Original Contribution

Short and long-term mortality of patients presenting with bleeding events to the Emergency Department☆,☆☆

Alberto Conti, MD [a],[*], Noemi Renzi, MD [a], Daniele Molesti, MD [a], Simone Bianchi, MD [a], Irene Bogazzi, MD [a], Giada Bongini, MD [a], Giuseppe Pepe, MD [b], Fabiana Frosini, MD [b], Alessio Bertini, MD [c], Massimo Santini, MD [d]

[a] North-West District Tuscany HealthCare, Apuane General Hospital, Emergency Department, Massa-Carrara, Italy
[b] North-West District Tuscany HealthCare, Versilia and San Luca General Hospital, Emergency Department, Viareggio-Lucca, Italy
[c] North-West District, Tuscany HealthCare, Spedali Riuniti Livorno, Emergency Department, Livorno, Italy
[d] North-West District Tuscany HealthCare, Cisanello General Hospital and University of Pisa, Emergency Department, Pisa, Italy

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ABSTRACT

Background: Death of patients presenting with bleeding events to the Emergency Department still represent a major problem. We sought to analyze clinical characteristics associated with worse outcomes including short- and long-term death, beyond antithombotic treatment strategy.
Methods: Patients presenting with any bleeding events during 2016–2017 years were enrolled. Clinical parameters, site of bleeding, major bleeding, ongoing anti-thrombotic treatment strategy and death were collected. Hard 5:1 propensity score matching was performed to adjust dead patients in baseline characteristics. Endpoints were one-month and one-year death.
Results: Out of 166,000 visits to the Emergency Department, 3.050 patients (1.8%) were enrolled and eventually 429 were analyzed after propensity. Overall, anticoagulants or antiplatelets were given to 234(54%). Major bleeding account for 111(26%) patients, without differences between those taking anticoagulants or antiplatelets versus others. Death at one-month and one-year was 26(6%) and 72(17%), respectively. Independent predictors of one-month death were major bleeding (Odds Ratio, OR 26, p < 0.001), female gender (OR 7, p < 0.001) and white blood cells (OR 1.2, p = 0.01); of one-year were major bleeding (OR 7, p < 0.001), age (OR 1.1, p < 0.001) and female gender (OR 2.3, p = 0.043). Of note, death rate of gastrointestinal and intracranial bleeding where higher than others (p < 0.001). Overall mortality was approximately 40% on one-month; 60% in older patients and 80% in female gender with CHA_2D_2VASC-score ≥ 2. Receiver operator characteristics analysis showed larger areas for major bleeding and age (0.75 and 0.72, respectively) over others; p < 0.05 on C-statistic.
Conclusions: In patients with bleeding events, death rate was driven by major bleeding on short-term and older age on long-term. Among dead patients mortality was approximately 40% on one-month; 60% in older patients, and 80% in female gender.

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1. Introduction

Increased risk of any bleeding events in general population is more likely to link with antitrombotic treatment strategies when prevention of arteriosclerotic vascular disease or pulmonary thrombo-embolism is planned. As longer courses of potent regimens are introduced, increased efficacy of treatment strategies may be offset by increases in any bleeding events due to similar importance in influencing mortality as ischemic events. Concern about net clinical benefit in the setting of prevention of thrombosis and thromboembolism still represent a major problem in clinical practice, due to bleeding events especially in aged population and patients with comorbidities, at least [1-4]. Indeed, risk of arteriosclerotic adverse outcomes and risk of bleeding are two sides of the coin in prevention of thrombosis and thromboembolism. Clinical characteristics associated with future increased bleeding risk include older age, female gender, comorbidities as hypertension, kidney disease, anemia, diabetes mellitus and previous history of bleeding [5-7]. In this setting, risk factors eventually associated with short-term or long-term worse outcomes including mortality, in patients with or without antithrombotics, need to be better focused.

Nowadays, evidence-based decision making should result in the choice of appropriate pharmacologic strategies among antiplatelets, indirect antithrombin therapy as vitamin K antagonist and direct oral

anticoagulants that will offer the best balance of benefit and risk with the goal of optimizing outcomes. However, structured data on bleeding patients has been limited to controlled clinical trial settings, based on major bleeding events, and the real life scenario in the general population presenting to the Emergency Department is still lacking [8].

Aim of the present study was to analyze clinical characteristics which could be associated with adverse outcomes, including one-month and one-year death, in patients with any bleeding events, with or without antithrombotics, as the main reason of presentation to the Emergency Department.

2. Patients and methods

2.1. Setting

The north-west district of the Tuscany healthcare with catchment area of 200,000 inhabitants and the Apuane community hospital, which play as referral center for 80–85.000 emergency department visits per year, were involved in the study.

2.2. Study design

This retrospective study was conducted during the years 2015 and 2016. Clinical data of all patients presenting to the Emergency Department were inserted in a structured medical chart review. Inclusion criterion was the presence of any recent-onset bleeding events regardless ongoing treatment strategy and comorbidities. The only criterion of exclusion was age <18 years. The Emergency Department institutional review board approved the protocol. Departmental sources supported the work and no contributorship or competing interest existed. Each patient gave informed consent to publication of personal data. The study was conducted in accordance with good clinical practice and principles of the Declaration of Helsinki.

2.3. Data collection and management of patients

Clinical data, comorbidities and pharmacological treatment of the patients enrolled in the study were self-reported and confirmed after reviewing the clinical charts. Patients were most likely to submit to instrumental evaluation, observation or discharged on the basis of clinical evolution. The therapeutic approach and disposition were at the discretion of the physician on duty. All the patients underwent clinical evaluation, serial blood tests, blood gas analysis and ECG, on presentation. Subgroup analysis based on clinical parameters, major or minor bleeding, site of bleeding, ongoing anti-thrombotic treatment strategy including low molecular weight heparin, warfarin, aspirin, clopidogrel, direct oral anticoagulants were collected. Need of reversal treatment or blood transfusion and adverse outcomes including admission to hospital and short- and long-term death were collected, too. Major bleeding was defined according to the statement of the International Society of Thrombosis and Haemostasis (6,7). Minor bleeding events were those which did not fulfilled criteria of major bleeding. If patient had previous bleeding event but stopped upon arrived, we considered haemoglobin level compared with previous data on hospital file or by reviewing charts, in order to confirm major or minor bleeding. Bleeding event as the main reason of presentation was self-reported by patients or certified by practitioners. All the patients with haemodynamic instability were strongly recommended for reversal treatment and blood transfusion, and eventually admission. Haemodynamic instability was defined by the presence of systolic blood pressure ≤ 100 mm Hg [9].

2.4. Endpoint

The primary endpoint was death; subgroup analysis based on short-term (one-month) and long-term (one-year) death was performed. Death patient, as all-cause mortality, was confirmed by phone follow-up or searching in the hospital electronic charts or eventually local municipal death registry.

2.5. Statistical analysis

Summary data are expressed as absolute numbers and percentage for categorical variables while mean ± SD for continuous values. Statistical comparisons of demographic and clinical features were performed using the χ^2 test and the Pearson exact test for categorical variables, whereas the Student's t-test was used for continuous variables (Wilcoxon rank-sum test). Indeed, the Student's t-test was used to compare the mean values of normally distributed continuous variables, whereas the Mann-Whitney U test was used to compare non-normally distributed continuous variables. The chi-squared or Fisher's exact test was used for categorical variables. A 2-sided P value of <0.05 was considered to be statistically significant. Kaplan–Meier methods were used to estimate death event rates at the one month and one-year follow-up in patients with any bleeding events and to plot time-to-event curves. Because there were differences in baseline characteristics between patients who died versus who did not, propensity score matching was used to adjust for possible confounders. SPSS software allows estimation of the propensity score using logistic regression and specifying nearest-neighbor matching. Detailed balance statistics and graphs are produced by the program. A hard 5:1 matched analysis based on the propensity score of each patient was conducted to adjust dead patients in baseline characteristics. To ensure good matches, a small caliper (maximum allowable difference between two participants) of 0,15 was defined. Variables included in the model were age, gender, hypertension, hypercholesterolemia, diabetes mellitus, active smoking, known coronary heart disease, known peripheral vascular disease, prior stroke/transient ischemic attack, cardiomyopaty, chronic kidney disease, heart rate, systolic arterial pressure, and CHA_2D_2VASC-score. Comparisons were made using the log-rank test or the stratified log-rank test in the propensity score–matched cohort. Cox analysis regression model was performed to identify independent predictors for death at one-month and one-year. Sensitivity analysis using backward logistic regression for all the clinical variables and comorbidities considered in the study were carried out; the clinical variables which were found to have a probability value < 0.05 were subjected to multivariate backward logistic regression analysis. Receiver Operator Curve analysis was obtained for variables of clinical interest in order to detect the optimal cut-off value of sensitivity/specificity in patients with any bleeding events who died during follow-up period. Calculations were performed using SPSS version 21(SPSS Inc., Chicago, Illinois, USA) for analysis.

3. Results

3.1. General

Out of 166,000 visits to the Emergency Department due to any bleeding events, 3050 patients (1.8%) were enrolled (mean age 72 ± 17 year), and 429 patients were eventually analyzed after propensity matching.

The chart of time to clinical evaluation, management and main outcomes on one-month and one-year follow-up of patients enrolled in the study is shown in the Fig. 1. Death on one-month and one-year account for 26(6%) and 72(17%), respectively. Overall, 200(47%) patients were admitted and 21(5%) underwent reversal treatment strategy or blood transfusion. Patients stratified by the different site of bleeding are shown in the Fig. 2. Major bleeding account for 111(26%) patients of whom 22% gastrointestinal bleeding, 21% intracranial, 18% epistaxis, 19% haematuria, 9% gynecological bleeding, 7% hemoptysis, and 4% eye bleeding. Baseline clinical characteristics of patients stratified according to one-month and one-year death are shown in the Table 1. Among comorbidities, ischaemic vascular diseases account for 112(26%) patients, cancer 169(39%), dilated cardiomyopathy 46(11%),