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Prognostic significance of a prolonged international normalized ratio in elderly patients in an internal medicine ward

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ABSTRACT

Purpose: To investigate clinical characteristics and the prognostic significance of a prolonged international normalized ratio (INR) without obvious cause or anticoagulant treatment, in elderly inpatients.
Methods: Demographic, clinical, and laboratory data, in-hospital death and 30 day-mortality were prospectively registered for 100 consecutive patients aged ≥75 years admitted to an internal medicine ward for a variety of acute medical disorders, and compared according to normal (≤1.15) and prolonged (> 1.15) INR on admission. Exclusion criteria were: anticoagulant therapy, disseminated intravascular coagulopathy, acute bleeding, liver disease, active malignant disorder, and known coagulopathy.
Results: Prolonged INR was found in 52% of patients. Patients with prolonged INR tended more likely to present with dementia and pressure sores than patients with normal INR. Moreover, patients with prolonged INR more often needed assisted feeding and presented lower mean levels of serum albumin on admission. In-hospital (21.2% vs. 6.2%) and 30-day (32.7% vs. 6.2%) mortality rates were significantly higher in patients with prolonged INR than those with normal INR. On stepwise logistic regression analysis, prolonged INR strongly predicted 30-day mortality (P = 0.004, relative risk 1.67, 95% confidence interval 1.07–2.60).
Conclusions: Prolonged INR without obvious cause or anticoagulant treatment is common among elderly patients admitted to an internal medicine ward, and is associated with a severe clinical profile. Prolonged INR is a powerful predictor of 30-day mortality. Assessment of INR my improve risk stratification for elderly inpatients.

1. Introduction

Measurement of prothrombin time (PT) by international normalized ratio (INR) is routine for screening hemostasis and for monitoring anticoagulant therapy (Kamal, Tefferi, & Pruthi, 2007; Levy, Szlam, Wolberg, & Winkler, 2014). Prolonged PT/INR may be caused by congenital deficiencies of coagulation factors, disseminated intravascular coagulation, liver failure, treatment with anticoagulants, and decreased nutritional intake or malabsorption of vitamin K (Kamal et al., 2007; Levy et al., 2014). Prolonged PT/INR has been shown to predict morbidity and mortality among patients with critical illness (Chakraverty et al., 1996), liver disease (Hernández-Gea & Berzigotti, 2015; Kamath et al., 2001), cancer (Tas, Kilic, Bilgin et al., 2013; Tas, Kilic, Serilmez et al., 2013), and anticoagulant therapy (Curtze et al., 2014; Habib, Nashashibi, Khateeb, Goichman, & Kogan, 2008; Sandén, Renlund, Svensson, & Själander, 2017).

We observed that prolonged INR without obvious cause or anticoagulant treatment is common among elderly patients admitted to an internal medicine ward. Such patients have risk factors for vitamin K deficiency that result in INR prolongation, including older age, impaired nutrition, and the use of broad spectrum antibiotics (Chakraverty et al., 1996; Harrington et al., 2008; Jie, Bots, Vermeer, Witteman, & Grobbee, 1995; Kamal et al., 2007; Tse, Chan, Wu, Cheung, & Kwok, 2002). However, possible differences in clinical characteristics between patients with normal vs. prolonged INR have not been studied. Moreover, the prognostic significance of prolonged INR in this clinical setting has not been investigated. Therefore, we aimed to compare clinical characteristics and short-term mortality between elderly patients admitted to an internal medicine ward according to normal and prolonged INR values.

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Table 1
Characteristics of the patients enrolled in the study.

Variable	Entire group (n = 100)	Normal INR (≤1.15, n = 48)	Prolonged INR (> 1.15, n = 52)	P-value*
Age (years)	84.5 ± 6	83.5 ± 6	85.4 ± 6	0.1
Male sex	53.00%	56.20%	50.00%	0.5
Main reason for admission				
Infection	46.00%	43.70%	48.10%	0.6
Pneumonia	**19.00%**	**18.80%**	**19.20%**	**0.9**
Urinary tract infection	**14.00%**	**8.30%**	**19.20%**	**0.1**
Infected chronic obstructive pulmonary disease	**9.00%**	**10.40%**	**7.70%**	**0.7**
Cellulitis	**4.00%**	**6.20%**	**2.00%**	**0.6**
Cardio-cerebrovascular disorder	39.00%	41.70%	36.50%	0.5
Chest pain	**12.00%**	**12.50%**	**11.50%**	**0.9**
Exacerbated heart failure	**11.00%**	**12.50%**	**9.60%**	**0.6**
Stroke	**5.00%**	**6.20%**	**3.85%**	**0.7**
Syncope	**4.00%**	**4.20%**	**3.85%**	**0.9**
Cardiac arrhythmia	**4.00%**	**4.20%**	**3.85%**	**0.9**
Aggravated hypertension	**3.00%**	**2.10%**	**3.85%**	**0.8**
Other disorder	15.00%	14.60%	15.40%	0.8
Anemia	**8.00%**	**6.20%**	**9.60%**	**0.6**
Acute renal failure	**4.00%**	**4.20%**	**3.90%**	**0.9**
Electrolytes disturbance	**3.00%**	**4.20%**	**2.00%**	**0.8**
Comorbid conditions				
Hypertension	70.00%	64.60%	75.00%	0.2
Diabetes mellitus	43.00%	47.90%	38.50%	0.3
Renal dysfunction	32.00%	25.00%	38.50%	0.1
Heart failure	17.00%	14.60%	19.20%	0.5
Dementia	10.00%	4.20%	15.40%	0.06
Pressure sores	15.00%	8.30%	21.20%	0.07
Independent/assisted feeding	60.00%/40.00%	68.70%/31.30%	51.90%/48.10%	**0.04**
Charlson comorbidity index	3.38 ± 1.8	3.06 ± 1.6	3.69 ± 1.9	0.08
Living in home/long-term care facility	87.00%/13.00%	83.30%/16.70%	90.40%/9.60%	0.3
Laboratory data				
INR (normal 0.84–1.15)	1.18 ± 0.2	1.05 ± 0.1	1.29 ± 0.1	**< 0.001**
Serum albumin on admission (normal 34–53 g/l)	34.1 ± 6	35.3 ± 5	33.0 ± 6	**0.04**
Hypoalbuminemia on admission (< 34 g/l)	42.00%	37.50%	46.20%	0.4
Length of hospital stay (days)	8.1 ± 6	7.8 ± 5	8.4 ± 6	0.6
In-hospital death	14.00%	6.20%	21.20%	**0.03**
30-day mortality	20.00%	6.20%	32.70%	**0.005**

Data are presented as means ± SD or percentages of presented cases.
INR, international normalized ratio.
* Statistical difference between groups with normal and prolonged INR values. Bold entries in the table indicate a *P*-value of ≤0.05.

2. Methods

2.1. Study population and design

The study population comprised consecutive patients aged ≥75 years, admitted for a variety of acute medical disorders to seven internal medicine departments in our medical center, during February 2014. Exclusion criteria were: treatment with any anticoagulant medication, disseminated intravascular coagulopathy, acute bleeding, liver disease, active malignant disorder, and known coagulopathy of any kind. Determinations of complete blood count, routine biochemical tests, and INR were performed within two days from admission. INR was measured using ACL TOP® 500 CTS coagulation analyzer and HemosIL® PT-Fibrinogen HS PLUS reagent, consisting of rabbit brain thromboplastin (Cat. No. 0008469820) with stabilizers, polybrene and buffer (Instrumentation Laboratory, Bedford, MA, USA) (Dargaud et al., 2013).

The study included 100 eligible patients who were divided into 2 groups, according to normal (≤1.15) and prolonged (> 1.15) INR on admission. The cut-off of 1.15 was chosen as the upper limit of normal (0.84–1.15) INR values provided by the laboratory device manufacturer. The primary endpoint of the investigation was 30-day mortality. Our aim was to compare 30-day mortality between the groups. The study was carried out in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee. Informed consent was obtained from the patients or their legally authorized representatives.

2.2. Data collection

Demographic, clinical and laboratory data were collected prospectively from patients' charts and hospital records. Assisted feeding was defined as tube feeding or oral nutrition provided by a caretaker. Pressure sores were defined as injuries that break down skin and underlying tissue, and result from prolonged pressure on the skin. The Charlson comorbidity index was calculated using the method reported by Charlson (Charlson, Szatrowski, Peterson, & Gold, 1994). In-hospital death and 30-day all-cause mortality rates were registered. Information about death was obtained from hospital records and from outpatient death certificates.

2.3. Statistical analysis

The statistical analysis was performed using the Biomedical Package software program (Dixon, 1993). The results were expressed as means and standard deviations for quantitative data and as percentages of presented cases for qualitative data. Statistical comparisons were performed between the data obtained for groups with normal vs. prolonged INR. We determined that a sample size of 50 for each group would provide power of 80.9% to yield a statistically significant result. This computation assumes that the difference in proportions of death is −0.20 (specifically, 0.05 versus 0.25). Pearson's chi-square or Fisher's exact test was applied for comparisons of categorical variables. Analysis of Variance (ANOVA) was used for continuous variables. A *P*-value ≤ 0.05 was considered statistically significant. Variables that