Assessment of prognosis factors in patients with upper non-variceal gastrointestinal bleeding

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Key words

Upper gastrointestinal bleeding, prognosis, risk factors, mortality, re-bleeding, prognostic score, gastric cancer, angiogenesis.
The stage of knowledge

Upper gastrointestinal bleeding (UGIB) represents one of the most common medical and surgical emergencies. That is the reason why we have to know very well the diagnosis and treatment methods, according to well established guidelines.

The advanced age of patients with UGIB and the high frequency of age-related comorbidities made obtaining good results with few adverse events a continuing challenge. Although recently the upper GI endoscopy made remarkable progresses and new interventional radiological techniques are now available, the mortality in UGIB remain stable, the increase of life expectancy being a plausible explanation.

The risk estimation is possible in the moment of patient admission, before proceeding UGIE, using the clinical and biological parameters, for the best management of these patients in the following hours. However, a complete and complex score that allows the accurate patient classification in one of the risk group is possible only after the upper GI endoscopy is performed.

The severity of bleeding is direct related to morbidity and mortality. The clinical markers of severity are the initial hemodynamic instability, persistent hypotension, the necessity of over 4 l of blood transfusion in the first 24 hours or the signs of bleeding (hematemesis or hematochesia, gastric aspiration of blood). Others risk factors related to negative prognosis are the advanced age, associated diseases (cardiac, pulmonary, hepatic, renal, central nervous system diseases), the onset of the bleeding during hospitalization, the recurrence (re-bleeding) that occurs in 20% of the patients, the presence of major bleeding stigmata, the ulcer localization (posterior duodenal bulb, the lesser curvature), the dimensions of the ulceration and the etiology of the bleeding.

The endoscopic findings are very important for the evaluation of the risk of mortality or recurrence of bleeding. The establishment of the cause of bleeding allows the estimation of the risk for re-bleeding or continuous bleeding; this risk is elevated in patients with esogastric varices, medium in those with small gastric or duodenal ulcer and low in patients with Mallory Weiss syndrome or hemorrhage erosive gastropathy.

From all the score systems developed since present, the Rockall and Blatchford scores are the most utilized, validated in many clinical randomized studies.

The Glasgow-Blatchford (GBS) score is a method of risk evaluation in UGIB that can predict with high accuracy the necessity of medical intervention (endoscopic therapy, blood transfusion necessity or surgical involvement) or the mortality. This score can identify the patients with indication of hospital admission after an episode of UGIB. The major advantage of this score comparing to the Rockall score is that it does not include the endoscopic parameters and can be used for risk stratification in the moment of patient admission.

The most common system is the one proposed by Rockall in an audit study of non-variceal upper GI bleeding. This score was therefore validated in many recent studies that established that it can be useful to detect the low risk patients that can be discharged as well as for those with high risk that requires endoscopic treatment and hospital attendance. In a Rockall score of 2 or less, in only 4.3% of patients are noticed the re-bleedings and the mortality is approximately 0.1% of cases.

The purpose of the study

The purpose of the study is to evaluate the prognostic parameters in the UGIB of non-variceal causes in a geographic area with few published data, with particular social and economical circumstances. I believe that the evaluation of the classical prognosis scores in the studied population and the establishment of the importance of these findings in a prospective study is very useful; the patients in this study presented in the Emergency Room with non-variceal UGIB and we included the patients admitted within one year.
I consider to be important the assessment of classical prognosis scores in this population and establishing their relative importance in a prospective study in patients with non-variceal UGIB presenting in the course of one year in our emergency hospital.

**Methods**

The study was performed during one year, between November 2004 – October 2005, in Craiova Emergency Hospital, and included patients admitted the general surgery and gastroenterology yards. All gastrointestinal endoscopies were performed in the Endoscopy Laboratory of the Gastroenterology Clinic. It is a prospective study, all patients were monitored from admittance till discharge. We assessed the UGIB risk and short-term prognosis, and in the gastric cancer subgroup, based on angiogenesis immunohistochemical markers: microvascular density, expression of the vasculo-endothelial growth factor in biopsy samples obtained by surgery or endoscopy.

The patients were divided in:
- Group I - 308 patients with UGIB:
  - Subgroup 1 - 179 patients UGIB caused by ulcer
  - Subgroup 2 - 91 patients with other cause of the bleeding
    - in 38 patients the cause could not be established.
- Group II - 40 patients with gastric cancer:
  - Subgroup 1 - gastric cancer and UGIB
  - Subgroup 2 - gastric cancer without UGIB.

**Group I**

**Database**

We created a database that included data from the history (age, sex, risk factors, co-morbidity), laboratory results (blood count, urea, creatinine), clinical data (hemodynamic status, bleeding, therapy with ), endoscopic exam (source of the bleeding, the presence of blood in the stomach, Forrest class, endoscopic therapy).

All these parameters were correlated by univariate and multivariate analysis with the evolution of the bleeding, blood transfusions necessity, duration of hospitalization, risk of recurrence, surgery necessity and mortality.

Informed consent was obtained before all procedures.

**Statistical analysis**

We performed the descriptive statistical analysis: standard deviation, variation coefficient, standard error of a mean, 95% confidence interval. The markers were analyzed by univariate and multivariate means. We utilized multivariate regression analysis, proportion, random (Backward Stepwise – Conditional LR Method) with covariates. We used *Statistic Package for the Social Sciences (SPSS)*, version 17.0.

**Group II**

We included 40 consecutive patients with gastric cancer admitted in the Gastroenterology Clinic of Craiova Emergency Hospital. Eight patients presented with UGIB as first symptom (subgroup 1) the rest were included in subgroup 2. All patients were examined by endoscopy; the diagnosis of cancer was established based on endoscopic features and histopathological examination of biopsies. At least 4 bioptic fragments were obtained during endoscopy. From these we calculated microvascular density (MVD) using CD31 and CD34 immunohistochemical markers. VEGF expression was considered positive when the marker was present in at least 5% of tumor cells. In the end, the relation between pathology parameters, tumor stage and the risk of bleeding was established.
Staging

Regarding the study for staging we used the TNM classification for gastric cancer according to the standardization manual of AJCC (American Joint Committee on Cancer).

The tumor stage was established using: transabdominal ultrasonography (to identify the metastases, especially in the liver, the ascites and sometimes for the visualization of the primary tumor) computed tomography (the most used method in the cancer patients evaluation, with high accuracy in the assessment of the N and M stage) and endoscopic ultrasound (used for the N and T staging).

Statistical analysis

For the statistical analysis of these subgroups we used univariate analysis and a 2X2 contingency table. The value for $p$ was calculated using the Fisher test. A $p$ value $< 0.05$ is considered statistically significant. We obtained a correlation between survival at 2 years and angiogenetic immunohistochemical markers.

Conclusions

Group I

Univariate analysis

Univariate analysis revealed numerous prognostic markers in non-variceal UGIB. Some of them were not validated in multivariate analysis. Univariate analysis showed:

1. **The risk factors for non-variceal UGIB** are mainly superimposed with the prognosis factors. With prognostic significance were:
   a. **The advanced age** is a predictive factor of mortality;
   b. **Male sex**, although known as a risk factor for UGIB was only significant correlated with high blood transfusion necessary;
   c. **The NSAIDs intake**. It was established a certain correlation with the majority of adverse events: the bleeding evolution, the duration of hospitalization, the time spent in the Intensive Care Unit, the blood transfusion necessary, the need for surgical involvement, without a correlation with the mortality.
   d. **The anticoagulants intake** - a confident correlation with the bleeding evolution and mortality. In the hemorrhagic ulcer subgroup there was no influence;
   e. **The *Helicobacter pylori* infection** only influences the surgical necessity in the all causes UGIB subgroup and in the ulcer induced UGIB small subgroup.

   *Smoking and alcohol intake were not correlated with the prognosis in patients with non-variceal UGIB.*

2. **The admission clinical parameters**
   a. **The exteriorization mode of bleeding** doesn’t influence the prognosis. The only correlation found were the presence of melena from the admittance with high transfusion needs;
   b. **The presence of comorbidities** represents a very useful prognostic factor. A clear correlation was found between comorbidities and the majority of adverse events: continuous bleeding, long hospitalization (especially in ICU) and mortality. In the group of patients with ulcer the only influenced parameter was the mortality.
   c. **The hemodynamic status**, characterized by systolic and diastolic blood pressure and ventricular rate (SBP, DBP and VR) was significantly correlated with the majority of events: continuous bleeding, high transfusional requirement,
surgical requirement, prolonged hospitalization and mortality. The hemodynamic status doesn’t represent a predictive factor for rebleeding.

3. **Biologic parameters**
   a. **Hemoglobin level** at admittance was significantly correlated with prolonged hospitalization (including ICU) and transfusion requirement. In the second group of patients were found the same correlations.
   b. **Blood urea and creatinine levels** represent very important prognostic factors. Significant correlations were found with: mortality, continuous bleeding and ICU hospitalization. In the second group same correlations were found but only for urea. Thus, urea seems to be a better predictor of prognosis in UGIB patients.

4. **Antisecretory treatment**
   a. Proton pump inhibitors (PPI) represent a predictive factor for better prognosis comparing to H2 receptors inhibitors: low transfusion requirement, shorter hospitalization in ICU and lower mortality. In the second group antisecretory treatment were correlated with transfusion requirement and mortality.

5. **Endoscopic parameters**
   a. Performing endoscopy after 24 hours from the admittance was correlated with a prolonged hospitalization in ICU only in the second group of patients;
   b. The presence of fresh blood in the stomach– represent the only parameter high correlated with all adverse events, including rebleeding;
   c. Forrest classification predicts the evolution of bleeding, hospitalization duration (including ICU), surgical requirement and rebleeding but the mortality is not correlated to this classification;
   d. Combined endoscopic treatment is better than single endoscopic treatment especially in first Forrest class.

**Multivariate analysis**

1. **Bleeding evolvement** was negative influenced by NSAID, anticoagulants, the presence of fresh blood in the stomach and unknown source of bleeding. In the group of patients with ulcer the only negative prognostic factor was Forrest classification.
2. **Higher transfusion requirement was correlated with NSAID**, the presence of fresh blood in the stomach, the presence of severe anemia and administration of H2 inhibitors (compared to PPI); in ulcer patients the predictive parameters for high transfusion needs were hemodynamic instability, severe anemia and first Forrest class.
3. **Prolonged hospitalization** was significantly correlated with severe anemia, the presence of fresh blood in the stomach and hemodynamic instability, in both group of patients.
4. **ICU hospitalization was influenced by NSAID**, presence of fresh blood in the stomach, the presence of comorbidities and hemodynamic instability; in the second group of patients two more factors are involved: severe anemia and ulcer diameter;
5. **Surgery necessity** was higher in patients with *H. Pylori*, with hemodynamic alteration and blood in the stomach at endoscopy. In patients with ulcer just 2 parameters were predictive: diastolic blood pressure and the presence of blood in the stomach. If the surgical intervention was done for hemostasys, the infection with HP was predictor for surgery also in patients with ulcer.
6. **Mortality** was influenced by: treatment with anticoagulants, presence of comorbidities, high serum urea, and treatment with H2 inhibitors.
7. **Rebleeding** was influenced by anemia, a history of ulcer and the presence of blood in the stomach at index endoscopy. In patients with ulcer it correlated with gastric ulcer.
Validation of classical prognosis scores

1. **Blatchford score** was validated as a useful prognostic tool, with the greatest predictive value for blood transfusion necessity, duration of hospitalization and mortality. It was not related to re-bleeding.

2. **Rockall score** was validated for the majority of parameters excluding re-bleeding and mortality. In the subgroup with ulcer it was an important predictor of mortality.

**Group II**

1. Microvascular density correlates with the local stage of the tumor;
2. Vasculo-endothelial growth factor is correlated with metastases;
3. There is a clear relation between VEGF expression, MVD and the risk for UGIB in patients with gastric cancer.

**Selective references**


Curriculum vitae

Name: Iordache Sevastița
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Profesional activity
1998 Graduated Faculty of Medicine, University of Medicine and Pharmacy “Iuliu Hațegianu” Cluj-Napoca
2000 Fellow in training in internal medicine
2005 Teaching assistant in internal medicine, University of Medicine and Pharmacy Craiova
2006 Specialist in internal medicine – Clinical County Emergency Hospital Craiova
2009 Fellow in training in gastroenterology

Postgraduate courses
2004 “Introduction in Endoscopic Ultrasound”
2004 “General Ultrasonography”
2005 “Advanced Post-graduate Course in Gastroenterology”, organized by Holland Digestive Disease Week (HDDW) Foundation, September 19th - 23rd in Zwolle and September 26th – 30th in Ámsterdam (Dr Fritz Nelis and Professor Chris Mulder).
2006 Postgraduate Teaching Program UEGW (Berlin 2006)
2007 Euroschool Course – Guidelines in Gastroenterological Ultrasound, under European Federation of Societies for Ultrasound in Medicine and Biology auspices
2008 Euroschool Course – Ultrasound in gastroenterology, under European Federation of Societies for Ultrasound in Medicine and Biology auspices
2008 Postgraduate course in “Diagnostic Endoscopy”

Representative papers


**Research activity**

- 2007-2010, Grant PNCD II (Ideas), *The role of endoscopic ultrasound and optical coherence tomography for minim-invasive assessment of neo-angiogenesis in digestive cancer patients* (*OCTEUS*), Project director Prof Adrian Săftoiu
- 2006-2008, financed by CNCSIS Project A type ‟*The role of contrast endoscopic ultrasound compared with angiogenesis markers for the improvement of therapeutic strategies in pancreatic cancer patients*”. Project director Prof Adrian Săftoiu
- 2006-2008 financed by CNCSIS Project A type – ‟*The involvement of vasculo-endothelial growth factor (VEGF) in the evolution of gastric adenocarcinoma and the correlation with the risk of upper GI bleeding and tumoral stage*”. Project director: Prof Tudorel Ciurea
- 2006/2008 CEEX / *The role of endoscopic ultrasound elastography compared with molecular techniques for the early diagnosis and prognostic assessment in patients with pancreatic cancer* (ELASTO-PAC), Project director: Prof Tudorel Ciurea.