Received: 4 May 2020 | Accepted: 31 July 2020

DOI: 10.1111/jth.15048

ORIGINAL ARTICLE

Definition of major bleeding: Prognostic classification

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Abstract

Background: In patients on anticoagulant treatment, the major bleeding (MB) definition released by the International Society of Thrombosis and Haemostasis (ISTH) is widely accepted. However, this definition identifies MBs with highly variable short-term risk of death.

Objectives: The study aims were to derive and validate a classification of ISTH-defined MBs for the risk of short-term death.

Methods: Consecutive patients admitted for ISTH-defined MB occurring while on treatment with oral anticoagulants were included in the study and divided into a derivation and a validation cohort. Death within 30 days was the primary study outcome.

Results: Among 1077 patients with MB, 64/517 and 63/560 patients in the derivation and validation cohort died, respectively. In the derivation cohort, Glasgow coma scale (GCS) <14 and shock were predictors of death; critical site bleeding and hemoglobin decrease ≥2 g/dL, or transfusion ≥ 2 units were not. GCS <14 (hazard ratio [HR], 8.67; 95% confidence interval [CI], 3.93-19.13) was predictor of death in intracranial hemorrhage (ICH) and shock at admission (HR, 4.84; 95% CI, 2.01-11.70) and pericardial bleeding (HR, 11.37; 95% CI, 1.33-97.31) in non-ICH MBs. The predictive value of GCS <14 in ICH and shock and pericardial bleeding in non-ICH MBs was confirmed in the validation cohort. None of the patients with isolated ocular or articular bleeding died.

A prognostic classification of ISTH-defined MBs for the risk of short-term death is proposed as "serious," "severe," and "life-threatening" (ICH with GCS <14 or non-ICH with shock) MBs.

Conclusion: According to our study, ISTH-defined MBs can be stratified for the risk of death within 30 days.

KEYWORDS

anticoagulants, bleeding, classification, hemorrhage, mortality

Manuscript handled by: Willem Lijfering

Final decision: Willem Lijfering, 31 July 2020

1 | INTRODUCTION

Major bleeding (MB) is the main complication of anticoagulant therapy. Several definitions of MB have been used in studies with antithrombotic agents. In 2005, the Control of Anticoagulation Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) released a definition for MB to be used in non-surgical patients receiving anticoagulant treatment.[1] The aim of this definition was to make interpretation of results and their comparisons from different studies easier. The ISTH definition of MBs is widely accepted and used in clinical trials. However, this definition identifies a highly heterogeneous group of bleeding events with variable severity in clinical presentation and clinical course, such making the assessment of the risk-to-benefit ratio of anticoagulant treatments difficult.[2] In clinical practice, heterogeneity translates in different early management strategies of MBs in terms of timings and strategies. A prognostic classification of MBs could be of value for practicing clinicians for the interpretation of the results of clinical trials as well as for clinical decision making.

Subanalyses of recent trials proposed categorizations of MBs based on their severity.[3-6] However, the optimal criteria for prognostic classification remain a matter of debate. To be useful for practicing clinicians the classification should include easily and rapidly available criteria. In a previous study we showed that Glasgow Coma Scale (GCS) and shock are associated with death in patients with MB occurring during anticoagulant treatment.[7]

The aim of this multicenter study was to derive and validate a prognostic classification of ISTH-defined MB that could be uniformly applicable to clinical trials, observational studies, and clinical practice.

Essentials

- The ISTH definition identifies MBs with highly variable short-term risk of death.
- The study aims were to derive and validate a prognostic classification of ISTH-defined MBs.
- Glasgow coma scale <14 and shock were predictors of death in patients with MB while on oral anticoagulants.
- A prognostic classification of MBs is proposed as 'serious', 'severe' and 'life-threatening'.

2 | METHODS

We performed a prospective, international, cohort study in patients with MBs occurring while on oral anticoagulant treatment. MBs was defined according to the ISTH criteria.

2.1 | Objectives

The objectives of this study were:

1. To derive a prognostic classification of ISTH-defined MB;
2. To validate the prognostic classification of ISTH-defined MBs

Both according to the risk of death within 30 days.

2.2 | Outcomes

The primary outcome of the study was short-term death defined as death occurring within 30 days from hospital admission.

2.3 | Patients

The study population for this analysis was obtained by merging two main ongoing prospective cohorts described elsewhere.[2] More specifically, the first cohort includes consecutive patients admitted for MB while on treatment with oral anticoagulants, either vitamin K antagonists or direct oral anticoagulants (DOACs), at participating centers, all in Italy.[2] The second cohort includes those patients from the Dresden NOAC registry who experienced an MB during follow-up.[8] The present analysis was conducted in patients included in the two cohorts from January 2013 to November 2018. Patients were excluded in case of incomplete data availability on clinical outcome of index MB. Patients were included regardless of the clinical indication for anticoagulation.

Major bleeding was defined according to the criteria of ISTH as clinically overt bleeding which was fatal or associated with any of the following: (a) a fall in hemoglobin level of 2 g/dL or more or documented transfusion of at least 2 units of packed red blood cells, (b) involvement of a critical anatomical site (intracranial, spinal, ocular, pericardial, articular, intramuscular with compartment syndrome, retroperitoneal).[1]

For the purpose of this analysis, the study population was divided into (a) a derivation cohort to assess predictors of death and derive a prognostic classification of ISTH-defined MBs; (b) a validation cohort to validate the prognostic value of the classification of ISTH-defined MBs.

The derivation and validation cohorts were obtained by dividing the study population in two groups with similar number of consecutive patients.

2.4 | Data collection

The following data were collected: patient characteristics (demographic data, comorbidities, indication to anticoagulant therapy, concomitant medications, vital signs, and GCS), features of bleeding episode and its management (site, hemoglobin value, number of transfusions, invasive or noninvasive procedures, reversal therapies), clinical outcome (length of hospital stay, death, complications).

Shock was defined as systolic blood pressure lower than 90 mm Hg or a pressure drop of 40 mm Hg or over for at least 15 minutes not due to a cause different from bleeding and associated with signs of hypoperfusion. Concerning the GCS, patients were categorized as having GCS <14 or GCS ≥14.

Renal impairment and liver diseases were defined as previously reported.[2]

2.5 | Statistical analysis

Continuous data are reported as means ± standard deviations. Student *t* test and the χ^2 test were used for comparisons of continuous and nominal variables, respectively. *P* values below .05 were considered statistically significant in all analyses. All *P* values were two-tailed, and 95% confidence intervals (CI) were also reported.

2.5.1 | Derivation

In the derivation cohort we determined the association between death within 30 days and the individual items of the ISTH definition of MB (fall in hemoglobin level of 2 g/dL or more or transfusion of at least 2 units of packed red blood cells and bleeding in a critical site) as well as predefined parameters of clinical severity (presence of shock and GCS <14) by univariate analyses. The association between individual critical sites of bleeding and death was also assessed. Univariate predictors of death ($P < .05$) were included in multivariate analyses. The prognostic classification of ISTH-defined MB was derived from the set of multivariate predictors of death ($P < .05$). Univariate and multivariate analyses were performed by the Cox proportional risk model and reported as hazard ratio (HR) and 95% CI, assuming that follow-up times could have been different for each patient.

According to the results of multivariate analyses, three categories of ISTH-defined MB were identified; the categories have to be associated with a low, intermediate, or high risk for death and would be denominated as "serious," "severe," and "life-threatening" MB.

2.5.2 | Validation

The prognostic classification of ISTH-defined MB was then validated in a different patient population (validation cohort). To assess the discriminatory power of our classification to predict death within 30 days, we used the area under the receiver operating characteristic curve. The C-statistics were also calculated.

3 | RESULTS

Between January 2013 and November 2018, 1455 patients who experienced MB while on oral anticoagulant therapy were evaluated for inclusion in the study. After case revision, 378 patients were excluded (305 were adjudicated as non-MB according to ISTH criteria and 73 because of incomplete data); thus, 1077 patients with MB were included in the analysis (Figure 1).

At the time of MB, 580 patients were on anticoagulant therapy with vitamin K antagonists (54%) and 497 (46%) with DOACs.

The study population of the derivation cohort, composed of 517 patients, experienced MB between January 2013 and December 2014, and the validation cohort, composed of 560 patients, experienced MB between January 2015 and November 2018. The flowchart of the study was reported in Figure 1.

Atrial fibrillation was the main indication for anticoagulant therapy both in derivation cohort (75%) or in validation cohort (82%).

The main patient features at the time of MB are reported in Table 1. The derivation and validation cohorts were similar except for the prevalence of MB occurring while on DOACs that was lower in the derivation compared with the validation cohort (34% vs 57%; odds ratio [OR], 0.38; 95% CI, 0.29-0.48). Patients in the derivation cohort had a higher prevalence of renal impairment (26% vs 18%; OR, 1.65; 95% CI, 1.23-2.20) compared with patients in the validation cohort. In both cohorts, the majority of MBs were spontaneous (66% and 68% in derivation and validation cohorts, respectively). The distribution of bleeding sites was similar in the derivation and validation cohorts (Figure S1).

Concerning the ISTH criteria for MB, the prevalence of MB in a critical site as well as the proportion of patients with a fall in hemoglobin level ≥2 g/dL or receiving transfusion of ≥2 units of red blood cells did not differ between the derivation and the validation cohort (Table 2).

Death within 30 days occurred in 12% (64/517) and 11% (63/560) of patients in the derivation and validation cohort, respectively. The mean duration of hospitalization was 12 days in both the cohorts.

3.1 | a) Derivation cohort

The results of the univariate analysis for death within 30 days are reported in Table 3.

Among ISTH criteria for MB, bleeding in a critical site was associated with increased risk for death within 30 days (HR, 2.94; 95% CI, 1.67-5.19), mainly if pericardial bleeding or intracranial hemorrhage (ICH). Fall in hemoglobin ≥2 g/dL or transfusion ≥2 units of red blood cells were inversely associated with death within 30 days (HR, 0.48; 95% CI, 0.29-0.82). None of the patients with isolated ocular or articular bleeding died as it was the case for the four patients with muscular hematoma with compartment syndrome. Among features of clinical severity, both shock and GCS <14 at admission were associated with death within 30 days (Table 3 and Table S2). Death rates for individual bleeding sites according to parameters of clinical severity in derivation cohort are reported in Table S1.

At multivariate analysis, shock at admission and GCS <14 were predictors of death within 30 days. Bleeding in a critical site and fall

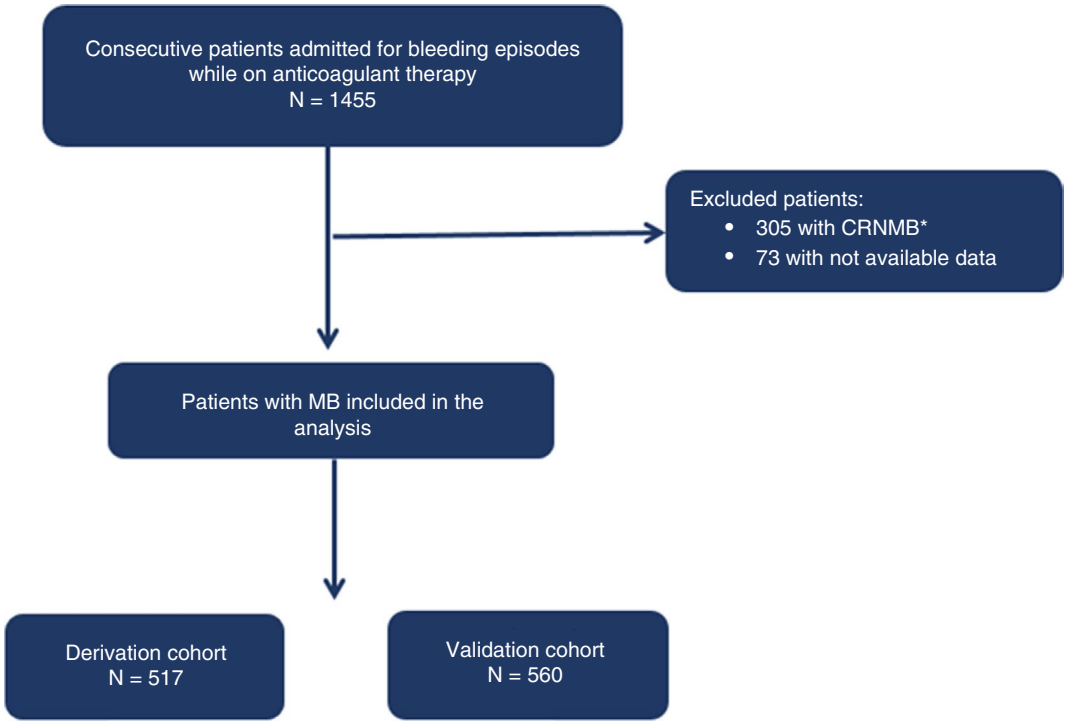

FIGURE 1 Flow-chart of the study. CRNMB, clinically relevant non-major bleeding

in hemoglobin level ≥2 g/dL or transfusion of 2 units of red blood cells were not associated with increased risk for death (Table 3 and Table S2).

A multivariate model including individual critical site of MB associated with death at univariate analysis, showed that shock at admission, GCS <14 and pericardial bleeding were predictors of death (Table 3 and Table S2). When testing for interaction between ICH and GCS <14, it emerged that none of the patients with GCS ≥14 and non-ICH MB died. Thus, an interaction could not be formally excluded. As expected, the rate of death within 30 days in patients with ICH, was higher in presence of GCS <14 compared with GCS ≥14 (51% vs 7%) (Table S1). Among patients with ICH, GCS <14 was a predictor of death within 30 days (HR, 8.67; 95% CI, 3.93-19.13). Among patients with non-ICH MB, shock at admission (HR, 4.84; 95% CI, 2.01-11.70) and pericardial bleeding (HR, 11.37; 95% CI, 1.33-97.31) were predictors of death within 30 days (Table 4).

3.2 | b) Validation

In the validation cohort, multivariate analysis in patients with ICH confirmed GCS <14 as a predictor of death within 30 days (HR, 5.38; 95% CI, 2.52-11.46). In patients with non-ICH MB, shock at admission (HR, 3.52; 95% CI, 1.21-10.22) and pericardial bleeding (HR, 9.37; 95% CI, 1.71-51.25) were predictors of death within 30 days (Table 5). None of the patients with bleeding in the ocular or articular sites in the validation cohort died within 30 days.

Finally, we classified MB as "serious" (site-related and not associated with death), "severe," and "life-threatening" (ICH with GCS lower than 14 or non-ICH MB with shock at admission), according to significant different mortality rate (Table 6, Figure 2, and Figure S2). Severe MB was defined as ICH with GCS ≥ 14 or non-ICH MB without shock and was associated with a mortality ranging between 4% and 8%. Life-threatening MB was associated with a risk of death ranging between 21% and 51%.

The C-statistic showed a good discriminatory power of our classification of ISTH-defined MB to predict death within 30 days (0.75; 95% CI, 0.67-0.83).

4 | DISCUSSION

Our study shows that ISTH-defined MBs are associated with different risk for death within 30 days. GCS <14 and shock at admission can be used to identify ICHs and non-ICH MBs, respectively, at highest risk for death. On the other hand, articular or ocular bleedings, although disabling, have a negligible risk for death. According to our results, ISTH-defined MBs can be classified as "disabling," "severe," and "life-threatening" according to their clinical course. Therapeutic implications of this classification require evaluation in ad hoc studies.

The ISTH definition of MB was released to identify as major those bleeds that result in death, are life-threatening, cause chronic sequelae or consume major health care resources and was extremely useful for standardization of outcome definition in clinical trials with

TABLE 1 Characteristics of patients with MB (ISTH criteria for MB), divided into derivation and validation cohorts

Characteristics, n (%)	Patients with MB		
	Overall (n = 1077)	Derivation Cohort (n = 517)	Validation Cohort (n = 560)
Male	605 (56)	269 (52)	336 (60)
Age, mean ± SD (range)	79 ± 9 (16-99)	78 ± 9 (36-97)	80 ± 10 (16-99)
AF VTE	855 (79) 118 (11)	392 (76) 61 (12)	463 (83) 57 (10)
DOACs	497 (46)	175 (34)	322 (57)
Arterial hypertension	772 (72)	371 (72)	401 (72)
Diabetes	278 (26)	134 (26)	144 (26)
Previous bleeding	277 (26)	134 (26)	143 (25)
Renal failure	234 (22)	135 (26)	99 (18)
Liver disease	38 (3)	22 (4)	16 (3)
Previous stroke	209 (19)	109 (21)	100 (18)
Active cancer	140 (13)	67 (13)	73 (13)
Vascular disease	293 (27)	145 (28)	148 (26)
Heart failure	296 (27)	145 (28)	151 (29)
NSAIDs/antiplatelets	149 (14)	82 (16)	67 (12)
Traumatic bleeding	351 (33)	174 (34)	177 (32)
Shock	88 (8)	40 (8)	48 (9)
GCS <14	143 (14)	60 (12)	83 (16)

Abbreviations: AF, atrial fibrillation; DOACs, direct oral anticoagulants; GCS, Glasgow Coma Scale; MB, major bleeding; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; VTE, venous thromboembolism.

TABLE 2 Clinical presentation of MB (ISTH criteria for MB)

	Patients with MB		
	Overall (n = 1077)	Derivation Cohort (n = 517)	Validation Cohort (n = 560)
Transfusion ≥2 units or Hb ≥2 g/dL	626 (58)	307 (59)	319 (57)
Transfusion ≥2 units	502 (47)	251 (48)	251 (45)
Hb ≥2 g/dL	597 (55)	294 (55)	303 (54)
Muscle (compartment syndrome)	12 (1)	4 (1)	8 (1)
Ocular	16 (1)	12 (2)	4 (1)
Pericardial	3	1	2
Retroperitoneal	33 (3)	16 (3)	17 (3)
Spinal	5	4 (1)	1
Articular	18 (2)	14 (3)	4 (1)
ICH	416 (39)	196 (38)	220 (39)

Abbreviations: Hb, hemoglobin; ICH, intracranial hemorrhage; MB, major bleeding.

anticoagulant agents.[9] However, this definition can be not appropriate in driving clinical management of MBs in the initial phase (reversal, invasive procedure, etc) and in the long-term phase (resumption of treatment, risk to benefit balance).[9] We derived and validated a classification of ISTH-defined MBs based on the risk for death within 30 days.

The acute management of bleedings occurring during anticoagulant treatment should be tailored on the severity of the event.[10-14] This is the case for the clinical use of antidotes for reversal of anticoagulant effect of direct oral anticoagulants that should be limited to patients with potentially life-threatening acute overt bleeding.[15-17] After evaluation in intervention studies,

TABLE 3 Univariate and multivariate analyses of predictors of death at 30 d in derivation cohort

	Death % (n/N)	Univariate		Multivariate I		Multivariate II	
Derivation Cohort	**12 (64/517)**	**HR (CI 95%)**	***P***	**HR (CI 95%)**	***P***	**HR (CI 95%)**	***P***
ISTH criteria for MB							
Fall Hb ≥ 2 g/dL or transfusion ≥ 2 units of RBCs	9 (28/307)	0.48 (0.29-0.82)	.007	0.78 (0.35-1.72)	.537	0.59 (0.25-1.40)	.232
Critical site	18 (45/247)	2.94 (1.67-5.19)	<.001	1.77 (0.72-4.30)	.209	-	
Pericardial	100 (1/1)	24.56 (3.29-183.45)	.008	-		15.70 (1.91-129.22)	.010[a]
ICH	20 (40/196)	3.17 (1.85-5.45)	<.001	-		1.09 (0.39-2.99)	.864
Spinal	25 (1/4)	2.38 (0.24-23.24)	.44	-		-	
Retroperitoneal	19 (3/16)	1.66 (0.46-6.01)	.43	-		-	
Muscle (compartment syndrome)[b]	0 (0/4)	-		-		-	
Ocular[b]	0 (0/12)	-		-		-	
Articular[b]	0 (0/14)	-		-		-	
Parameters of clinical severity							
Shock	27 (11/40)	3.03 (1.43-6.43)	.003	4.56 (2.02-10.29)	<.001	3.75 (1.60-8.81)	.002
GCS <14	49 (29/60)	11.69 (6.28-21.77)	<.001	5.33 (3.02-9.42)	<.001	5.93 (3.15-11.17)	<.001

Note: Multivariate model I includes ISTH criteria for MB and parameters of clinical severity that were significant univariate predictors of death. Multivariate model II includes individual critical sites bleeding that were significant univariate predictors of death.

Abbreviations: CI, confidence interval; GCS, Glasgow Coma Scale; Hb, hemoglobin; HR, hazard ratio; ICH, intracranial hemorrhage; RBCs, red blood cells.

[a]Only one patient with pericardial bleeding (risk for overfit).

[b]No patient died in this subgroup.

TABLE 4 Multivariate analysis for predictors of death at 30 d in the derivation cohort

Derivation Cohort	HR (CI 95%)	*P*
ICH		
Fall Hb ≥2 g/dL or transfusion ≥2 units of RBCs	0.58 (0.20-1.67)	.316
GCS <14	8.67 (3.93-19.13)	<.001
Non-ICH		
Fall Hb ≥2 g/dL or transfusion ≥2 units of RBCs	0.58 (0.13-2.62)	.484
Shock	4.84 (2.01-11.70)	<.001
Pericardial	11.37 (1.33-97.31)	.026

Abbreviations: CI, confidence intervals; GCS, Glasgow Coma Scale; Hb, hemoglobin; HR, hazard ratio; ICH, intracranial hemorrhage; RBCs, red blood cells.

TABLE 5 Multivariate analysis for predictors of death at 30 d in the validation cohort

Validation Cohort	HR (CI 95%)	*P*
ICH		
Fall Hb ≥2 g/dL or transfusion ≥2 units of RBCs	1.70 (0.40-7.18)	.469
GCS <14	5.38 (2.52-11.46)	<.001
Non-ICH		
Fall Hb ≥2 g/dL or transfusion ≥2 units of RBCs	0.45 (0.14-1.42)	.175
Shock	3.52 (1.21-10.22)	<.021
Pericardial	9.37 (1.71-51.26)	.010

Abbreviations: CI, confidence interval; GCS, Glasgow Coma Scale; Hb, hemoglobin; HR, hazard ratio; ICH, intracranial hemorrhage; RBCs, red blood cells.

our prognostic classification could be used to drive clinical management of MBs in the initial phase. Moreover, our prognostic classification could be of value for a more appropriate balance between thrombotic and bleeding complications when assessing either the indication for anticoagulation or the results of clinical trials with anticoagulant treatments. In fact, although evaluation of all bleeding events associated with antithrombotic treatments is of some interest, the emphasis is generally on the most clinically relevant MB.

The prognostic stratification of MBs is of renewed interest in the DOACs era. These agents are replacing vitamin K antagonists in several clinical conditions for their improved safety profile and practicality. MBs seem to be less common with DOACs than with vitamin K antagonists and to have different pattern with DOACs or vitamin K antagonists[3-5,18-21]; in patients receiving DOACs, ICH is less frequent and gastrointestinal and urogenital MBs more common compared with patients receiving vitamin K antagonists.[2,22-24] Post hoc analyses of randomized

TABLE 6 Prognostic classification of MBs according to risk of death within 30 d

Categories of MB	Grade	Definition	Mortality	
			Derivation	Validation
Serious	I	Articular, ocular	0/26 (0%)	0/8 (0%)
Severe	IIa	ICH with GCS ≥14	8/114 (7%)	9/117 (8%)
	IIb	Non-ICH MBs without shock or hypotension	15/260 (6%)	12/294 (4%)
Life-threatening	IIIa	ICH with GCS <14	29/57 (51%)	30/74 (40%)
	IIIb	• Non-ICH MBs with shock or hypotension • Pericardial	10/38 (26%)	9/43 (21%)

Colors indicates the underline categories with different risk of death (from mild= green to maximum of severity= red).

Abbreviations: GCS, Glasgow Coma Scale; ICH, intracranial hemorrhage; MB, major bleeding.

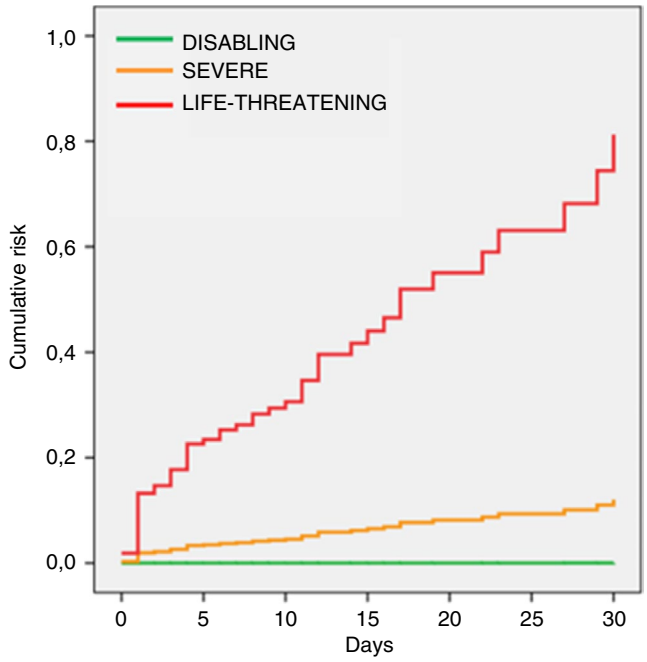

FIGURE 2 Risk of death at 30 days, according to category of MB. Serious: articular or ocular MB. Severe: ICH with GCS ≥14 or non-ICH MBs without shock or hypotension. Life-threatening: ICH with GCS <14, non-ICH MBs with shock or hypotension or pericardial MB

trials in patients treated for venous thromboembolism were recently performed aimed at comparing the severity of MB occurring with DOACs versus standard anticoagulant therapy.[3-6] For the purpose of these analyses, MBs were post hoc classified as being or not a clinical emergency or to rapidly leading to death.[3-6] The retrospective nature of the analyses and the subjective component of the severity assessment may have influenced the results and may limit their clinical value.[3] The value of the prognostic classification of MBs derived and validated in our study mainly consists on the use of standardized parameters of clinical severity (GCS and shock) that are easy to evaluate and promptly available in clinical practice.

In our study, the site of MB influenced the clinical outcome. Ocular or articular MB (ISTH-defined critical sites) may result in organ disability without being a life-threatening medical condition. The remaining MBs are associated with death, the rate ranging from 7% to 100%. However, beside the site of MB, prognosis is driven by features of clinical severity like the GCS in patients with ICH and the presence of shock in patients with non-ICH MB. According to our results, ICH should be considered as life-threatening only when associated with GCS <14. Non-ICH MBs only when associated with shock. Moreover, it should be considered that some MB such as pericardial or spinal bleeding are rare events. The statistical power of the analysis including these variables is therefore limited; however, beyond statistics, the concept of pericardial bleeding as a life-threatening condition is also clinically plausible.

A fall in hemoglobin level ≥ 2 g/dL or transfusion of 2 units of red blood cells was not a predictor of death in our study. This ISTH criterion has two main limits: (a) lacking of a temporal limit for definition of hemoglobin reduction and (b) lacking of standard criteria for prescription of blood transfusions. Moreover, assessment of fall in hemoglobin requires availability of sequential values over time.

We used death within 30 days as the primary outcome. Having MB-related death instead of all-cause death as primary outcome could have been more appropriate but this approach was limited by the lack of autopsy confirmation in almost all the patients. Moreover, having all-cause death as primary outcome will allow a comprehensive evaluation of the burden of the bleeding event. Similar studies on this issue also considered death within 30 days as the primary outcome.[8,25]

Our study has a number of limitations. First, this is an observational registry, and data from registries are susceptible to selection bias. This could be related to the exclusion of cases for data unavailability on clinical outcome. The inclusion of patients regardless of the clinical indication for anticoagulation could represent an additional issue. However, our analysis was based on data from two countries and different departments and settings, increasing the representativeness of our study population in comparison to the general population. Second, given the observational nature of the study, the

management of MBs were left to the attending physician and this could have influenced patients' clinical course. Moreover, because the management of MBs is highly dependent on several factors (clinical presentation, availability of agents and facilities, local experience), we preferred not to include it as a criterion for classification of the severity of the event. Finally, the follow up of our study is limited to the hospital stay or to 30 days, whichever came first; no follow up was scheduled after discharge. Finally, although our study includes a large population of patients with MB while on anticoagulant treatment, the sample size is small at least for some subgroups, this potentially leading to underpower in some analyses.

Our study has also some strengths. First, the prospective design of the study allowed the severity assessment in a more reproducible way. The criteria for the proposed prognostic classification are promptly available and reproducible in clinical practice also in the urgent setting such making it a promising tool for decision making in clinical practice as well as in potential future studies.

In conclusion, in this observational, multicenter study, we derived and validated a prognostic classification of ISTH-defined MB. This prognostic classification could be uniformly applicable to clinical trials, observational and epidemiologic studies. Whether this classification may be useful for driving the management of ISTH-defined MB should be evaluated in further studies.

CONFLICT OF INTEREST

Dr. Becattini reports lectures fees from Boehringer Ingelheim, Bayer HealthCare, Daiichi-Sankyo, Bristol-Myers Squibb, and Pfizer. Dr. Agnelli reports lectures fees from Sanofi, Bayer HealthCare, Daiichi-Sankyo, Bristol-Myers Squibb, and Pfizer. Dr. Beyer-Westendorf has received honoraria and research support from Bayer HealthCare, Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer. The authors report no relationships that could be construed as a conflict of interest.

AUTHOR CONTRIBUTIONS

Laura Franco contributed to the conception and design of the study, to the interpretation of data, drafting and critical revision of the manuscript as well as supervision of all statistical analyses and is the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article; Cecelia Becattini and Giancarlo Agnelli contributed to the conception and design of the study, to the interpretation of data, drafting and critical revision of the manuscript; Jan Beyer-Westendorf, Simone Vanni, Cinzia Nitti, Roberta Re, Giorgia Manina, Fulvio Pomero, Roberto Cappelli, and Alberto Conti contributed to the interpretation of data, drafting, and critical revision of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Franco L, Becattini C, Beyer-Westendorf J, et al. Definition of major bleeding: Prognostic classification. *J Thromb Haemost*. 2020;18:2852–2860. https://doi.org/10.1111/jth.15048