points, and 3 had breathing problems. Nevertheless, since the overall mortality of our patients is low, our results

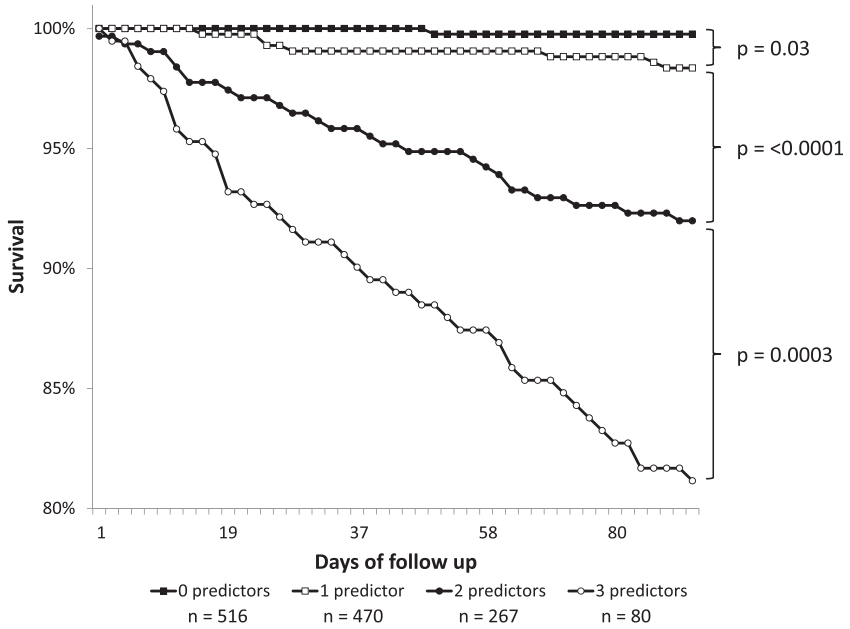


Figure 1. Kaplan-Meier 100 days survival curve of a predictive model that provided one point for each of the following predictor variables: albumin <35 ml/l, d-dimer >0.51 mg/l, and IMOP. All four survival curves were all significantly different. The 100 day survival was 0.19% for a model score of zero points, 3.4% for one point, 9.4% for two points, and 31.3% for three points.

should be interpreted with caution as they may not be applicable to other patient populations. As there will be only a small number of events, and one more or less death might have a major impact, studies to identify universally reliable and valid predictors of survival in acutely ill patients will have to be large and require the cooperation of as many and varied health facilities as possible.

We found the d-dimer level with the highest Chi-square for 100 days mortality was very close the standard 'cut-off' of 0.5 mg/l. Since age was eliminated as a significant predictor of mortality by logistic regression, an age adjustment is unlikely improve d-dimer's prediction of either mortality or survival.

Generalizability

In this study, although none of the 443 patients discharged (33% of the total) died within 7 days, 3 (0.7%) died within 30 days. If the decision to admit had been based on the patients' mobility, serum albumin and d-dimer levels instead of clinical judgement, 39% would have been discharged and none of them would have died within 30 days. However, the discharge of the 3 patients who died within 30 days might have been entirely appropriate if they were receiving palliative care at home, and hospital admission would have had nothing further to offer them. Moreover, all physicians can think of good reasons why a patient with normal gait, d-dimer and albumin levels should be admitted to hospital: no physician would send home a young patient with a headache who has an evolving sub-arachnoid hemorrhage and will be alive at 100 days but with gross morbidity.

Unlike clinical judgement, albumin and d-dimer levels are easy to interpret, but would never be the only laboratory tests needed in an ED evaluation. In clinical practice other laboratory tests, such as those included in the Asadollah score, will provide important diagnostic information to guide clinical management. Although nearly 30% of the patients admitted to hospital in this study had no predictor variables, many reasons may have mandated their admission: 20% had a NEWS ≥3, pain and other symptoms may have required prompt relief, some treatments may only have been available in hospital and some patients may have needed admission because care at home had become impossible and/or palliative care may have been required.[27] Nevertheless, we believe that it is probable that many of the patients admitted, especially those with normal mobility, might have been safely managed outside of hospital had their physicians been sure they had no risk of dying or severe morbidity.

Unfortunately, many clinicians have difficulty grasping the concept that d-dimer is a sensitive, but not a specific test. It can be elevated in far more conditions than venous thrombo-embolic disease, such as infection, syncope, heart failure, trauma, cancer, arterial diseases including thrombosis and dissection, renal disease, liver disease, bleeding and disseminated intravascular coagulation.[28,29] Therefore, a considerable amount of professional education may be required before d-dimer could be introduced as a test on every patient.

Conclusion

This prospective study with 100% patient follow-up found that none of 516 acutely ill patients attending an ED with a stable independent gait and normal d-dimer and albumin levels died within 30 days, and only one (0.19%) died within 100 days. These patients represented 39% of ED attendees during the study period. Of the remaining 816 patients 66 (8.1%) died within 100 days. However, further studies are needed to confirm these findings, and ensure that these variables also identify patients at low risk of preventable morbidity who could be safely managed outside of hospital.

Supplementary material

Supplementary material is available at *QJMED* online.

Conflict of interest: All costs were borne by the authors. John Kellett is a major shareholder, director and chief medical officer of Tapa Healthcare DAC. The other authors have no potential conflicts of interest.

References

1. Lasserson DS, Harris C, Elias T, Bowen J, Clare S. Clare S What is the evidence base for ambulatory care for acute medical illness? *Acute Med* 2018; **17**:148–53.
2. Bingisser R, Dietrich M, Nieves Ortega R, Malinovska A, Bosia T, Nickel CH, *et al*. Systematically assessed symptoms as outcome predictors in emergency patients. *Eur J Int Med* 2017; **45**: 8–12.
3. Pompei P, Charlson ME, Douglas RG Jr. Clinical assessments as predictors of one year survival after hospitalization: implications for prognostic stratification. *J Clin Epidemiol* 1988; **41**:275.
4. 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**:465–70.
5. Brabrand M, Kellett J, Opio M, Cooksley T, Nickel CH. Should impaired mobility on presentation be a vital sign? *Acta Anaesthesiol Scand* 2018; **62**:945–52.
6. Charlson ME, Pompei P, Ales KL, Mackenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis* 1987; **40**:373–83.
7. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi J-C, *et al*. Coding algorithms for defining comorbidities in ICD-9 CM and ICD-10 administrative data. *Med Care* 2005; **43**:1130–9.
8. Brabrand M, Knudsen T, Hallas J. Identifying admitted patients at risk of dying: a prospective observational validation of four biochemical scoring systems. *BMJ Open* 2013; **3**: e002890.
9. Asadollahi K, Hastings IM, Gill GV, Beeching NJ. Prediction of hospital mortality from admission laboratory data and patient age: a simple model. *Emerg Med Australas* 2011; **23**: 354–63.
10. Jellinge ME, Henriksen DP, Hallas P, Brabrand M. Hypoalbuminemia is a strong predictor of 30-day all-cause mortality in acutely admitted medical patients: a prospective, observational, cohort study. *PLoS One* 2014; **9**:e105983.
11. Zacho J, Tybjaerg-Hansen A, Nordestgaard BG. C-reactive protein and all-cause mortality—the Copenhagen City Heart Study. *Eur Heart J* 2010; **31**:1624–32.
12. Crawford F, Andras A, Welch K, Sheares K, Keeling D, Chappell FM. D-dimer test for excluding the diagnosis of pulmonary embolism. *Cochrane Database Syst Rev* 2016; **8**: Cd010864.
13. Shitrit D, Izbicki G, Shitrit AB, Kramer MR, Rudensky B, Sulkes J. Prognostic value of a new quantitative D-dimer test in critically ill patients 24 and 48 h following admission to the intensive care unit. *Blood Coagul Fibrinolysis* 2004; **15**:15–9.
14. Shorr AF, Trotta RF, Alkins SA, Hanzel GS, Diehl LF. D-dimer assay predicts mortality in critically ill patients without disseminated intravascular coagulation or venous thromboembolic disease. *Intensive Care Med* 1999; **25**:207–10.
15. Nickel CH, Kuster T, Keil C, Messmer AS, Geigy N, Bingisser R, *et al*. Risk stratification using D-dimers in patients presenting to the emergency department with nonspecific complaints. *Eur J Int Med* 2016; **31**:20–4.
16. Di Castelnuovo A, de Curtis A, Costanzo S, Persichillo M, Olivieri M, Zito F, *et al*. Association of D-dimer levels with all-cause mortality in a healthy adult population: findings from the MOLI-SANI study. *Haematologica* 2013; **98**: 1476–80.
17. Nickel CH, Kellett J, Cooksley T, Bingisser R, Henriksen DP, Brabrand M, *et al*. Combined use of the national early warning score and D-dimer levels to predict 30-day and 365-day mortality in medical patients. *Resuscitation* 2016; **106**: 49–52.
18. Lyngholm LE, Nickel CH, Kellett J, Chang S, Cooksley T, Brabrand M, *et al*. A negative d-dimer identifies patients at low risk of death within 30 days: a prospective observational emergency department cohort study. *QJM* 2019. doi: 10.1093/qjmed/hcz140.
19. Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, *et al*. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *Epidemiology* 2007; **18**:805–35.
20. Kellett J, Clifford M, Ridley A, Murray A, Gleeson M. A four item scale based on gait for the immediate global assessment of acutely ill medical patients – one look is more than 1000 words. *Eur Geriatr Med* 2014; **5**:92–6.
21. Royal College of Physicians. National Early Warning Score (NEWS): Standardising the Assessment of Acute Illness Severity in the NHS. Report of a Working Party. London, RCP, 2012. www.rcplondon.ac.uk/resources/nationalearlywarning score-news.
22. Pedersen CB. The Danish civil registration system. *Scand J Public Health* 2011; **39**:22–5.
23. Dallal GE. LOGISTIC: a logistic regression program for the IBM PC. *Am Stat* 1988; **42**:272.
24. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and cox regression. *Am J Epidemiol* 2007; **165**:710–8.
25. Yang J-S, Nam H-J, Seo M, Han SK, Choi Y, Nam HG, *et al*. OASIS: online application for the survival analysis of lifespan assays performed in aging research. *PLoS One* 2011; **6**:e23525.
26. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983; **148**:839–43.
27. Rutschmann OT, Chevalley T, Zumwald C, Luthy C, Vermeulen B, Sarasin FP, *et al*. Pitfalls in the emergency department triage of frail elderly patients without specific complaints. *Swiss Med Weekly* 2005; **135**:145–50.
28. Lippi G, Bonfanti L, Saccenti C, Cervellin G. Causes of elevated D-dimer in patients admitted to a large urban emergency department. *Eur J Int Med* 2014; **25**:45–8.
29. Koracevic GP. Pragmatic classification of the causes of high D-dimer. *Am J Emerg Med* 2009; **27**:1016.e5–e7.

OXFORD

QJM: An International Journal of Medicine, 2019, 675–680

doi: 10.1093/qjmed/hcz140
Advance Access Publication Date: 10 June 2019
Original paper

ORIGINAL PAPER

A negative D-dimer identifies patients at low risk of death within 30 days: a prospective observational emergency department cohort study

L.E. Lyngholm[1], C.H. Nickel[2], J. Kellett [1], S. Chang[3,4], T. Cooksley[5] and M. Brabrand [1,6]

From the [1]Department of Emergency Medicine, Hospital of South West Jutland, Denmark, [2]Emergency Department, University Hospital Basel, Switzerland, [3]Unit for Thrombosis Research, Department of Regional Health Research, University of Southern Denmark, [4]Department of Clinical Biochemistry, Hospital of South West Jutland, Denmark, [5]Department of Acute Medicine, University Hospital of South Manchester, UK and [6]Department of Emergency Medicine, Odense University Hospital, Denmark

Address correspondence to Dr Tim Cooksley, University Hospital of South Manchester, Manchester, UK. email: cooks199@hotmail.com

Summary

Objective: To determine the ability of a normal D-dimer level (<0.5 mg/l) to identify emergency department (ED) patients at low risk of 30-day all-cause mortality.
Design: In this prospective observational study, D-dimer levels of adult medical patients were assessed at arrival to the ED. Data on 30-day survival status were extracted from the Danish Civil Registration System with complete follow-up.
Setting: The Hospital of South West Jutland.
Patients: All patients aged 18 years or older who required any blood sample on a clinical indication on arrival to the ED. Participants were required to give written informed consent before enrollment.
Main results: The study population of 1 518 patients with median age 66 years of which 49.4% were female. Of the 791 (52.1%) patients with normal D-dimer levels, 3 (0.4%) died within 30 days; one death resulted from an unrelated traumatic accident. Of the 727 (47.9%) patients with abnormal D-dimer levels (≥0.50 mg/l), 32 (4.4%) died within 30 days. Patients with normal D-dimer levels had a significantly lower 30-day mortality compared to patients with abnormal D-dimer levels (odds ratio 0.08, 95% CI 0.02–0.28): of the 35 patients who died within 30 days, 19 (54.3%) had normal or near normal vital signs when first assessed.
Conclusion: Normal D-dimer levels identified patients at low risk of 30-day mortality. Since most patients who died within 30 days presented with normal or near normal vital signs, D-dimer levels appear to provide additional prognostic information.

Received: 15 April 2019; **Revised (in revised form):** 27 May 2019

Introduction

The great concern in any emergency department (ED) or acute hospital service is the risk of unanticipated death after discharge.[1,2] Risk stratification of ED patients is commonly based on vital signs and presenting symptoms.[3,4] However, additional tools, such as laboratory investigations, may be needed to ensure safe discharge. Although D-dimers are routinely used to rule out thromboembolic diseases,[5] high D-dimer levels have been associated with increased rates of mortality in healthy adults independently of other risk factors.[6] Moreover, D-dimer levels have also been used to predict morbidity and all-cause mortality in both medical and surgical patients in intensive care units,[7,8] and in ED patients with nonspecific complaints.[9]

In a retrospective study of Danish ED patients, we found that no patients with a D-dimer <0.50 mg/l and normal or near normal vital signs died within 30 days.[10] This study was limited by only including patients who had a D-dimer level measured if it was indicated as part of the diagnostic investigation and, therefore, included patients that were not representative of all medical patients seen in an ED. In this study, we prospectively examined D-dimer levels as a predictor of 30-day mortality in a cohort of unselected acutely ill patients attending a Danish hospital's ED.

Materials and methods

Study design: prospective observational cohort study performed on adult patients attending an ED.

Setting: the Hospital of South West Jutland, a 450-bed regional teaching hospital in the region of Southern Denmark that serves ~220 000 inhabitants. Patients are referred to the ED by general practitioners (GP), outpatient clinics, out-of-hours GP service and emergency medical services.

Participants: all patients aged 18 years or older who required any blood sample on a clinical indication on arrival to the ED were eligible for inclusion in the study. Participants were asked for written informed consent before enrollment. Patients incapable of giving informed consent (e.g. language barriers or lacking mental capacity) were excluded. Patients could only be included in the study once.

Screening and inclusion: three trained research assistants performed the screening and inclusion process. All medical patients presenting to the ED were screened for eligibility between the 24 April 2017 and 19 August 2017 between 10 am and 10 pm, 7 days a week.

Data collection

Vital signs: vital signs were routinely collected upon presentation to the ED and entered into the hospital database by the regular staff. Vital sign changes were determined using the National Early Warning Score (NEWS) [4]: patients with an NEWS <3 were considered to have normal or near normal vital signs.

D-dimer levels: D-dimers were measured in all consenting patients included in the study. Plasma D-dimer was quantitatively measured using a latex agglutination test (STA Liatest D-dimer; Diagnostica Stago, Asnieres-sur-Seine, France). As D-dimer levels can be ordered up to 10 h after the blood sample is initially collected, patients who arrived between 10 pm and 1 am could not be included.

Patient outcomes: ICD10 discharge codes were extracted from the patients' medical records and 30-day survival status from the Danish Civil Registration System for all patients to secure complete 100% follow-up.[11]

Blinding: the treating physicians were unaware of the study while it was ongoing, and were only given the D-dimer result if it had been ordered as part of the patients' care. This was done to avoid unnecessary investigations and treatment of potential thromboembolic disease that had not been suspected. All results were registered in a confidential research database that could only be accessed by the study investigators after the study was completed.

Ethics

The study design was approved by the Danish Regional Committee of Health Research Ethics (Identifier: S-20170005) and the Danish Data Protection Agency (Identifier: Region Syddanmark 2452). The study protocol was registered at ClinicalTrials.gov 3 April 2017, before enrollment of patients (ClinicalTrials.gov, Identifier: NCT03108807). The results are reported in accordance with the STROBE guidelines.[12]

Statistics

Calculations were performed using Epi-Info version 6.0 (Center for Disease Control and Prevention, USA). Numeric variables were compared using Student's *t*-test and categorical variables were compared using Chi-square analysis that applied Yates continuity correction. The *P*-values for statistical significance were 0.05. Continuous variables were converted into categorical variables using the value with the highest Chi-square number the 'cut off'. Survival analysis was performed using the Online Application for the Survival Analysis software (OASIS) available at http://sbi.postech.ac.kr/oasis/surv/.[13] Kaplan–Meier survival curves were compared by the log-rank test.

Results

The study population was 1518 patients and 35 patients (2.3%) died within 30 days: the median time to death from the time of inclusion was 18.5 (range: 1–29, IQR 12–24) days. Most patients had normal or near normal vital signs on presentation (i.e. NEWS <3), as did 19 (54.3%) of those who died. Patients who died were older and had higher D-dimer levels than survivors; more of the patients who died were men than women, but this was not statistically significant (Table 1).

Table 1. Baseline demographics for all patients, 30-day survivors and 30-day non-survivors

Characteristics	All patients $n = 1518$	30-Day survivors $n = 1482$ (97.6%)	30-Day non-survivors $n = 36$ (2.4%)
Age (years)			
Median (IQR)	66 (52.0–77.0)	66 (51.0–76.0)	77.5 (69.5–86.0)
Min–max	18–97	18–97	51–94
Sex			
Female, *n* (%)	750 (49.4)	735 (49.6)	15 (41.7)
Male, *n* (%)	768 (50.6)	747 (50.4)	21 (58.3)
D-dimer (mg/l)			
Median (IQR)	0.5 (0.2–1.2)	0.5 (0.2–1.1)	2.3 (1.3–6.9)
Min–max	0–20	0–20	0.11–20
NEWS			
Median (IQR)	1 (0–2)	1 (0–2)	2 (1–6)
Min–max	0–11	0–11	0–9

IQR, interquartile range; min–max, minimum to maximum value; *n*, patient number.

The majority of patients had medical conditions: 795 (52.4%) had general medical complaints, 490 (32.3%) cardiac complaints, 217 (14.3%) neurological disorders and only 16 (1.1%) were deemed non-medical. Six hundred and nineteen patients (41% of the total) were discharged without a definite diagnosis and 11 of them (1.8%) died within 30 days: 329 had a factor influencing health status (ICD10 code Z00-Z99) and 290 had symptoms, signs or laboratory abnormalities not classified elsewhere (ICD10 code R00-R99). The two commonest definite discharge diagnoses made were circulatory disease (ICD10 code I00-I99) in 261 patients and respiratory disease (ICD10 code J00-J99) in 199 patients. These four ICD10 groupings accounted for 71% of all patients and 51% of all deaths. Sixteen patients (1%) were diagnosed with pulmonary embolus and one (6.3%) died.

Table 2 shows the differences in patient characteristics between those with a positive and negative D-dimer. Patients with an abnormal D-dimer were more likely to die within 30 days and they had worse survival curves: no patients with a D-dimer <0.50 mg/l died within 14 days of ER assessment (Figure 1). Out of the 791 (52.1%) patients with a D-dimer <0.50 mg/l only 3

Table 2. Differences in patient characteristics between those with a positive and negative D-dimer

	All	Positive D-dimer	Negative D-dimer	*P*-value
Number	1518	727	791	
Female, *n* (%)	768 (50.6%)	374 (51.4%)	394 (49.8%)	0.53
Age, median (IQR)	66 (52–77)	72 (60–80)	60 (47–72)	<0.001
Death at 30 days, *n*	35 (2.3%)	32 (4.4%)	3 (0.4%)	<0.001
NEWS, median (IQR)	1 (0–2)	1 (0–3)	0 (0–2)	<0.001
Length of stay, days median (IQR)	1 (0–4)	2 (0–5)	1 (0–2)	<0.001
Charlson score, median (IQR)	1 (0–2)	1 (0–3)	0 (0–2)	<0.001
Any cancer diagnosis within 5 years prior to inclusion, *n* (%)	234 (15.4%)	144 (19.8%)	90 (11.4%)	<0.001

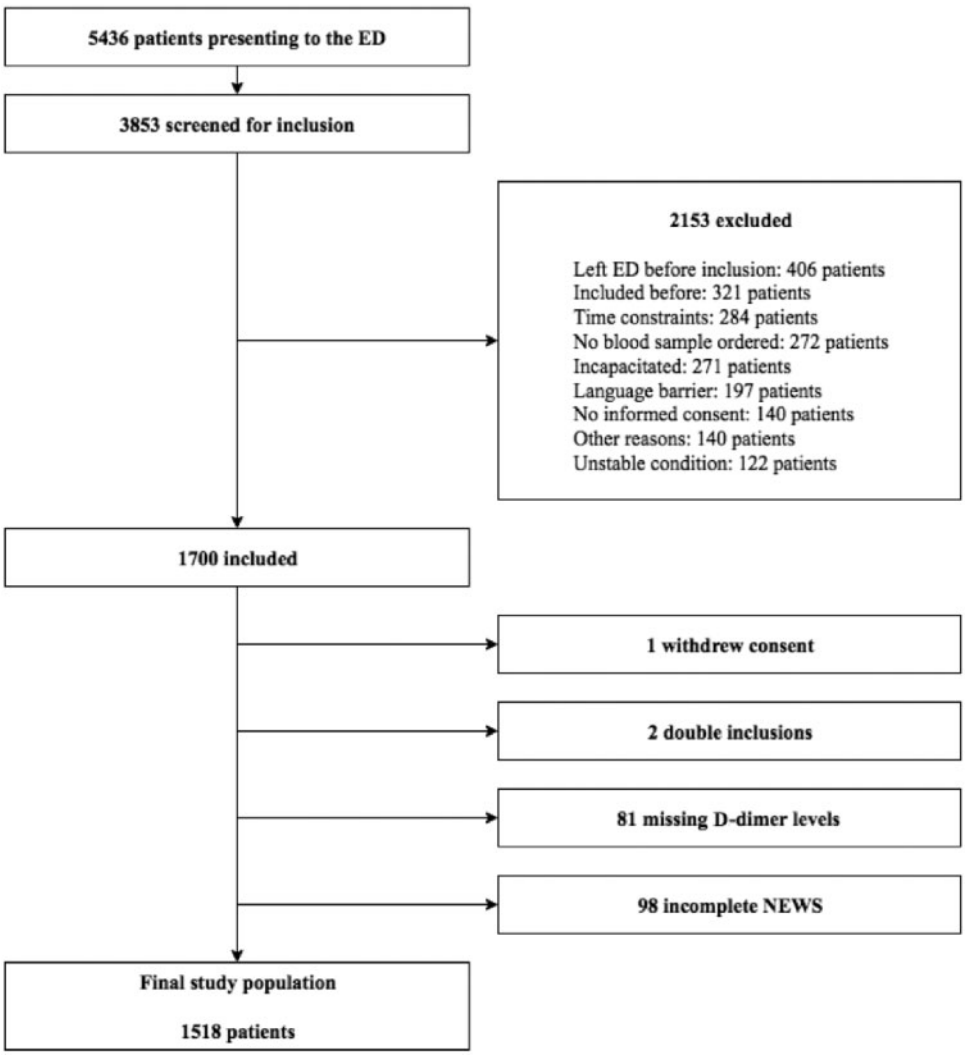


Figure 1. Overview of all patients presenting to the ED: numbers screened, included, excluded and reasons for exclusion.

died (0.4%) within 30 days compared with 32 (4.6%) of the 727 (47.9%) patients with a D-dimer ≥0.50 mg/l (OR 0.08, 95% CI 0.02–0.27). The sensitivity for 30-day mortality for a D-dimer ≥0.5 mg/l was 91.4%, the negative likelihood ratio of a negative D-dimer test was 0.16 (95% CI 0.05–0.48) and, in this population, the negative predictive value was 99.6%. Of the three deaths of patients with D-dimer <50 mg/l two occurred in patients with metastatic cancer, and one patient died from a traumatic accident that occurred 24 days after discharge (Table 3).

Nine hundred and sixty-one (63.3%) patients had a length of stay of 1 day or more reflecting admission from the ED. Of these patients, 423 (44.0%) had a negative D-dimer; 53.5% of patients with a negative D-dimer were admitted (Figures 2 and 3).

Discussion

Principle findings

This prospective study shows that low D-dimer levels identified patients at low risk of 30-day mortality, confirming the findings of our previous retrospective study.[10] Vital signs alone cannot be used to risk assess ED patients as 19 of the 35 (54%) patients who died within 30 days presented with normal or near normal vital signs. Of the three out of 791 patients with low D-dimer levels who died, two were known to have metastatic cancer and the third died from an unforeseeable traumatic accident. Other studies of D-dimer levels in ED patients have focused on identifying patients at high risk of mortality.[5,7] The only other study that prospectively evaluated the use of D-dimer levels to identify low risk ED patients was on patients with nonspecific complaints such as generalized weakness: it also found an association between low D-dimer levels and reduced 30-day mortality.[9]

Strengths

The major strength of the study is the complete follow-up on all patients. The other strength is that the study was not confined to patients with suspected venous thromboembolic disease: the majority of patients either had no definite discharge diagnosis made or was suffering from circulatory or respiratory disease.

Table 3. Demographic information for all 36 patients who suffered 30-day mortality sorted by low to high D-dimer levels

Patient	D-dimer (mg/l)	NEWS	Age (years)	Primary complaint at arrival	Final diagnosis per medical records	Time to death (days)
1	<0.5	0–1	50–59	Dyspnea	Dyspnea	20–29
2	<0.5	2–6	70–79	Nausea	Pancreatic cancer with liver metastases	20–29
3	<0.5	0–1	80–89	Edema	Lung cancer with liver metastases	10–19
4	0.5–2	0–1	70–79	Dyspnea	Chronic bleeding anemia	10–19
5	0.5–2	2–6	80–89	Bleeding	Colon polyp	20–29
6	0.5–2	0–1	80–89	Chest oppression	Suspicion of lung tumor	20–29
7	0.5–2	2–6	70–79	Dyspnea	Bacterial pneumonia	10–19
8	0.5–2	0–1	70–79	Fatigue	Heart failure	10–19
9	0.5–2	2–6	90–99	General deterioration	Pneumonia	0–9
10	0.5–2	2–6	70–79	Laboratory abnormalities	Chronic obstructive pulmonary disease with acute exacerbation	10–19
11	0.5–2	7+	80–89	Dyspnea	Bacterial pneumonia	0–9
12	0.5–2	7+	90–99	Chest pain	Stroke	10–19
13	0.5–2	2–6	60–69	Fatigue	Lung cancer	20–29
14	2–5	2–6	50–59	Abdominal pain	Ileus	0–9
15	2–5	0–1	80–89	Generalized weakness	Acute duodenal ulcer with bleeding	10–19
16	2–5	2–6	80–89	Dyspnea	Stroke	10–19
17	2–5	2–6	70–79	Edema	Acute kidney failure	20–29
18	2–5	0–1	60–69	Dizziness	Bacterial infection	20–29
19	2–5	2–6	80–89	Dyspnea	Anemia	20–29
20	2–5	2–6	80–89	Generalized weakness	Pulmonary embolism	10–19
21	2–5	7+	50–59	Swollen arm	Cellulitis	10–19
22	2–5	2–6	70–79	Abdominal pain	Pneumonia	20–29
23	2–5	2–6	80–89	Dyspnea	Pulmonary embolism	0–9
24	2–5	2–6	60–69	Dyspnea	Heart failure	20–29
25	2–5	0–1	80–89	Back pain	Prostate cancer with metastases	20–29
26	5+	0–1	90–99	Abdominal pain	Suspected illness or condition	20–29
27	5+	2–6	50–59	Headache	Convulsions	20–29
28	5+	0–1	70–79	Chest pain	Suspicion of myocardial infarction	0–9
29	5+	0–1	80–89	General deterioration	Neutropenic fever of cytostatic treatment	10–19
30	5+	7+	60–69	Dyspnea	Hepatocellular carcinoma with metastases	0–9
31	5+	0–1	50–59	Dyspnea	Dyspnea	10–19
32	5+	2–6	80–89	No complaints	Bradycardia	0–9
33	5+	2–6	70–79	General deterioration	Acute myeloid leukemia	10–19
34	5+	0–1	70–79	Abdominal pain	Tumor of the digestive tract	20–29
35	5+	0–1	70–79	Headache	Pancreatic cancer	10–19
36	5+	2–6	80–89	Dyspnea	Hyperglycemia	10–19

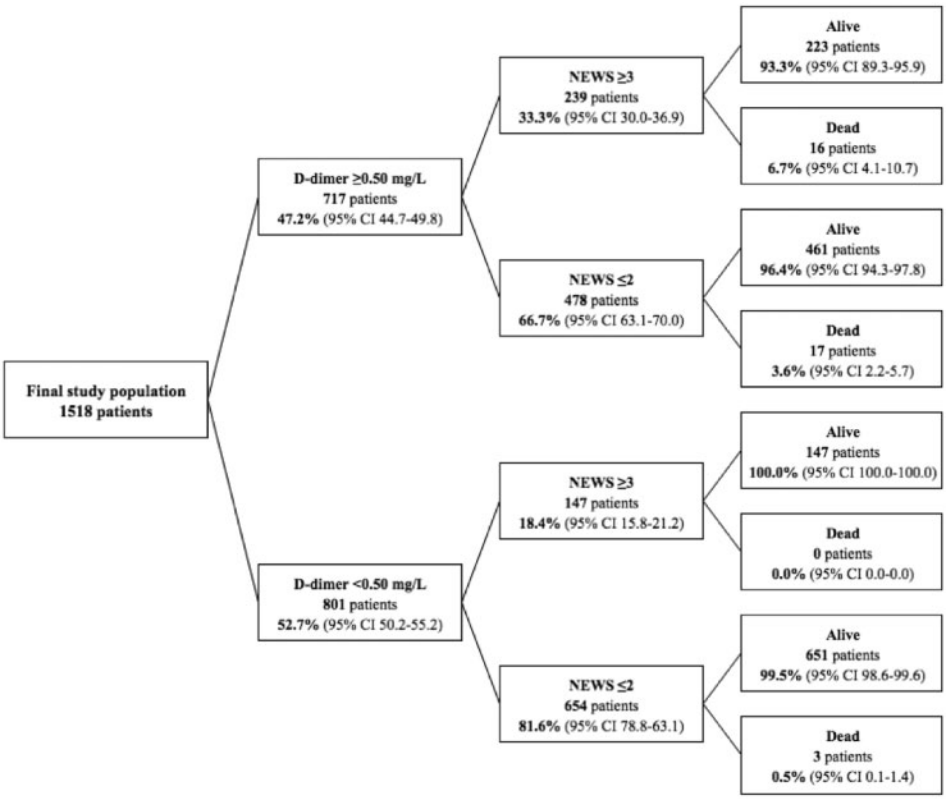


Figure 2. Flow chart of survival status after 30 days of all 1518 patients stratified by D-dimer level (<0.5, ≥0.5 mg/l) and NEWS (≤2, ≥3).

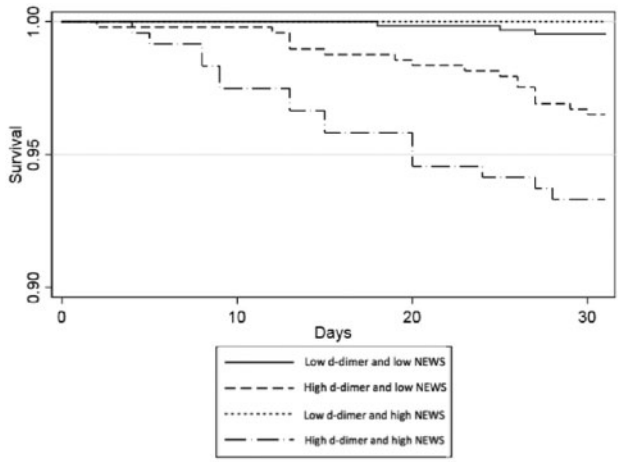


Figure 3. Kaplan–Meier survival curves for 30-day survival status for all 1518 patients stratified into 4 groups by low or high D-dimer level (<0.5, ≥0.5 mg/l) and low or high NEWS (≤2, ≥3). Patients with a low D-dimer and a NEWS ≥3 had the same 30-day survival as those with a low D-dimer and a NEWS ≤2 (log rank *P* 0.41). Patients with a high D-dimer and a NEWS ≥3 had a lower 30-day survival than those with a high D-dimer and a NEWS ≤2 (log rank *P* 0.02).

Only 16 patients were diagnosed with pulmonary embolus and only one of them died.

Limitations

There are several limitations to this study. It is a single-center study performed in a Danish ED. The cohort consists only of patients who required a blood sample on clinical indication. We chose a standard cut-off for D-dimer levels of 0.50 mg/l, but this might not have been optimal. Patients needed to give their informed consent before enrollment, which made it impossible for patients with altered mental status to participate. It is important to note that every patient received treatment, which might have prevented death within the initial 30 days.

Interpretation and clinical applicability

How D-dimer predicts survival is not explained by this study. However, if confirmed by larger multi-centered studies, our findings imply that D-dimer levels should be used more often in clinical practice to ensure safer ED discharges. Currently, D-dimer testing is mostly used to rule out of venous thromboembolic disease in low or intermediate risk patients.[9] More extensive use of D-dimer levels in emergency patients has been proposed,[14] but has not been widely adopted. The test is quick and inexpensive and a low level makes death unlikely. However an abnormal D-dimer level neither predicts death (i.e. 693 patients with a D-dimer ≥0.5 mg/l did not die) nor any particular diagnosis (i.e. it is a nonspecific test). Therefore, D-dimer can be elevated by many different factors and conditions.[15] Unfortunately many clinicians have difficulty grasping the concept that D-dimer is a sensitive, but not a specific test. Therefore, in addition to confirmatory larger studies, a considerable amount of professional education may be required before D-dimer could be used wisely as a routine test.

Conclusion

Normal D-dimer levels identified patients at low risk of 30-day mortality. Since most patients who died within 30 days

presented with normal or near normal vital signs, D-dimer levels appear to provide additional prognostic information.

Funding

This study was performed entirely by the authors and received no outside funding or support.

Conflict of interest: J.K. is a major shareholder, director and chief medical officer of Tapa Healthcare DAC. The other authors have no potential conflicts of interest.

References

1. Sklar DP, Crandall CS, Loeliger E, Edmunds K, Paul I, Helitzer DL. Unanticipated death after discharge home from the emergency department. *Ann Emerg Med* 2007; **49**:735–45.
2. Plesner LL, Iversen AK, Langkjaer S, Nielsen TL, Ostervig R, Warming PE, *et al*. The formation and design of the TRIAGE study—baseline data on 6005 consecutive patients admitted to hospital from the emergency department. *Scand J Trauma Resusc Emerg Med* 2015; **23**:106.
3. 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**:465–70.
4. Royal College of Physicians: National Early Warning Score (NEWS). Standardising the assessment of acute-illness severity in the NHS. *Report of a working party*. RCP, 2013.
5. Crawford F, Andras A, Welch K, Sheares K, Keeling D, Chappell FM. D-dimer test for excluding the diagnosis of pulmonary embolism. *Cochrane Database Syst Rev* 2016; Cd010864.
6. Di Castelnuovo A, de Curtis A, Costanzo S, Persichillo M, Olivieri M, Zito F, *et al*. Association of D-dimer levels with all-cause mortality in a healthy adult population: findings from the MOLI-SANI study. *Haematologica* 2013; **98**:1476–80.
7. Shitrit D, Izbicki G, Shitrit AB, Kramer MR, Rudensky B, Sulkes J, *et al*. Prognostic value of a new quantitative D-dimer test in critically ill patients 24 and 48 h following admission to the intensive care unit. *Blood Coagul Fibrinolysis* 2004; **15**:15–9.
8. Shorr AF, Trotta RF, Alkins SA, Hanzel GS, Diehl LF. D-dimer assay predicts mortality in critically ill patients without disseminated intravascular coagulation or venous thromboembolic disease. *Intensive Care Med* 1999; **25**:207–10.
9. Nickel CH, Kuster T, Keil C, Messmer AS, Geigy N, Bingisser R. Risk stratification using D-dimers in patients presenting to the emergency department with nonspecific complaints. *Eur J Intern Med* 2016; **31**:20–4.
10. Nickel CH, Kellett J, Cooksley T, Bingisser R, Henriksen DP, Brabrand M. Combined use of the National Early Warning Score and D-dimer levels to predict 30-day and 365-day mortality in medical patients. *Resuscitation* 2016; **106**:49–52.
11. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011; **39**:22–5.
12. Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, *et al*. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Epidemiology* 2007; **18**:805–35.
13. Yang JS, Nam HJ, Seo M, Han SK, Choi Y, Nam HG, *et al*. OASIS: online application for the survival analysis of lifespan assays performed in aging research. *PLoS One* 2011; **6**:e23525.
14. Wakai A, Gleeson A, Winter D. Role of fibrin D-dimer testing in emergency medicine. *Emerg Med J* 2003; **20**:319–25.
15. Lippi G, Bonfanti L, Saccenti C, Cervellin G. Causes of elevated D-dimer in patients admitted to a large urban emergency department. *Eur J Intern Med* 2014; **25**:45–8.