In-hospital Mortality in Patients with Lower Gastrointestinal Bleeding: Development and Validation of a Prediction Score.

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Abbreviations: AUROC: area under ROC curve; CCI: Charlson Comorbidity Index; INR: international normalised ratio; LGIB: lower gastrointestinal bleeding; NSAID: nonsteroidal anti-inflammatory drugs.

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Abstract

Background and study aims:

Lower gastrointestinal bleeding (LGIB) is a common condition linked to increased morbidity, healthcare costs, and mortality. Currently, no prospectively validated prognostic model exists to predict mortality in LGIB patients. Our aim was to develop and validate a risk score that could accurately predict in-hospital mortality of patients admitted for LGIB.

Patients and methods:

Patient data from a nationwide cohort study in 15 centers in Italy (2019-2020) were used to derivate the risk score (Acute Lower gastrointestinal Bleeding and In-hospital mortality, ALIBI score); the model was then externally validated in a cohort of consecutive patients hospitalized for LGIB in 12 centers from six countries (Italy, Spain, France, Greece, Iran, Brazil) in 2020-2024. The main outcome was in-hospital mortality; we also reported rebleeding rates and in-hospital mortality rate stratified by risk score and timing of colonoscopy.

Results:

Among 1,198 patients in the derivation cohort, 105 (8.8%) rebled, 41 (3.4%) died. Age, Charlson Comorbidity Index (CCI), in-hospital onset, hemodynamic instability, and creatinine levels were independent predictors of in-hospital mortality. The model demonstrated excellent discrimination (AUROC=0.813, 95%-CI: 0.752-0.874) and calibration. In the validation cohort (n=752 patients), the model's good discrimination (AUROC=0.792, 95%-CI: 0.720-0.863) and calibration were confirmed. Patients were categorized as low (0-4 points, 1% mortality), intermediate (5-9 points, 4.6% mortality), or high risk (10-13 points, 19.1% mortality).

Conclusions:

A new validated score effectively predicts in-hospital mortality in LGIB patients, aiding in risk stratification and management.

Keywords: endoscopy, colonoscopy, gastrointestinal bleeding, survival, prognostic score.

Introduction

Acute lower gastrointestinal bleeding (LGIB) is a common cause of hospitalization and it is associated with high morbidity, healthcare burden, and cost.[1] It accounts for up to 20% of all admissions for gastrointestinal bleeding, but its incidence and mortality may have risen in recent decades due to an increase in the average age of the population and in the use of antithrombotic agents.[2,3] The severity of LGIB varies widely from self-limiting hematochezia to major bleeding with anemia and hemodynamic instability;[4] older age, comorbidities, smoking, alcohol consumption, use of non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin are the main risk factors for bleeding.[4] However, mortality from LGIB is a relatively rare event, ranging from 3.4% to 8.8%.[5–7] Therefore, risk assessment at initial clinical presentation is of paramount importance in predicting unfavourable outcomes, need for hospitalization, interventions, and death.

Differently from upper gastrointestinal bleeding, clinical risk scores developed specially to predict morbidity and mortality in patients with LGIB are limited.[8] The Oakland score is the most widely used score in this setting, and it was designed to identify patients with LGIB that can be safely discharged for outpatient investigations.[4,5,9] Other scores have been developed to predict severe bleeding or composite outcomes,[4,8,10] but the definition of the outcome is heterogeneous, some variables are subjective or unavailable at the emergency setting (e.g. albumin), and prospective validation is lacking. To date, no risk score has been developed to predict a hard clinical outcome such as in-hospital mortality in patients with LGIB, and the discriminative ability of the above scores is insufficient to evaluate this outcome.[5,11]

We aimed to develop and validate a prognostic score that could accurately predict the risk of mortality in hospitalized patients with LGIB. We also described the mortality rates of patients with LGIB stratified by their risk score at baseline and the timing of colonoscopy.

Material and Methods

Study design and population

To develop the new prediction model, we used data from consecutive patients with LGIB hospitalized across 15 Italian centers between April 2019 and March 2020. As previously reported,[12] this was a prospective observational cohort study aiming at benchmarking the etiology, management, and outcomes of patients with LGIB in Italy. Briefly, the main inclusion

criteria were: i) age ≥18 years; ii) recent (<3 days) onset of LGIB, either leading to the emergency room (ER) with subsequent admission or occurring in patients already hospitalized for other reasons. Patients presenting with melena who did not undergo upper endoscopy or who had a proven or probable source of bleeding identified during the upper endoscopy were excluded from the analysis.

To externally validate the new model both temporally and geographically, we specifically conducted a prospective international cohort study across 12 centers and 6 countries (Italy, Spain, France, Greece, Brazil, Iran) from December 2022 until February 2024. None of the Italian centers participating in the external validation cohort had participated in the derivation cohort. The eligibility criteria, the clinical setting, and the outcome measures were the same as the ones used in the derivation cohort. The number of patients enrolled in each participating center is reported in **Supplemental Table 1**.

Data collection

For each patient, we collected the following data at the time of LGIB manifestation: age, sex, comorbidities, symptoms, hemodynamic status, setting (ER vs hospitalized, weekday vs weekend diagnosis), laboratory tests (haemoglobin levels, platelet count, coagulation, serum creatinine), list of medications, history of a previous admission for LGIB. Hemodynamic instability was defined as systolic blood pressure <100 mmHg and/or heart rate >100 bpm at manifestation. The variable "in-hospital onset" was considered as positive if the bleeding episode occurred in a patient who had already been hospitalized for another medical reason, as opposed to a patient who presented to the ER and was hospitalized specifically for the episode of LGIB. Data on comorbidities were defined using the Charlson Comorbidity Index (CCI) with no additional points assigned according to age, as reported in **Supplemental Table 2**. In the validation cohort, we also collected variables required to calculate the Oakland score that were not available in the derivation cohort (blood pressure, heart rate, rectal examination findings). We also collected data on patient management (first examination performed, type and timing of endoscopy, need for endoscopic, radiological, or surgical treatment, management of anticoagulation or antiplatelet drugs, need for transfusion), cause of bleeding, and patient outcomes (rebleeding and mortality). Rebleeding was defined as one of the following: overt LGIB, new hemodynamic instability or haemoglobin level drop ≥2

g/dL after initial stabilization. Illustration of patients with LGIB managed by endoscopic or interventional radiology are provided in **Figure 1**.

Statistical analysis

Categorical data were expressed as numbers (percentages), and continuous variables as medians (interquartile range). The statistical plan for model development and validation is reported in **Supplemental Table 3**.

The main outcome was in-hospital mortality. In the derivation cohort, logistic regression analysis was performed starting from a pre-specified set of fifteen candidate variables that were both readily available and plausibly related to the dependent variable (in-hospital mortality): age, sex, Charlson Comorbidity Index (CCI), previous hospitalization for LGIB, antiplatelet therapy, anticoagulation therapy, use of NSAIDS, LGIB onset setting (out-of-hospital vs in-hospital), weekend diagnosis, symptoms at presentation, hemodynamic instability, haemoglobin levels, platelet count, international normalised ratio, serum creatinine. After evaluation of multicollinearity, multivariable logistic regression analyses were performed on variables that reached $p<0.1$ at univariable analysis. The final multivariable model was built from the set of candidate variables by removing the predictors based on p values, in a stepwise manner. The linearity assumption underlying the logistic regression model was tested using the Box-Tidwell model.[13]Model discrimination was assessed by the area under the receiver operating characteristic (AUROC) curve; the DeLong test was performed to test the equality between two or more AUROCs.[14] Calibration was assessed by a calibration curve showing the relationship between the estimated risk (on the x-axis) and the observed proportion of events (y-axis). The accuracy of the final model was internally validated using 1000 bootstrap samples[15] and the optimism-corrected AUROC was calculated.[16,17] We used the regression coefficient estimates from the multivariable model to derive the equation for predicting the main outcome, which was then validated in the external validation cohort.

Finally, we constructed a new scoring system following the methodology proposed by Sullivan et al. in the Framingham Study[18] to enhance the use of the model in routine clinical practice (**Supplemental Table 3**). The score's discriminative ability and calibration for predicting the main outcome was evaluated as mentioned above and externally validated in an independent cohort.

Patients were then stratified into levels of low, intermediate, and high risk, with thresholds reflecting clinically meaningful (at least 2-fold) gradients in risk from one group to the next.
In the validation cohort, we compared the performance of our score with that of the Oakland score. . Moreover, we reported the rate of in-hospital mortality according to the risk categories (low vs intermediate-to-high), colonoscopy procedure (yes vs no) and timing (early <24 hours vs delayed). The rate of missing data in the validation set was very low (0.8%), so we excluded these patients from the analysis and did not use any imputation method.
All p-values refer to two-tailed significance tests. P<0.05 was considered significant. Statistical analyses were performed with Stata/SE (Version 18; Stata Corp, Texas, United States of America) for Windows. We followed the TRIPOD statement for reporting this clinical prediction model study.[19]

Ethics

The study protocol adhered to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as was approved by the ethics committee and the local institutional review board of each participating centre. Informed consent was obtained from each patient included in the study.

Results

Patient characteristics

The flowchart of patient inclusion in the derivation and validation cohorts is reported in **Supplemental Figure 1**. Briefly, of the 1345 eligible patients in the derivation cohort, 1198 (89%) were included in the main analysis. The median age was 78 (67-84) years and 626 (52%) were male. Half (626) of the patients had a CCI score of at least two; 327 (27%) were on antiplatelet therapy and 258 (22%) were on anticoagulation (**Table 1**). The most common manifestation was bright red blood per rectum (820, 69%); the median hemoglobin levels were 10.3 (8.3-12.3) g/dL and 110 (9%) of the patients were hemodynamically instable. The bleeding episode occurred in 138 (12%) patients who were already hospitalized for other reasons and during the weekend in 126 (11%) of the patients. Colonoscopy was performed in 772 (64%) patients; early (≤24 hours) in 197 (26%) cases and delayed (>24 hours) in 575 (74%) cases. Only 22 (20%) of the patients with hemodynamic instability underwent computed tomography angiography (CTA) as first

examination (as per guidelines recommendation).[4] The source of bleeding was identified in 1048 (87%) of the patients, with diverticular disease (257, 22%), malignancy (147, 12%), angiodysplasia (124, 10%), ischemic colitis (115, 10%), and hemorrhoids (10, 9%) being the most frequent causes. At the end of follow-up, 105 (8.8%, 95%-CI: 7.2-10.5) presented with rebleeding and 41 (3.4%, 95%-CI: 2.5-4.6) patients died.

In the validation cohort, after the exclusion of one patient for age <18 years and five patients for incomplete data, 752 patients were included in the analysis. Patient demographics and medical history were comparable between the two cohorts, but patients in the validation cohort were more often hemodynamically instable (18%) or hospitalized at LGIB onset (26%). Colonoscopy was performed in 548 (74%) patients, and it was delayed in most cases (492, 73%). Also in this cohort, only 27 (20%) of the patients with hemodynamic instability underwent CTA as first examination, with comparable outcomes in terms of mortality between the adherent (CTA first) and non-adherent group (p=0.560). The overall rebleeding and mortality rates in the validation cohort were respectively 9% (95%-CI: 7.1-11.3) and 5.1% (95%-CI: 3.6-6.9). Patient characteristics and outcomes in the derivation and validation cohorts are reported in **Table 1**. Details of diagnosis, treatment, and etiology of the LGIB in the two cohorts are reported in **Supplemental Table 4**.

Development of a new model to predict mortality

In the univariable analysis, age, CCI, use of NSAIDs, LGIB onset in hospitalized patients, weekend diagnosis, bright red blood at presentation, hemodynamic instability, hemoglobin, INR, and creatine were associated with mortality (**Supplemental Table 5**). The final multivariable analysis included age (coefficient 0.082, 95%-CI: 0.036-0.128, p<0.001), CCI (coefficient 0.161, 95%-CI: 0.048- 0.274, p=0.020), onset in hospitalized patients (coefficient 1.024, 95%-CI: 0.188-1.859, p=0.009), hemodynamic instability (coefficient 1.185, 95%-CI: 0.434-1.936, p=0.002), and creatinine (coefficient 0.257, 95%-CI: 0.011-0.522, p=0.037) (**Supplemental Table 6**). The discriminative ability (AUROC=0.813, 95%-CI: 0.752-0.874) and calibration of the model were excellent (**Figure 2A-B**).

We then developed a pragmatic scoring system based on these five component variables (**Table 2**): the Acute Lower gastrointestinal Bleeding and In-hospital mortality (ALIBI) score. The cumulative score reaches a maximum of 13 points, and the median value was 5 (2-6) points. This risk score showed adequate accuracy and calibration (**Supplemental Figure 2**) and the predicted

risk for each point is reported in **Supplemental Table 7**. Patients could be classified into low (0-4 points), intermediate (5-9 points), and high (≥10 points) risk, with a predicted risk of death of 1% (95%-CI: 0.3-1.6%), 4.6% (95%-CI: 3.2-6%), and 19.1% (9.4-28.8%), respectively. The expected and observed mortality rates within these three risk groups are reported in **Figure 2C**, showing good calibration.

Performance of the novel model in the external validation cohort

Using the regression coefficient established in the derivation cohort, we evaluated the diagnostic performance of our multivariable logistic model in an independent cohort of 752 patients. The model showed adequate discrimination (AUROC=0.808, 95%-CI: 0.737-0.878) and calibration (**Supplemental Figure 3**). The same was valid also when the numerical score (0-13) was used; discrimination was maintained (AUROC=0.792, 95%-CI: 0.720-0.863), and the score could estimate the risk of death between 0-50% with excellent calibration (**Figure 3A-B**). The probability of death in the three risk categories was 1.2% (95%-CI: 0.3-2.1%), 6.5% (95%-CI: 4.7-8.6%), and 28.4% (95%-CI: 14.3-42.4%), with good calibration (**Figure 2D**).

In the validation cohort, we also evaluated the performance of the Oakland score in predicting mortality (n=736 patients, 16 (2%) patients had missing data for this score). The model showed adequate accuracy (AUROC=0.729, 95%-CI: 0.657-0.801), which was numerically lower compared to the new model (DeLong test, p=0.154). However, the model was not well calibrated, as it underestimated the risk of mortality after a certain threshold (**Figure 3C-D**).

Impact of colonoscopy timing according to the risk strata

We described the mortality rates in patients at low (0-4 points) vs high risk (>4 points) and the timing of colonoscopy (**Table 3**). The details of the subpopulation and the methods used for this analysis are reported in **Supplemental Table 8**. Colonoscopy was defined as early when performed within 24 hours and delayed if performed >24 hours from admission. Patient characteristics in the three groups (no colonoscopy, early colonoscopy, delayed colonoscopy) are reported in **Supplemental Table 9-10**. In patients at low risk, mortality rates were 4.8% in patients not undergoing colonoscopy and 0.4% in patients undergoing colonoscopy (adjusted OR: 0.081, 95%-CI: 0.008-0.875), independently from the timing of the examination. The rate of re-bleeding was

higher in patients undergoing early colonoscopy (18% vs 5%, adjusted OR: 5.064, 95%-CI: 1.332-19.250, ref. no colonoscopy). In high-risk patients, mortality rates were 14% in patients not undergoing colonoscopy and 6.4% in patients undergoing colonoscopy (adjusted OR: 0.363, 95%-CI: 0.158-0.835); the lower mortality rate was seen only in the delayed colonoscopy group (mortality rate 4%, adjusted OR: 0.264, 95%-CI: 0.100-0.711, ref. no colonoscopy). In the early colonoscopy group, patients underwent more frequently an endoscopic hemostatic treatment (47% vs 22%), but the mortality rate was comparable to that seen in patients who did not undergo colonoscopy at all (12% vs 13%; adjusted OR: 1.549, 95%-CI: 0.570-4.209).

Discussion

Main findings

In this prospective study, we have proposed a novel clinical score that can predict the risk of mortality in patients with acute lower gastrointestinal bleeding. We developed a model based on five readily available variables (age, Charlson Comorbidity Index, setting of bleeding onset, hemodynamic instability, and serum creatine) which was well-calibrated and showed good-to-excellent discriminative ability in both the derivation (AUROC=0.813, 95%-CI: 0.752-0.874) and the validation (AUROC=0.808, 95%-CI: 0.737-0.878) cohort. We then transformed the model into a simple clinical risk score (the ALIBI score) that stratified the risk of death as low (1%, 0-4 points), intermediate (5%, 5-9 points), or high (10-13 points, 19%) and maintained good discrimination and calibration in both cohorts.

Comparison to other scores

To our knowledge, this is the first prospective study to develop and validate a score that specifically predicts in-hospital mortality in patients with LGIB, so there are no direct comparators. However, we chose to assess the prognostic performance of the Oakland score, because is the most commonly used score in this setting and the only one recommended by current guidelines.[20,21] This score[5] was developed to identify patients at low risk of complications who can be safely discharged,[4] but it could also predict mortality with variable accuracy (AUROC 0.67-0.89).[22–24] Our study showed that the Oakland score has acceptable accuracy (AUROC=0.729, 95%: 0.657-0.801) but poor calibration for the prediction of in-hospital mortality, making it unsuitable for assessing this outcome. To some extent, this is to be expected as the score was developed to

predict a different endpoint (a composite outcome of absence of rebleeding, blood transfusion, therapeutic intervention, readmission, or death). Among the recently proposed scores,[24–26] the ABC score was developed to predict mortality in patients with upper gastrointestinal bleeding,[25] but also showed promising accuracy in patients with LGIB (AUROC= 0.84); yet, its calibration has not been evaluated and its performance has not been validated in other LGIB cohorts. Unfortunately, we could not assess this score in our patients, as the data on albumin levels and ASA Physical Status required for the calculation were not routinely collected in our external validation cohort, therefore future studies are required to compare the prognostic accuracy between the two models. Several scores have also been previously developed to identify high-risk patients, i.e. to predict "severe bleeding", such as the BLEED,[27] NOBLADS,[28] and Strate[29] score. However, these scores use a composite endpoint as a surrogate for survival and are underpowered or have limited accuracy in predicting mortality in patients with LGIB.[11] Other limitations of such scores include the development only in patients undergoing endoscopy (spectrum bias), and the lack of prospective validation or inconsistent prognostication results,[11] likely due to the heterogeneity in patient management and outcomes in LGIB. As a result, none of these scores has been introduced into clinical practice or is recommended by guidelines.[11]

Implications for clinical practice

We propose an easy, reliable, and informative tool that can estimate the risk of in-hospital mortality during the admission for an episode of LGIB. Our score was able to accurately predict the likelihood of an uncommon, but not negligible, event such as death in LGIB, which on the other hand remains a frequent, burdensome, and costly condition.

The population at risk includes admitted patients with LGIB who are generally outside the safe discharge criteria according to the Oakland score, yet represent around 90%[22,30] of patients with this condition. These patients are often frail, and the burden of the comorbidities is relevant,[31] so care is generally nuanced, patient-centered and individualized. In this complex setting, a score that reflects both the severity of the bleeding episode and the general condition of the patient may better evaluate prognosis and inform clinicians, patients, and their families in the decision-making process.

Regarding the timing of endoscopy, data from randomized trials have failed to show the benefit of early colonoscopy in terms of improved clinical outcomes, and current guidelines recommend

performing a colonoscopy *sometime* during admission.[4,32,33] However, a universal strategy may not fit for all patients with LGIB, and the extent to which the severity of the bleeding episode influences the harms and benefits of an early colonoscopy is largely unknown. In our study, we benchmarked the mortality rates according to the predicted risk (low vs intermediate-high), the choice/possibility to undergo a colonoscopy, and the timing (early vs delayed). In patients at intermediate-high risk, the delayed colonoscopy group was associated with a lower mortality rate, even after adjustment for the severity of the bleeding episode. These observations could reflect the importance of patient stabilization and supportive care in this category of patients,[34] but may also be subject to residual confounding, as no cause-effect relationship can be assumed from our study design. Therefore, future studies and trials are needed to investigate whether a score identifying high-risk patients can contribute to personalized management in LGIB.

At an institutional level, the score can be useful for auditing purposes or monitoring local outcomes over different periods of time.

Finally, only 20% of patients with hemodynamic instability underwent a CTA as first examination, suggesting suboptimal adherence to guidelines. However, the implications of non-adherence in terms of prognosis go beyond the scope of the present study and deserve further investigation.

Implications for research

In the research field, our study provides a robust framework for the assessment of prognosis in patients with LGIB. It can be used to assess the interactions between disease severity, diagnostic work-up, treatment, and clinical outcomes in observational studies or to design future clinical trials in this field. For instance, focusing on high-risk patients could reduce the sample size required to evaluate the potential benefit of diagnostic or therapeutic interventions. Future prospective studies conducted by independent investigators should provide further external validation of the prognostic model.

Strength and limitations

The main strengths of our study lie in the prospective design, the sample size, and the external validation. The multicenter and international nature of the validation cohort support the generalizability of our findings. A limitation is the lack of longer follow-up data on mortality; however, post-discharge events could be influenced more by age and the comorbidities rather than

the bleeding episodes and introduce a bias. Moreover, we did not compare the performance of our model to that of other published scores, besides the Oakland score. Finally, the observational nature of the study does not allow to establish a causative relationship between timing of colonoscopy and mortality in high-risk patients, so these data should be interpreted with caution and future randomized controlled trials are required to address this issue.

Conclusions

In conclusion, we propose a new pragmatic risk score (the ALIBI score) based on readily available variables at diagnosis that can predict the risk of in-hospital mortality in patients with acute lower gastrointestinal bleeding. The risk categories can be used to inform patients and support medical decisions regarding diagnostic work-up and treatment of patients with this condition.

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Figure Legends

Figure 1 – Case 1: Patient with severe lower gastrointestinal bleeding; computed tomography shows arterial bleeding in the cecum (A-B), confirmed by angiographic images (C). Super-selective glue embolization is performed (D) with shows resolution of bleeding (E)**.** Case 2: Patient with bleeding due to endoscopic submucosal dissection (F-G), treated by combined mechanical and energy-based hemostasis (H), with subsequent control of the bleeding (I).

Figure 2 – Discriminative ability (A) and calibration (B) of the newly developed multivariable model*. Predicted and observed risk of death according to the ALIBI risk groups in the derivation cohort (C) and the validation cohort (D).

*Prediction of mortality: 0.082*Age (years) + 0.161* CCI (points) + 1.024*In-hospital + 1.185* Instability + 0.257*Creatinine (mg/dl) – 13.368. Discrimination: AUROC (95%-IC) = 0.813 (0.752-0.874)

Figure 3 – Discrimination and calibration of the ALIBI score (A-B) and the Oakland score (C-D) in the external validation cohort. The area under the curve (AUROC) for the ALIBI score was 0.799 (0.724-0.875) and for the Oakland score was 0.729 (0.657-0.801) (n=736 patients with both scores).

Supplemental Figure 1 – Flowchart of patients' inclusion in the derivation (A) and validation (B) cohort.

Supplemental Figure 2 – Discrimination (A) and calibration (B) of the ALIBI score for the prediction of mortality in the derivation cohort.

Supplemental Figure 3 – Discrimination (A) and calibration (B) of the novel model for the prediction of mortality in the validation cohort.