Critical Review Form

Clinical Prediction or Decision Rule

Differentiation between patients with acute upper gastrointestinal bleeding who need early urgent upper gastrointestinal endoscopy and those who do not: A prospective study
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Objective: **"To define the clinical and laboratory variables available on initial evaluation that can be used to identify, among patients with an initial diagnosis of UGI bleeding, those who are at low risk of ongoing bleeding and who, therefore, do not need an early, urgent UGI endoscopy". (p 382)**

Methods: **Prospective derivation (May 1999 – May 2001) and validation (June 2001 – Aug 2002) of consecutive patients presenting to the ED of Sotiria General Hospital in Athens, Greece with hematemesis, coffee-ground vomit, or melena. Exclusion criteria included severe co-morbidity (AMI, CVA within three months, grade IV CHF, respiratory failure, chronic renal failure, major neurological deficit, severe hematological derangements or profound immunosuppression), anti-coagulation, already hospitalized for another illness, suspected perforation, or senility.**

All enrolled subjects underwent endoscopy within 12-hours by a single, blinded endoscopist and prior to any medical management except nasogastric (NG) lavage and aggressive intravenous therapy for hemodynamically unstable patients. A portion of ulcers were biopsied. Ulcer lesions were classified by Wara's classification, while active bleeding was defined by the presence of spurting (Forrest 1A), oozing (Forrest 1B) visible vessels, oozing from ulcer base without visible vessel (Forrest 1B) or variceal hemorrhage. Hemodynamically stable patients with a clear ulcer base were discharged within 24-48 hours while those with stigmata of recent bleeding, signs of re-bleeding, or recipients of endoscopic therapy had repeat endoscopy at 48-72 hours (p. 382)

A structured data collection form was used. Using SPSS all candidate variables significantly related to active bleeding by univariate analysis were entered into multivariable logistic regression analysis using backward selection algorithms. The coefficients for independently significant variables were then divided by 0.5 and rounded to the nearest integer to facilitate the simple numeric CDR below. (p. 385)

I.	***Is this a newly derived instrument* (Level IV)?**	
A.	Was validation restricted to the retrospective use of statistical techniques on the original database? (If so, this is a Level IV rule & is not ready for clinical application).	No, this new CDR was prospectively validated on another 110 subjects following derivation, though the results was not computed and applied during the clinical encounter as they would be in routine care.
II.	**Has the instrument been validated? (Level II or III). If so, consider the following:**	
1a	Were all important predictors included in the derivation process?	No. "17 variables that were initially evaluated showed that nine were significantly associated with active bleeding ($p < 0.05$)". Unfortunately, the investigators do not clearly state which 17 variables were incorporated. Table 1 contains 20 variables. Looking at the PGY-I paper these investigators did not consider such variables as presenting symptom of syncope, dyspepsia, or abdominal pain. Nor did they consider use of steroids, acid-blocking drugs, smoking, or alcohol consumption. Finally, the investigators never reference or discuss previous UGI bleed CDRs which could be a rich source of candidate variables even if the outcomes being assessed differ slightly (mortality, re-bleed or need for intervention vs. active-bleeding).
1b	Were all important predictors present in significant proportion of the study population?	Yes, as illustrated in Table 1 (p. 383). Candidate variables were present in 10-94% of the population.
1c	Does the rule make clinical sense?	No. The rule lacks *face validity* because the biological plausibility of WBC being related to active UGI bleeding seems tenuous. Furthermore, failure to consider all potentially relevant candidate variables means the CDR potentially lacks *content validity*.
2	Did validation include prospective studies on several different populations from that used to derive it (II) or was it restricted to a single population (III)?	Prospective validation on single hospital population so this rule is a Level III CDR pending validation on more heterogeneous groups.

3	*How well did the validation study meet the following criteria?*	
3a	Did the patients represent a wide spectrum of severity of disease?	Unknown since little demographic data provided.
3b	Was there a blinded assessment of the gold standard?	Yes. "All 190 patients underwent emergency endoscopy within 12h from presentation, by the same endoscopist, who was blinded to the patients' histories". (p. 382). Presumably the 110 in the validation set, so had endoscopist blinded to clinical data, but the authors do not clearly state this fact.
3c	Was there an explicit and accurate interpretation of the predictor variables & the actual rule without knowledge of the outcome?	Unknown since the authors fail to state who collected the clinical variables, whether this data collector was blinded to the study hypothesis or the primary outcome of endoscopic evidence of active bleeding. Furthermore, the authors do not conduct any reliability assessment of candidate variables so readers cannot be certain that two clinician provided the same variables would interpret them the same or incorporate them into the rule to compute the same result.
3d	Did the results of the assessment of the variables or of the rule influence the decision to perform the gold standard?	No – all subjects in both cohorts had endoscopic evaluation within 12-hours.

4	How powerful is the rule (in terms of sensitivity & specificity; likelihood ratios; proportions with alternative outcomes; or relative risks or absolute outcome rates)?	• 190 consecutive patients in derivation set and 110 in the validation set; mean age 63.7 years and 64.7% male. • Melena was the most frequent finding in the derivation (66%) and validation (68%) sets with active bleeding observed in 51/190 (26.8%) and 28/110 = (25.5%). • During their hospitalization 2.6% and 2.7% had re-bleed with 1.6% mortality. • Four variables were independently associated with active-bleed: hemodynamic instability; fresh blood in NG tube; Hg < 8g/dL; WBC > 12000/μL. By incorporating and weighting these variables by their LR coefficient the Athens UGI bleed CDR was derived (below) with low-risk defined as < 7 demonstrating the following diagnostic test characteristics for active bleed: **Derivation set** Active Bleeding Athens Yes No High-risk 46 14 Low-risk 5 125 Sen 90.2% (81.4 – 95.4) Spec 89.9% (86.7 – 91.8) LR+ 8.95 (6.3 – 11.69) LR- 0.11 (0.005 – 0.21) **Validation set** Active Bleeding Athens Yes No High-risk 27 10 Low-risk 1 72 Sen 96.4% (85 - 99) Spec 87.8% (94 - 100) LR+ 7.91 (5.2 – 8.5) LR- 0.04 (0.007 – 0.180) • Using < 7 as low-risk and ≥ 11 as high-risk the authors compute sensitivity 96% specificity 98% with 9% left in the intermediate 7 – 10 zone. • Among the highest risk group (11 – 17 points) only EGD identified active bleeding in 89%.

III.	**Has an impact analysis demonstrated change in clinical behavior or patient outcomes as a result of using the instrument? (Level I). If so, consider the following:**	
1	How well did the study guard against bias in terms of differences at the start (concealed randomization, adjustment in analysis) or as the study proceeded (blinding, co-intervention, loss to follow-up)?	Small chance of *selection bias* given consecutive patient sampling. The potential for *ascertainment bias* was reduced by blinding the endoscopist. *Co-intervention bias* excluded because nobody received any pre-EGD PPI.
2	What was the impact on clinician behavior and patient-important outcomes?	No Level I CDR impact analysis performed. Before widespread use of this CDR recommended outside of Athens, prospective validation in multiple heterogeneous sites are necessary, while assessing reliability and clinician acceptance. Based upon the current results, the rule has the potential to identify a low-risk subset of significant size (68% of derivation cohort and 66% of validation set).

Limitations

1) **Incomplete consideration of potential candidate variables or prior UGI CDRs (see II 1a above).**
2) **Lacking face-validity with inclusion of WBC (see II 1c above)**
3) **No assessment for independent variable reproducibility (Kappa).**
4) **No objective assessment of CDR cut-points with receiver operating curve (ROC) area under the curve (AUC). How did authors select < 7 as low-risk?**
5) **No assessment or reporting of quantitative diagnostic test characteristics: sensitivity, LR's, AUC all with 95% CIs. Furthermore, the authors do not even provide 2x2 tables to permit readers to independently calculate these parameters.**
6) **Incomplete reporting of patient characteristics to permit extrapolation of findings to other populations.**
7) **Failure to separately analyze biopsied from non-biopsied ulcers which could have impacted observed active-bleeding or re-bleeding rates.**
8) **Failure to provide CONSORT-diagram like description of how many subjects were excluded.**

9) **Failure to reference or utilize Stiell's CDR methodology.**

Bottom Line

Single-center derivation and validation of simple 4-component rule appears to accurately identify a substantial subset at low-risk for active UGI bleeding at could safely permit delayed endoscopic evaluation for many patients. These findings should not be extrapolated to those with severe co-morbidities, anti-coagulation, suspected perforation, or senility since such patients were excluded. Furthermore, future trials should verify the rules accuracy in different populations while also assessing the reproducibility and clinician acceptance when incorporated into real-time clinical decision-making.

The Athens UGI Active Bleeding CDR

	Points
Fresh Blood in NG tube	**6**
Hemodynamic ally unstable *	**4**
Hg < 8g/dL	**4**
WBC > 12000/µL	**3**

*Systolic BP < 100 and/or heart rate > 100 and/or orthostatic changes in SBP (decrease by more than 10%) or heart rate (increase of > 10%) between supine and seated position.

Low-risk is defined as score < 7 with $LR^+ = 7.9$
$LR^- = 0.04$