#TheSecretIngredient is D-dimer

In this PDF you will find the front page of the papers - and hence the abstracts - published so far by Nickel & Lyngholm *et al* about the *potential* for D-dimer to be used as a biomarker to help identify patients at zero-or-thereabouts risk of dying in the 30 days after ED discharge. We're sorry we can't make the full PDFs downloadable, but sadly they aren't from Open Access journals.

Remember - these are only early evaluations. They do look promising, but **D-Dimer is not yet validated for use in this way in clinical settings.**

D-dimer results must not, at present, influence your clinical decision-making outside how you use them currently (most usually to risk-stratify patients being evaluated for possible VTED in conjunction with a validated risk assessment tool such as the Wells Score). You may have to set this entire discussion from your mind for a few years!

I hope you've enjoyed#TheSecretIngedient discussion… it's really nothing to do with me, but I thought the issues the work throws up are fascinating!
- Dr Linda Dykes @DrLindaDykes

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

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.
© 2016 European Federation of Internal Medicine. Published by Elsevier B.V. All rights reserved.

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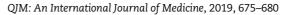
As D-dimer levels increase with age, cut-off values varied significantly between the cited studies; and several studies proposed the adoption of age-dependent reference intervals in clinical practice in the setting of pulmonary embolism [12,13,30–33].

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).

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.

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

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 $\geq 0.50\,mg\,L^{-1}$: 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 $\geq 0.50\,mg\,L^{-1}$. 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

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