Early Prediction of In-Hospital Mortality of Patients with Hemoptysis: An Approach to Defining Severe Hemoptysis

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Key Words

Severe hemoptysis • In-hospital mortality • Scoring • Outcome • Prediction

Abstract

Background: The severity of hemoptysis is usually assessed on the amount of blood expectorated, although no threshold has been agreed upon. Respiratory or hemodynamic failures are additional severity criteria but occur in few cases. **Objectives:** Early identification of the in-hospital mortality determinants might be helpful to best characterize severe hemoptysis. **Methods:** This is a retrospective cohort study of consecutive patients with hemoptysis admitted to the ICU of a teaching hospital during a 14-year period. The model for early prediction of in-hospital mortality was developed on a derivation sample (67% of patients) using multiple logistic regression. Calibration and discrimination of the model were tested using the remaining validation sample. A scoring system was developed for clinical use. **Results:** The in-hospital mortality of the 1,087 patients (age 54 years, 71% male) was 6.5% (95% CI 5–8). Chronic alcoholism, cancer or aspergillosis, pulmonary artery involvement, infiltrates involving two quadrants or more on the admission radiograph, and me-

chanical ventilation at referral predicted independently mortality. The model showed good concordance between predicted and observed probabilities of death and good discrimination (receiver operating characteristic curve area 0.87; 95% CI 0.82–0.92). The model-based score (chronic alcoholism, pulmonary artery involvement, and radiographic patterns, 1 point each; cancer, aspergillosis, and mechanical ventilation, 2 points each) predicted the probability of death as follows: score 0, 1%; score 1, 2%; score 2, 6%; score 3, 16%; score 4, 34%; score 5, 58%; score 6, 79%, and score 7, 91%. **Conclusions:** Our results provide useful information about the short-term prognosis of patients with hemoptysis, which could help design therapeutic approaches and management plans according to the risk of in-hospital mortality.

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Introduction

Hemoptysis remains a challenging condition for physicians because of the variety of etiologies and the large panel of clinical presentations that may range from a nonalarming bloody expectoration to a life-threatening bleeding condition [1]. Early assessment of the severity of

hemoptysis is a crucial step for designing the most appropriate management and therapeutic plan in a timely fashion. The amount of blood expectorated has been suggested to be associated with in-hospital mortality [2, 3]. In surgical series, a mortality rate as high as 75% was reported in patients having a bleeding rate of more than 600 ml within 16 h [2]. However, no threshold for the volume or rate of blood expectorated has been agreed upon in the literature to define the severity of hemoptysis [3]. Since the threshold varies extensively across the literature, some authors recommend that life-threatening hemoptysis should be defined as any hemoptysis that is >100 ml in 24 h (the smallest amount reported in the literature to threaten life) or causes abnormal gas exchange, airway obstruction, or hemodynamic instability [3, 4]. However, the situation wherein patients with hemoptysis are mechanically ventilated occurs in only 10–20% of cases [5]. Comorbid conditions (bleeding diathesis, poor pulmonary reserve) have also been considered as additional poor prognostic factors in selected populations of patients [6–9]. Both the cause [5, 8, 10–12] and the source [12, 13] of hemoptysis should also be integrated in the reasoning process of the severity assessment of hemoptysis.

Intensive care-related generic scores of severity and organ dysfunction such as the Simplified Acute Physiologic Score (SAPS II) [14] might be useful for the most severe cases but have not been evaluated in the specific setting of hemoptysis. Currently, there is no well-defined assessment tool for severe hemoptysis which takes into account all of the above-mentioned prognostic factors. Moreover, early identification of patients with hemoptysis at high risk for death would be of great interest in clinical practice to help define management strategies.

In this study, we analyze a large cohort of consecutive patients referred to a single tertiary referral center for hemoptysis. Our aims were: (i) to identify the severity criteria of hemoptysis by investigating the early predictors of in-hospital mortality, available within the first hours of referral of patients to the intensive care unit (ICU), and (ii) to develop a scoring system for clinical use.

Patients and Methods

Patient Selection

This was a retrospective analysis of prospective collected data of consecutive patients admitted from June 1995 to April 2009 to the ICU and step-down unit of Tenon Hospital, a tertiary university hospital and referral center for hemoptysis in Paris, France. During the 14-year study period, 1,087 patients with 1,174 epi-

Fig. 1. Selection of patients. Thirty-eight patients (3%) among 1,125 consecutive patients referred for the management of hemoptysis were excluded. Overall, 1,087 patients with 1,174 episodes of hemoptysis were eligible. The analysis focused on the first episodes of hemoptysis.

sodes of hemoptysis were eligible (fig. 1). Only the first episode of hemoptysis was analyzed.

Data Collection

All data were recorded prospectively over the study period as part of an ongoing follow-up program of the management of hemoptysis, including the decision to treat the patients with vascular interventional radiology or surgical lung resection.

Baseline Demographics, Lifestyle, and Comorbid Conditions

Baseline demographic and lifestyle characteristics included age, sex, tobacco and alcohol use, and performance status (PS) [15]. Comorbid conditions were stratified into respiratory diseases, cardiovascular diseases, renal diseases, central nervous system disorders, hepatic diseases, solid tumor or hematological diseases, HIV infection, and diabetes mellitus. Respiratory comorbidities included a history of chronic obstructive pulmonary disease, bronchiectasis, tuberculosis, cancer, aspergillosis, and others. A past history of hemoptysis was also recorded. Long-term anticoagulation included long-term treatment with heparin and/or vitamin K antagonists.

Causes and Source of Hemoptysis

The causes and sources of hemoptysis were based on the combination of medical history, physical examination, CXR, and CT scan [16] or vascular interventional radiology. The sources of hemoptysis were stratified into systemic bronchial and nonbronchial hypervascularization or pulmonary artery involvement. The CT scan was either available at referral or performed within the first hours of referral in most patients.

Amount of Hemoptysis

The amount of hemoptysis was assessed at referral on: (i) the estimated cumulated volume expectorated, (ii) the radiographic pattern, (iii) the hemoglobin level, and (iv) the need for the administration of mechanical ventilation. We divided each lung into 2 quadrants, and each scored as 0 (no infiltrate) and 1 (alveolar infiltrate), considering that alveolar infiltrate is a sign of the alveoli filling with blood, whether or not a potential etiologic lesion was present. The radiographic involvement could range from 0 to 4 (all quadrants showing alveolar opacities).

Management

All patients received standardized medical management as described previously [5, 17].

Outcome

The primary outcome was vital status at hospital discharge (patients either died or discharged alive), and this was recorded for all patients.

Statistical Analysis

The data set ($n = 1,087$) was randomly divided into a derivation sample, comprising 67% of patients ($n = 717$) and a validation sample including the remaining 33% ($n = 370$). No patient was included in both the derivation and the validation data sets.

To identify early predictors of in-hospital mortality in patients referred to the ICU for hemoptysis, we first studied crude associations between each potential predictor and in-hospital mortality in the derivation sample. Data are expressed as means $\pm$ SD (range) or as numbers (percentage). The Mann-Whitney U test was used to test the associations between in-hospital mortality and quantitative predictors and the χ^2 test or Fisher's exact test was used for nominal predictors. Associations were measured using odds ratios (OR) and corresponding 95% confidence intervals (CI). The predictors analyzed included demographics and lifestyle characteristics (age, sex, chronic alcoholism, and PS), comorbid conditions (respiratory and cardiovascular comorbidities, history of hemoptysis, and long-term anticoagulation), the cause and source of hemoptysis, and the variables reflecting the amount of hemoptysis (volume, number of CXR quadrants involved, hemoglobin, and mechanical ventilation at referral). Quantitative variables (age, volume, and hemoglobin) and nominal variables stratified into several classes (PS and CXR quadrants) were split into binary variables, according to their distribution in univariate analysis and their clinical relevance, as follows: age (<40 years; ≥ 40 years), PS (0 or ≥ 1), volume (≤ 300 ml; > 300 ml), CXR quadrants (<2 quadrants; ≥ 2 quadrants), and hemoglobin (≥ 9 g/dl; < 9 g/dl). The causes of hemoptysis were separated into cancer, aspergillosis and others, taking cryptogenic hemoptysis as the reference category because it had the lowest associated rate of in-hospital mortality in univariate analysis. To control for the year of hospitalization, we stratified the study period into 3 consecutive time periods averaging 4 years each: June 1995 to December 2000 ($n = 345$), January 2001 to December 2005 ($n = 382$), and January 2006 to April 2009 ($n = 360$).

Independent predictors of in-hospital mortality were then determined using multivariate logistic regression models. The number of events per variable entered into the final multivariate model averaged a ratio of 1/10 to avoid overfitting [18]. We performed a stepwise backward multivariate logistic regression analysis by

proceeding in 2 steps. In the first step, we entered in the model variables related to the baseline demographics, lifestyle, and comorbid conditions associated with in-hospital mortality with a p value ≤ 0.15 in the univariate analysis, i.e. age, sex, chronic alcoholism, PS, respiratory and cardiovascular comorbid conditions, history of hemoptysis, and long-term anticoagulation. In the second step, we added the cause and source of hemoptysis and the variables reflecting the amount of hemoptysis, i.e. the hemoptysis-related variables (volume, CXR quadrants, and hemoglobin) and the initial administration of mechanical ventilation, to the preceding variables that remained associated with in-hospital mortality with a p value ≤ 0.15 . The SAPS II score was not entered in the analyses as it incorporates some of the variables entered into the models (age, shock, and mechanical ventilation). These models were estimated using data from the derivation data set. The final model was then tested using the validation data set. To assess the performance of the model, goodness-of-fit (Hosmer-Lemeshow) tests were performed for both the derivation and validation data sets to evaluate calibration [19]. The area under the receiver operating characteristic (ROC) curve [20] was used in the two data sets to evaluate discrimination.

We attempted to develop an additive scoring system using the β coefficients of the final regression model. For simplicity of use, the points of the score were approximated by rounding the coefficients to the nearest integer. Once the score was calculated for each patient, the predicted and observed probabilities of in-hospital mortality were estimated and compared.

Statistical analysis was performed with StataTM 10.1 software (StataCorp, College Station, Tex., USA).

Ethical Considerations

The study was conducted in accordance with French law, which does not require approval of an Institutional Review Board or individual patients' consent for such observational, noninterventional, and retrospective analyses of medical records. The data base was approved by the National Commission for Protection of Patients' Rights and Electronic Data Recording (Commission Nationale de l'Informatique et des Libertés; CNIL, www.cnil.fr).

Results

Overall, 1,087 patients (773 males) were referred to our unit for the management of hemoptysis. Eighty patients (7%) were mechanically ventilated at referral. Mechanical ventilation ($n = 122$) and vasoactive drugs ($n = 54$) were administered within the first 24 h of admission in 123 patients (11%) presenting or developing acute respiratory or hemodynamic failure, overall. Vascular interventional radiology ($n = 773$) or surgical lung resection ($n = 118$) was performed in two thirds of the patients ($n = 792$; 73%) during hospitalization. Overall, 71 patients (6.5%) died during hospitalization, including one third ($n = 23$; 32%) within 48 h of admission. The in-hospital mortality rate was evenly distributed throughout the study period [June 1995 to December 2000: 27/345 (8%), January 2001 to De-

Table 1. Characteristics and outcomes of 1,087 patients with hemoptysis, contrasting the derivation and validation data sets

Variables	All patients (n = 1,087)	Derivation data set (n = 717)	Validation data set (n = 370)	p value
Demographics and lifestyle				
Age, years	54 ± 17 (16–92)	54 ± 17 (16–90)	54 ± 18 (16–92)	0.9
Male:female	773 (71):314 (29)	514 (72):203 (28)	259 (70):111 (30)	0.6
Tobacco use ^a	724 (67)	474 (66)	250 (68)	0.7
Chronic alcoholism ^b	230 (21)	154 (22)	76 (21)	0.7
PS ≥1	455 (42)	312 (44)	143 (39)	0.1
Past medical history and comorbid conditions				
Long-term anticoagulation ^c	96 (9)	68 (10)	28 (8)	0.3
Cardiovascular comorbid conditions	345 (32)	228 (32)	117 (32)	0.95
Respiratory comorbid conditions	509 (47)	351 (49)	158 (43)	0.05
Prior history of hemoptysis	306 (28)	203 (28)	103 (28)	0.9
Cause and source of hemoptysis^a				
Cryptogenic	193 (18)	119 (17)	74 (20)	0.3
Bronchiectasis	216 (20)	144 (20)	72 (20)	
Cancer	184 (17)	129 (18)	55 (15)	
Tuberculosis (active)	129 (12)	79 (11)	50 (14)	
Tuberculosis (sequelae)	142 (13)	93 (13)	49 (13)	
Aspergillosis	63 (6)	48 (7)	15 (4)	
Others	158 (15)	103 (14)	55 (15)	
Pulmonary artery involvement	50 (5)	38 (5)	12 (3)	0.2
Variables reflecting the amount of hemoptysis				
Cumulated volume ^d , ml	218 ± 190 (10–1,000)	211 ± 181 (10–1,000)	231 ± 205 (10–1,000)	0.1
Mean CXR quadrants ^e , n	0.6 ± 0.8 (0–4)	0.6 ± 0.8 (0–4)	0.6 ± 0.8 (0–4)	0.8
Hemoglobin ^a , g/dl	12.2 ± 2.3 (3.9–18.4)	12.2 ± 2.3 (3.9–18.4)	12.3 ± 2.3 (5.7–17.7)	0.4
Initial mechanical ventilation	80 (7)	53 (7)	27 (7)	0.96
Outcome				
Mechanical ventilation within 24 h	123 (11)	82 (11)	41 (11)	0.9
In-hospital mortality	71 (6.5)	47 (6.6)	24 (6.5)	0.97

Results are expressed as means ± SD (range) or as numbers (percentage). The data set (n = 1,087) was randomly divided into a derivation data set comprising 67% of the data (n = 717), and a validation data set with the remaining 33% (n = 370).

^a Two missing values (tobacco use, hemoglobin, cause, and source). ^b Five missing values (chronic alcoholism). ^c One missing value (long-term anticoagulation). ^d Fifty missing values (cumulated volume). ^e Nine missing values (CXR).

Fig. 2. ROC curves for the derivation and validation data sets of patients with hemoptysis admitted to the ICU. The area under the ROC curve was 0.87 (95% CI 0.83–0.92) for the derivation data set (n = 710), which indicates an excellent discrimination of the model. The model was tested against the validation data set (n = 362), providing an area under the ROC curve of 0.80 (95% CI 0.70–0.89). The areas under the ROC curves did not differ (p = 0.16).

Table 2. Univariate analysis of variables associated with in-hospital mortality in 717 patients with hemoptysis admitted to the ICU (derivation data set)

Variables	n	In-hospital mortality % (n)	OR (95% CI)	p	Variables	n	In-hospital mortality % (n)	OR (95% CI)	p
Sex					Cause ^a				
Female	203	4.4 (9)	1	0.15	Cryptogenic	119	1.7 (2)	1	<0.0001
Male	514	7.4 (38)	1.72 (0.81–3.63)		Cancer	129	20.9 (27)	15.49 (3.34–71.79)	
Age					Aspergillosis	48	8.3 (4)	5.32 (0.91–30.94)	
<40 years	158	2.5 (4)	1	0.021	Other	419	3.3 (14)	2.02 (0.45–9.05)	
≥40 years	559	7.7 (43)	3.21 (1.13–9.12)		Pulmonary artery involvement ^a				
PS					No	677	5.6 (38)	1	<0.0001
0	405	2.7 (11)	1	<0.0001	Yes	38	23.7 (9)	5.22 (2.28–11.94)	
≥1	312	11.5 (36)	4.67 (2.31–9.45)		Volume ^d				
Tobacco use ^a					≤300 ml	576	4.9 (28)	1	0.029
No	241	6.6 (16)	1	0.96	>300 ml	108	10.2 (11)	2.22 (1.07–4.62)	
Yes	474	6.5 (31)	0.98 (0.53–1.84)		CXR quadrants ^b				
Alcohol use ^b					0–1	622	4.3 (27)	1	<0.0001
No	560	4.8 (27)	1	0.0008	≥2	92	20.7 (19)	5.74 (2.99–11.01)	
Yes	154	12.3 (19)	2.78 (1.49–5.17)		Hemoglobin ^c				
Long-term anticoagulation ^c					≥9 g/dl	641	5.6 (36)	1	0.0028
No	648	6.0 (39)	1	0.069	<9 g/dl	75	14.7 (11)	2.89 (1.39–5.98)	
Yes	68	11.8 (8)	2.08 (0.93–4.67)		Mechanical ventilation at referral				
Cardiovascular comorbid conditions					No	664	4.2 (28)	1	<0.0001
No	489	4.9 (24)	1	0.009	Yes	53	35.8 (19)	12.69 (6.18–26.05)	
Yes	228	10.1 (23)	2.17 (1.19–3.95)		Mechanical ventilation during the first 24 h				
Respiratory comorbid conditions					No	634	2.4 (15)	1	<0.0001
No	366	8.2 (30)	1	0.07	Yes	82	39 (32)	25.89 (12.04–55.67)	
Yes	351	4.8 (17)	0.57 (0.31–1.05)		SAPS II score ^b				
Prior history of hemoptysis					<20	371	0.5 (2)	1	<0.0001
No	514	7.6 (39)	1	0.076	20–24	152	2.6 (4)	4.99 (0.89–27.75)	
Yes	203	3.9 (8)	0.5 (0.23–1.09)		25–34	111	7.2 (8)	14.33 (2.89–70.82)	
					35–44	34	17.6 (6)	39.54 (6.85–228.16)	
					≥45	46	58.7 (27)	262.18 (30.11–2,283)	

Hemoptysis-related variables were split into binary variables according to their distribution and corresponding in-hospital mortality rates as follows: volume (≤300 ml; >300 ml), CXR quadrants (<2 quadrants; ≥2 quadrants), and hemoglobin (≥9 g/dl; <9 g/dl).

^a Two missing values (tobacco use, cause, and source). ^b Three missing values (chronic alcoholism, chest X-ray, SAPS II score). ^c One missing value (long-term anticoagulation, hemoglobin). ^d Thirty-three missing values (volume).

cember 2005: 23/382 (6%), January 2006 to April 2009: 21/360 (6%); $p = 0.5$].

Patients' characteristics in the derivation and validation data sets were similar (table 1). Variables associated with in-hospital mortality in univariate analysis are listed table 2. In the final multivariate model, alcohol use, cancer, aspergillosis, involvement of 2 quadrants or more on the admission radiograph, and mechanical ventilation at referral were independently associated with in-hospital mortality. Pulmonary artery involvement was marginally associated with in-hospital mortality (table 3). The

area under the ROC curve of the final model was 0.87 (95% CI 0.83–0.92), which indicates an excellent discrimination of the model, and the Hosmer-Lemeshow statistic for lack of fit was not statistically significant, suggesting an adequate goodness of fit. The validation sample confirmed a similar pattern: area under the ROC curve, 0.80 (95% CI 0.70–0.89); nonsignificant Hosmer-Lemeshow statistic ($\chi^2 = 11.88$; $p = 0.10$). The ROC curves for the derivation and validation data sets are shown in figure 2.

A 7-point score based on information available within the first hours of referral was then developed. Table 4 pro-

Table 3. Multivariate analysis of variables associated with in-hospital mortality in 717 patients with hemoptysis admitted to the ICU (derivation data set)

Variables	First step: demographics, lifestyle, and comorbid conditions		Second step: cause, mechanism, and amount of hemoptysis		Final model	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age ≥40 years	1.46 (0.46–4.59)	0.52				
Sex	1.27 (0.55–2.89)	0.58				
Chronic alcoholism	2.57 (1.28–5.16)	0.008	2.74 (1.23–6.07)	0.01	2.71 (1.32–5.55)	0.007
PS ≥1	5.02 (2.27–11.13)	0.0001	1.78 (0.74–4.26)	0.2		
Respiratory comorbid conditions	0.41 (0.21–0.79)	0.009	0.54 (0.24–1.25)	0.16		
Prior history of hemoptysis	0.54 (0.24–1.23)	0.14	0.59 (0.23–1.56)	0.29		
Cardiovascular comorbid conditions	1.78 (0.58–2.38)	0.65				
Long-term anticoagulation	1.26 (0.51–3.09)	0.61				
<i>Cause and source of hemoptysis</i>						
Cancer			6.96 (1.43–33.93)	0.002	7.39 (1.62–33.75)	0.0002
Aspergillosis			7.17 (1.07–47.85)		4.65 (0.79–27.40)	
Other cause			1.59 (0.33–7.72)		1.55 (0.33–7.19)	
Pulmonary artery involvement			2.57 (0.87–7.61)	0.089	2.40 (0.86–6.69)	0.093
<i>Amount of hemoptysis at referral</i>						
CXR quadrants ≥2			2.15 (0.90–5.11)	0.08	2.37 (1.12–5.02)	0.024
Volume >300 ml			1.00 (0.39–2.59)	0.99		
Hemoglobin <9 g/dl			0.47 (0.16–1.40)	0.18		
Initial mechanical ventilation			8.32 (3.06–22.59)	0.0001	8.59 (3.94–18.75)	0.0001
Goodness of fit (prob >χ ²)	10.22	0.25	5.13	0.64	8.64	0.12
ROC curve area	0.78 (0.73–0.84)		0.87 (0.81–0.93)		0.87 (0.83–0.92)	

The multivariate analysis of in-hospital mortality was performed by first integrating the baseline demographics, lifestyle, and comorbid conditions selected by univariate analysis ($p \leq 0.15$), i.e. age, sex, chronic alcoholism, PS, respiratory and cardiovascular comorbid conditions, history of hemoptysis, and long-term anticoagulation. The model was completed with the cause

and source of hemoptysis, and the variables reflecting the amount of hemoptysis, i.e. volume (≤ 300 ml; >300 ml), number of CXR quadrants involved (<2 quadrants; ≥ 2 quadrants), hemoglobin level (≥ 9 g/dl; <9 g/dl), and initial mechanical ventilation, after having excluded the preceding variables with $p > 0.15$.

vides details of the corresponding points assigned to each of the final risk variables, which were obtained using the β coefficients of the final model performed on the derivation dataset. The score included chronic alcoholism (1 point), cancer or aspergillosis (2 points), pulmonary artery involvement (1 point), involvement of 2 quadrants or more on the admission radiograph (1 point), and mechanical ventilation at referral (2 points). There was good concordance between predicted and observed in-hospital mortality rates in the derivation data set. The predicted risk of in-hospital mortality as a function of the score was: score 0, 1%; score 1, 2%; score 2, 6%; score 3, 16%; score 4, 34%; score 5, 58%; score 6, 79%, and score 7, 91%. The final model and the model-based score predicted the risk of in-hospital mortality almost as well as the SAPS II score for the derivation data set; the ROC curve areas were 0.87

Table 4. Mortality risk score in patients with hemoptysis (derivation data set)

Variables	β (standard error)	points
Chronic alcoholism	0.99 (0.37)	1
Cancer	1.99 (0.78)	2
Aspergillosis	1.54 (0.91)	2
Other cause	0.44 (0.78)	0
Pulmonary artery involvement	0.88 (0.52)	1
CXR quadrants ≥2	0.86 (0.38)	1
Initial mechanical ventilation	2.15 (0.39)	2

The corresponding points assigned to each of the final risk variables were obtained by using the β coefficients of the final model performed on the derivation data set ($n = 710$ patients). The score could vary from 0 to 7.

Fig. 3. ROC curves for the SAPS II score, the final model, and the model-based score in the derivation and validation samples of patients with hemoptysis admitted to the ICU. **a** The final model and the model-based score predicted the risk of in-hospital mortality almost as well as the SAPS II score for the derivation data set (n = 707); the ROC curve areas were 0.87 (95% CI 0.82–0.92), 0.86 (95%

CI 0.81–0.91), and 0.91 (95% CI 0.86–0.96) for the final model, the model-based score, and the SAPS II score, respectively; p = 0.12. **b** The validation data set (n = 363) confirmed a similar pattern; the ROC curve areas were 0.80 (95% CI 0.70–0.89), 0.80 (95% CI 0.71–0.89), and 0.88 (95% CI 0.79–0.97) for the final model, the model-based score, and the SAPS II score, respectively; p = 0.12.

(95% CI 0.82–0.92), 0.86 (95% CI 0.81–0.91), and 0.91 (95% CI 0.86–0.96) for the final model, the model-based score, and the SAPS II score, respectively; p = 0.12. The validation data set confirmed a similar pattern (fig. 3).

Discussion

In this study, we assessed the severity criteria of hemoptysis by investigating the predictors of in-hospital mortality in a large series of patients with hemoptysis, based on information available within the early hours of referral, and developed a simple scoring system for clinical use. The overall in-hospital mortality rate was 6.5%. Predictors independently associated with in-hospital mortality were alcoholism, the cause (cancer or aspergillosis), the source (pulmonary artery involvement), and variables reflecting the amount of hemoptysis (CXR pattern and initial mechanical ventilation). A simple prediction score based on these predictors showed good discrimination and calibration with good agreement between the predicted and observed probabilities of death.

Series of patients with hemoptysis admitted to the ICU and possibly mechanically ventilated are sparse and in-

volve a small number of patients [1, 6]. Mal et al. [6] described the management of 56 patients admitted to the ICU within a 10-year period (1986–1996), 7 of whom (12.5%) died within the first month of referral. Ong and Eng [1] reported an overall in-hospital mortality rate of 13% in a series of 29 patients with 31 episodes of hemoptysis of more than 300 ml/24 h or requiring intubation, during a 45-month period from August 1997 to April 2001. In our center, hemoptysis accounts for 15–20% of all ICU admissions as our hospital is a referral center for hemoptysis. The in-hospital mortality was 6.5% overall (95% CI 5–8) and reached 32.5% (95% CI 22–43) in patients receiving mechanical ventilation at referral.

Apart from mechanical ventilation, the criteria used to characterize severe hemoptysis are ill defined and traditionally limited to an estimated amount of blood expectorated within the 48–72 h preceding referral, although no threshold for the bleeding amount has been agreed upon in the literature to define ‘life-threatening’ or ‘massive’ hemoptysis [2, 8, 21–24]. In our study, a threshold value of 300 ml was the best predictor of in-hospital mortality in univariate analysis. After adjustment for other predictors, however, the estimated volume expectorated did not remain predictive of death, which

may question the reliability of its routine quantification. It is important to note that in our study the volume could not be assessed upon admission in 50 patients, 10 of whom (20%) died in hospital. The imprecision in its measurement may have underestimated the impact of the volume of expectorated blood on the outcome in our study.

The extent of radiological involvement, another marker of the amount of hemoptysis, has been found to be significantly greater in patients who were mechanically ventilated or who died [25]. Conversely, the hemoglobin level at referral has not been established as a prognostic factor as hemoptysis-related death usually occurs by asphyxiation prior to profound anemia [26]. In our study, the admission CXR involvement was associated with in-hospital mortality in univariate analysis and after adjustment for the other prognostic variables, using a cutoff of 2 or more radiological quadrants involved. A more functional approach combining the baseline respiratory reserve with the bleeding amount has been suggested for defining life-threatening hemoptysis [6, 9]. In our study, patients having respiratory comorbid conditions ($n = 509$; 47%) were not more likely to receive mechanical ventilation within the first hours of referral (data not shown). Other significant univariate risk factors of in-hospital mortality related to general health were age, PS, alcohol use, anticoagulant therapy, and cardiovascular comorbid conditions, as previously reported in selected populations of patients [8, 9, 12, 27–30]. Among these, chronic alcoholism remained the only factor independently associated with in-hospital mortality after adjustment for the other prognostic factors. In-hospital mortality was also strongly related to the cause, especially cancer and aspergillosis, and to the source of hemoptysis, as previously reported [5, 10, 11, 30–36].

The prediction score combining the above-mentioned prognostic markers enables the stratification of patients according to their increasing risk of in-hospital mortality. The overall discrimination of the score is comparable to that of the SAPS II score. The advantage of such a score is that it is based on hemoptysis-related variables (cause, source, and amount) and it may be obtained before the first 24 h of admission, which may be helpful to inform management strategies for these patients. For example, patients in the low-risk group (score 0–1 and 1% risk of mortality) might be suitable for a planned management in a step-down unit, and the opportunity for vascular interventional radiology can be discussed. Patients in the intermediate-risk group (score 2 and 12% risk of mortality) might be rapidly considered for vascular interventional radiology, whereas patients

with a score >2 and at high risk for mortality ($>20\%$) should be managed in the ICU and receive emergency vascular interventional radiology, particularly those with a score of 5 or more ($>50\%$).

Our study has several limitations. It was conducted in a referral center with extensive experience with hemoptysis, which may limit the generalizability of our results. A referral center may select the most severe patients, who are presumed to have a worst prognosis. Conversely, a referral center may certainly induce a better management, in terms of resource facilities, therefore contributing to a better prognosis. As a consequence, it is difficult to assess the impact of the selection of our population on the frequency of the complications of hemoptysis. There is no reason to speculate that such a selection, if any, might induce a bias in the estimation of the associations, and the literature does not provide adequate information to precisely position our population.

Although we adjusted for the study period, the inclusion of patients in our cohort spanned over 14 years and our results may not necessarily reflect current practices and patients outcomes. However, the strengths of our study include the large series of consecutive patients, the homogeneous and prospective recording of data, and the expected reproducibility of our results as we developed and validated our model based on two randomly selected groups of patients. However, external validation of the score is needed to assess its characteristics as they might have been overestimated in the population in which it was constructed [37], and also for assessing its generalizability among other similar populations [38].

In conclusion, we developed a simple score for assessing the severity of hemoptysis by predicting in-hospital mortality. There was good concordance between predicted and observed probabilities of death. Our results on evaluating the performance of the proposed score suggest that it can help identifying patients with hemoptysis admitted to the ICU who are at different levels of risk for in-hospital mortality. This may in turn provide useful information to clinicians about the patients' prognosis and thereby help improve the information provided to the patients and their families and possibly improve management strategies for such patients. The potential utility of the score in improving the management and outcomes of patients needs to be evaluated in future prospective studies.

Financial Disclosure and Conflicts of Interest

The authors declare that they have no conflict of interest.

References

- Ong TH, Eng P: Massive hemoptysis requiring intensive care. *Intensive Care Med* 2003; 29:317–320.
- Crocco JA, Rooney JJ, Fankushen DS, DiBenedetto RJ, Lyons HA: Massive hemoptysis. *Arch Intern Med* 1968;121:495–498.
- Dweik RA, Stoller JK: Role of bronchoscopy in massive hemoptysis. *Clin Chest Med* 1999;20:89–105.
- Ibrahim WH: Massive haemoptysis: the definition should be revised. *Eur Respir J* 2008; 32:1131–1132.
- Fartoukh M, Khalil A, Louis L, Carette MF, Bazelly B, Cadranet J, Mayaud C, Parrot A: An integrated approach to diagnosis and management of severe haemoptysis in patients admitted to the intensive care unit: a case series from a referral centre. *Respir Res* 2007;8:11–20.
- Mal H, Rullon I, Mellot F, Brugiere O, Sleiman C, Menu Y, Fournier M: Immediate and long-term results of bronchial artery embolization for life-threatening hemoptysis. *Chest* 1999;115:996–1001.
- Flume PA, Yankaskas JR, Ebeling M, Hulsey T, Clark LL: Massive hemoptysis in cystic fibrosis. *Chest* 2005;128:729–738.
- Hirshberg B, Biran I, Glazer M, Kramer MR: Hemoptysis: etiology, evaluation, and outcome in a tertiary referral hospital. *Chest* 1997;112:440–444.
- Coss-Bu JA, Sachdeva RC, Bricker JT, Harrison GM, Jefferson LS: Hemoptysis: a 10-year retrospective study. *Pediatrics* 1997; 100:E7.
- Kim YG, Yoon HK, Ko GY, Lim CM, Kim WD, Koh Y: Long-term effect of bronchial artery embolization in Korean patients with haemoptysis. *Respirology* 2006;11:776–781.
- van den Heuvel MM, Els Z, Koegelenberg CF, Naidu KM, Bolliger CT, Diacon AH: Risk factors for recurrence of haemoptysis following bronchial artery embolisation for life-threatening haemoptysis. *Int J Tuberc Lung Dis* 2007;11:909–914.
- Andrejak C, Parrot A, Bazelly B, Ancel PY, Djibre M, Khalil A, Grunenwald D, Fartoukh M: Surgical lung resection for severe hemoptysis. *Ann Thorac Surg* 2009;88: 1556–1565.
- Gillet Y, Issartel B, Vanhems P, Fournet JC, Lina G, Bes M, Vandenesch F, Piémont Y, Brousse N, Floret D, Etienne J: Association between *Staphylococcus aureus* strains carrying gene for Panton-Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. *Lancet* 2002;359:753–759.
- Le Gall JR, Lemeshow S, Saulnier F: A new Simplified Acute Physiology Score (SAPS II) based on a European-North American multicenter study. *JAMA* 1993;270:2957–2963.
- Zubrod CG, Schneiderman M, Frei E 3rd: Appraisal of methods for the study of chemotherapy of cancer in man: comparative therapeutic trial of nitrogen mustard and triethylene thiophosphoramide. *J Chronic Dis* 1960;11:7–33.
- Mori H, Ohno Y, Tsuge Y, Kawasaki M, Ito F, Endo J, Funaguchi N, La BL, Kanematsu M, Minatoguchi S: Use of multidetector row CT to evaluate the need for bronchial arterial embolization in hemoptysis patients. *Respiration* 2010;80:24–31.
- Sakr L, Dutau H: Massive hemoptysis: an update on the role of bronchoscopy in diagnosis and management. *Respiration* 2010;80:38–58.
- Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR: A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol* 1996;49: 1373–1379.
- Hosmer DW, Lemeshow S: *Applied Logistic Regression*. New York, Wiley, 1989.
- Egan JP: *Signal Detection Theory and ROC Analysis*. New York, Academic Press, 1975.
- Amirana M, Frater R, Tirschwell P, Janis M, Bloomberg A, State D: An aggressive surgical approach to significant hemoptysis in patients with pulmonary tuberculosis. *Am Rev Respir Dis* 1968;97:187–192.
- Brinson GM, Noone PG, Mauro MA, Knowles MR, Yankaskas JR, Sandhu JS, Jaques PF: Bronchial artery embolization for the treatment of hemoptysis in patients with cystic fibrosis. *Am J Respir Crit Care Med* 1998;157:1951–1958.
- Corey R, Hla KM: Major and massive hemoptysis: reassessment of conservative management. *Am J Med Sci* 1987;294:301–309.
- Knott-Craig CJ, Oosthuizen JD, Rossouw G: Management and prognosis of massive hemoptysis. *J Thorac Cardiovascular Surg* 1993;105:394–397.
- Khalil A, Soussan M, Mangiapan G, Fartoukh M, Parrot A, Carette MF: Utility of high-resolution chest CT scan in the emergency management of haemoptysis in the intensive care unit: severity, localization and aetiology. *Br J Radiol* 2007;80:21–25.
- Lordan JL, Gascoigne A, Corris PA: The pulmonary physician in critical care: illustrative case 7 – assessment and management of massive haemoptysis. *Thorax* 2003;58:814–819.
- Arozullah AM, Daley J, Henderson WG, Khuri SF: Multifactorial risk index for predicting postoperative respiratory failure in men after major noncardiac surgery: the National Veterans Administration Surgical Quality Improvement Program. *Ann Surg* 2000;232:242–253.
- Murphy SA, Mydin HH, Fatah S, Antunes G: Predicting end-of-life in patients with an exacerbation of COPD by routine clinical assessment. *Respir Med* 2010;104:1668–1674.
- Neuenschwander AU, Pedersen JH, Krasnik M, Tønnesen H: Postoperative outcome in chronic alcohol abusers after curative resection for lung cancer. *Eur J Cardiothorac Surg* 2002;22:287–291.
- Roques S, Parrot A, Lavole A, Ancel PY, Gouinant V, Djibre M, Fartoukh M: Six-month prognosis of patients with lung cancer admitted to the intensive care unit. *Intensive Care Med* 2009;35:2044–2050.
- Ayed A: Pulmonary resection for massive hemoptysis of benign etiology. *Eur J Cardiothorac Surg* 2003;24:689–693.
- Jougon J, Ballester M, Delcambre F, Bride TM, Valat P, Gomez F, Laurent F, Velly JF: Massive hemoptysis: what place for medical and surgical treatment. *Eur J Cardiothorac Surg* 2002;22:345–351.
- Boussat S, El'rini T, Dubiez A, Depierre A, Barale F, Capellier G: Predictive factors of death in primary lung cancer patients on admission to the intensive care unit. *Intensive Care Med* 2000;26:1811–1816.
- Ewer MS, Ali MK, Atta MS, Morice RC, Balakrishnan PV: Outcome of lung cancer patients requiring mechanical ventilation for pulmonary failure. *JAMA* 1986;256:3364–3366.
- Reichner CA, Thompson JA, O'Brien S, Kuru T, Anderson ED: Outcome and code status of lung cancer patients admitted to the medical ICU. *Chest* 2006;130:719–723.
- Soares M, Darmon M, Salluh JJ, Ferreira CG, Thiery G, Schlemmer B, Spector N, Azoulay E: Prognosis of lung cancer patients with life-threatening complications. *Chest* 2007;131: 840–846.
- Royston P, Moons KG, Altman DG, Vergouwe Y: Prognosis and prognostic research: developing a prognostic model. *BMJ* 2009; 338:b604.
- Altman DG, Vergouwe Y, Royston P, Moons KG: Prognosis and prognostic research: validating a prognostic model. *BMJ* 2009; 338:b605.