REVIEW

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Subject:

Defense of the dissertation "Risk Factors and Clinical Follow-up in Patients with Upper Gastrointestinal Bleeding", with scientific supervisor Assoc. Prof. Milko Bozhidarov Mirchev, MD, PhD, for the award of the educational and scientific degree "Doctor"

Field of higher education 7. Healthcare and Sport; professional area 7.1. Medicine

Scientific specialty: Gastroenterology

Author: Dr. Aleksandar Valeriev Yordanov

Scientific organization: Medical University "Prof. Dr. Paraskev Stoyanov" – Varna

Form of doctoral training: Independent preparation

I was presented with a complete set of documents related to the official defense of the dissertation for the award of the educational and scientific degree "Doctor". The procedure fully complies with the Act on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for its application at MU – Varna, as well as the Regulations on the conditions and procedures for acquiring scientific degrees and holding academic positions at MU – Varna.

By Order No. R-109-189/19.05.2026 of the Rector of Medical University "Prof. Dr. Paraskev Stoyanov" – Varna, I was appointed as a member of the Scientific Jury.

At the first remote (non-attendance) meeting of the Scientific Jury, I was selected to present a review.

Dr. Aleksandar Valeriev Yordanov was born on 12.06.1994. He graduated in medicine from Medical University – Varna in 2020 with full honors and won the "Golden Hippocrates" award. From the same year he has been an assistant professor in gastroenterology, hepatology and nutrition at MU – Varna, and since the beginning of 2021 he has worked as a physician at "Sveta Marina" University Hospital, Varna. Since 2025 he has held a recognized specialty in

gastroenterology. After graduating, he has attended almost annually the national conferences on gastroenterology and hepatology, as well as the national congresses of the young gastroenterologist. He has also demonstrated his interest in international achievements in gastroenterology through his participation in international forums such as UEGW and ESGE Days. During his studies he completed an internship in internal medicine in Saint Petersburg, Russia. The candidate has command of German and English, has been a gastroenterology specialist for one year, and demonstrates a clear intent toward an academic career and interests in the field of gastrointestinal endoscopy.

In connection with the dissertation, the author presents 5 publications – review articles in local journals, of which 2 in Scripta Scientifica Medica (Medical University Varna) and 3 in "Varna Medical Forum".

Acute upper gastrointestinal bleeding remains a topical subject in emergency gastroenterology. Despite the indisputable progress in endoscopic hemostasis techniques and intensive care medicine, a number of questions remain unresolved, and morbidity and mortality continue to be unacceptably high. Given the aging of the population, the high cardiovascular morbidity, and the widespread use of antiplatelet agents and anticoagulants, the problem of "acute non-variceal GI bleeding" is not expected to lose its relevance. Questions such as optimal risk stratification and the timely identification of high-risk patients, the optimal timing of emergency endoscopy, the management of anticoagulant therapy, and the optimization of endoscopic hemostasis techniques continue to be insufficiently clarified. On the other hand, the epidemic of liver injury associated with metabolic dysfunction, increasingly complicated by portal hypertension, shows that variceal bleeding will also not lose its relevance, despite the progress in the control of viral hepatitis, which until recently was a leading cause of advanced liver disease alongside alcohol abuse. For the reasons outlined, the topic developed by the doctoral candidate is undoubtedly relevant and suitable for a dissertation.

Structure of the work: The dissertation is written on 231 standard typewritten pages and contains 149 tables and 76 figures. The bibliography includes 266 references, of which 262 in English and 4 in Bulgarian.

The literature review is correctly structured. Special attention is paid to the epidemiology and global burden of acute upper gastrointestinal bleeding, as well as to the unresolved problems regarding transfusion strategy, the correct identification of high-risk patients, the

timing of endoscopy, and others. An appropriate definition of acute upper gastrointestinal bleeding (UGIB) is used, taking into account the location of the source relative to the ligament of Treitz. Severe acute hemorrhage is also defined. Further in the exposition, the author introduces the two main types – variceal and non-variceal bleeding – highlighting the differences in management and prognosis. The seriousness of the problem is emphasized, as are the roles of timely diagnosis, intensive care, and the multidisciplinary approach. The indisputable role of the precise analysis of risk factors, endoscopic findings, and clinical course in optimizing the diagnostic and therapeutic strategy is underlined. Non-variceal bleeding is examined in detail, with attention paid to its epidemiology, the major role of Helicobacter pylori (HP) infection, and the use of ulcerogenic medications – nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin. The reduction in its incidence is noted, mainly due to the decrease in peptic ulcer disease amid the limited prevalence of HP infection in the Western world. On the other hand, mortality continues to be high – around and above 10% – despite the progress in resuscitation care and endoscopic hemostasis techniques, against a background of increased occurrence in elderly and multimorbid patients. The risk factors are examined consistently and in detail, with great attention paid to the role of HP and ulcerogenic medications and their widespread use. The antiplatelet agents are well addressed, with attention paid to their leading role in connection with the aging of the population and the high incidence of cardiovascular disease. Interesting data are also presented on the increased risk of bleeding with the use of direct oral anticoagulants, as well as data on the increased risk of UGIB with the use of selective serotonin reuptake inhibitors – agents of growing importance and prevalence in modern society. Data are also provided on bisphosphonates, as well as on the role of comorbidity and advanced age. The role of concomitant advanced renal or hepatic disease in increasing the risk of recurrent bleeding and mortality is emphasized. An interesting fact to which attention is drawn is liver cirrhosis, which is not only a leading risk factor for variceal bleeding but also has an indisputable role in worsening the prognosis of non-variceal bleeding as well. The etiological causes of non-variceal bleeding are examined concisely and competently, followed by a concise presentation of the pathogenesis, with appropriate attention paid to the key role of HP and the importance of its eradication, the significance of ulcerogenic medications and the additional inhibition of platelet aggregation they cause, and the important role of pH. The main lines of management of non-variceal bleeding are outlined, the scoring systems are introduced, and their leading role in risk stratification is emphasized. The Glasgow-Blatchford Score, AIMS-65, ABC score, MAP (ASH), CANUKA, Rockall score, Cedars Sinai Medical Centre Predictive Index (CSMCPI),

and Progetto Nazionale Emorragia Digestiva (PNED) are explained in detail. The comparatively scarce literature data comparing the individual scoring systems are also presented, underscoring the need for the present work and its aim to provide a comparative analysis of the individual prognostic scoring systems in patients with acute UGIB under real clinical conditions. The literature review also presents, in sequence, the treatment strategies for non-variceal bleeding, the role of proton pump inhibitors and prokinetics, as well as controversial issues such as the timing of endoscopy and the role of the nasogastric tube and endotracheal intubation. For endoscopic diagnosis and prognostic assessment, the Forrest classification is presented, which has retained its relevance for over 40 years. The author also presents the endoscopic hemostasis techniques for non-variceal bleeding, illustrating them with images from his own archive. He also presents the latest techniques, such as the application of topical agents and "over-the-scope" clips. He presents the available endoscopic strategies through the prism of the latest recommendations of the European Society of Gastrointestinal Endoscopy (ESGE). Creating a complete picture of the management algorithm, the author examines strategies for ongoing or recurrent bleeding and explains, in practical terms, post-endoscopic management. In the next section, the author examines in detail variceal bleeding, the risk factors, the indications for primary prophylaxis, hemostasis strategies, and secondary prophylaxis, referring to the Baveno VI consensus. Transfusion strategies are also addressed, as are the controversial issues surrounding the transfusion of plasma and platelet concentrate, as well as therapeutic strategies according to the ESGE recommendations. A favorable impression is made by the presentation and command of the most modern endoscopic therapeutic techniques, including endosonography-guided obliteration with coils, as well as the combination of coils and glue. The author also presents in depth the endovascular techniques such as the transjugular intrahepatic portosystemic shunt (TIPS) and balloon-occluded retrograde transvenous obliteration (BRTO), supporting them with current literature data. The author does not omit to discuss rescue techniques as well, such as balloon tamponade and esophageal stent placement.

In conclusion, the author emphasizes the need for rapid diagnosis and timely risk stratification, which should determine adequate therapeutic management. He outlines age, comorbidity, anticoagulant use, and the severity of hepatic dysfunction in patients with cirrhosis as the individual risk factors of greatest importance for prognosis, as well as the need to validate the scoring systems and to select the most appropriate one, which would

adequately identify the risk profile of the individual patient and support the timely choice of resuscitation and endoscopic therapy ensuring an optimal outcome.

The aim is clearly formulated: to analyze the clinical, laboratory, endoscopic, and therapeutic characteristics of patients with upper GI bleeding with a view to identifying the risk factors for recurrence, severe course, and unfavorable outcome, and on this basis to optimize the diagnostic and therapeutic approach and follow-up.

The tasks are seven in number and are directly related to the fulfillment of the aim. The author performs a retrospective analysis of both patients with non-variceal and patients with variceal bleeding, with the aim of identifying risk factors for severe course and recurrence in non-variceal bleeding, as well as risk factors for the occurrence of variceal bleeding. An assessment of the prognostic value of the known scoring systems is declared, as well as a comparison between them with respect to the risk of severe course, mortality, and the need for reintervention. The assessment of the time to recurrence, as well as the analysis of the risk factors for its occurrence, is another important focus of the retrospective observational study. The last but not least task is the analysis of in-hospital mortality.

Material and methods: The study is retrospective, observational, single-center, and comprises 209 patients with acute bleeding who underwent upper endoscopy, in accordance with the ESGE definitions, over a four-year period. The inclusion criteria are clearly defined – clinical suspicion of acute bleeding and upper endoscopy performed during the hospital stay. An important limiting inclusion criterion is the endoscopically verified source of bleeding, which, as is known, is not always possible. The data were collected over a four-year period from the electronic hospital records via the hospital information system (HIS). The retrospective identification of patients in the HIS predetermines possible inaccuracies and deficits in the available data, notwithstanding the author's claim of a "multicomponent approach". Data on history, physical examination, and laboratory tests were extracted from the hospital documentation. Despite the retrospective nature of the data collection, the author states that he assessed liver function and portal hypertension in all patients, calculating established non-invasive indices and using information from imaging studies when available. On the basis of retrospective data, several scores were calculated in all patients – GBS, AIMS65, ABC-score, CANUKA, MAP(ASH), Rockall – without it being specified whether they were applied in variceal bleeding or only in suspected non-variceal bleeding. Post-endoscopically, the full Rockall score, PNED, and CSMCPI were calculated. It is not specified how the absence of parameters required for calculating a given score and not

entered into the HIS was handled, nor how data deficits were managed, nor how reliable the results obtained in such a situation would be.

Data from emergency endoscopy were also collected, as was the time of its performance relative to the hour of hospitalization. A standard endoscopy examination protocol was applied, but it is not specified how an incomplete protocol was handled, bearing in mind that emergency endoscopy is often performed outside working hours by endoscopists of varying qualifications, which casts doubt on the reproducibility of the data entered into the endoscopy protocol.

The statistical software IBM SPSS Statistics, version 26.0, was used.

The prognostic value of the different scoring systems was analyzed by ROC analysis and area under the curve (AUC). Logistic regression analysis, correlation analysis, and other statistical methods were also used.

Results: Of the 209 patients with bleeding included in the study, only 19 (9.1%) had variceal bleeding, which predetermines statistical unreliability and the impossibility of reliable comparisons between the two groups.

Men predominate in the cohort, and the mean age is 68 years. Melena as the first clinical manifestation was registered in 86.1%, and hematemesis in 42.1%. Hematochezia was observed in 20.1%. The term is conflated with rectorrhagia, with the author not specifying the difference between the two clinical findings. A nasogastric tube, although not mentioned in the current international recommendations, was placed in 9.6% of patients, and, interestingly, in all those in whom it was placed the lavage was positive. It is known from practice that very often, especially with a post-pyloric source, the lavage is negative.

Hemodynamics were recorded in all patients and a shock index was calculated, which was above 1 in almost 40% of patients. Anemia on admission was registered in over 86% of the studied cohort. The author defines clinically significant coagulopathy as one in which the INR is above 1.5 and observes it in 40.8% of patients. It should not be forgotten that this cohort includes a considerable proportion of patients with liver cirrhosis, in whom an INR above 1.5 should not automatically be taken as an indicator of impaired coagulation, given the different levels of pro- and anticoagulants in these patients. The author also finds a more frequent occurrence of renal failure among patients with non-variceal bleeding. The interpretation of these indicators should likewise be cautious, given the fact that in patients with cirrhosis creatinine values are lower. With respect to comorbidities, the most common

are cardiovascular, observed in over 74% of the cohort, with over 40% having a history of an acute vascular event. Liver cirrhosis as a comorbidity was observed in almost 20% of patients, with the majority (over 40%) being decompensated – Child-Pugh class C. The use of high-risk medications, including corticosteroids, NSAIDs, antiplatelet agents, and anticoagulants, was carefully examined. The use of proton pump inhibitors and H2 blockers was registered in only 15.8% of patients.

With respect to emergency gastroscopy, the mean time to its performance was 4.04 ± 4.66 hours, with 82.8% of cases performed immediately – within less than 6 hours of hospitalization. It is a known fact that early gastroscopy in suboptimally resuscitated patients correlates with high mortality, and such early performance is acceptable only in suspected variceal bleeding or hemodynamic instability despite optimal resuscitation.

The most common endoscopic finding was gastroduodenal erosions, described in 76.3% of the endoscoped patients. The description of gastroduodenal erosions, especially in the context of clinical data of massive bleeding, in reality suggests a failure to identify a bleeding source at the endoscopy performed. The inability to visualize and recognize the bleeding source in an unprepared patient with a large amount of blood or hematin material in the stomach, as well as the description of erosions, could also explain the high mortality in the cohort.

On the other hand, endoscopic hemostasis was undertaken in 37.8% of patients, without it being specified what it consisted of or whether the ESGE recommendations were followed. In the same context, recurrence was observed in almost 30%, and repeat hemostasis was performed in 22% – again without details being provided. Almost 30% recurrence amid over 70% erosions points to an unrecognized source during the first endoscopy.

Using descriptive statistics, the laboratory and clinical abnormalities, comorbidities, and use of high-risk medications were analyzed in detail, with the author reaching and confirming some already known facts regarding the risks of recurrence and unfavorable outcome depending on the additional factors. The endoscopic findings are described in detail, and the lesions in non-variceal bleeding are classified according to Forrest. Recurrent bleeding was observed in 27.8%, and interventional radiological or surgical treatment was required in 7.2% of patients, with almost 25% mortality at the same time. An interesting fact is also the comparatively high proportion of patients in whom bleeding occurred during their hospital stay for another reason (27.3%), which is one of the possible explanations for the reported

comparatively high mortality (almost 30%). The risk factors for severe course established by the author fully overlap with those already established and reported in the literature.

Using logistic regression analysis, the author creates three models that are useful for everyday clinical practice. The first demonstrates that severe non-variceal bleeding is associated with markers of systemic impairment (anemia, respiratory failure), an active ulcer, and recent surgical intervention. The second proves the prognostic role of serum albumin, with its low values indicating a severe course. The author also creates a third model that combines quantitative and qualitative variables, demonstrating the multifactorial nature of non-variceal bleeding.

Notwithstanding the small number of patients in the cohort, the author separately examines the risk factors for the occurrence of variceal bleeding in patients with chronic liver disease. Main trends are outlined regarding the risk factors for variceal bleeding in patients with cirrhosis – known varices, greater severity of hepatic dysfunction, hemostatic disturbances, thrombocytopenia, and hyperbilirubinemia.

One of the greatest merits of the work is the assessment of the prognostic value of the clinical scoring systems in patients with acute upper GI bleeding.

The high prognostic value of the Glasgow-Blatchford score is demonstrated with respect to in-hospital mortality, recurrence of bleeding, the need for endoscopic hemostasis, the need for surgical treatment, and the need for blood transfusions. The AIMS65 score, ABC, CANUKA (Canada–United Kingdom–Adelaide), MAP (ASH), pre-endoscopic Rockall score, PNED, and CSMCPI are also examined and calculated in detail, and their prognostic value with respect to the risk of recurrence, in-hospital mortality, and the need for intervention is assessed; their good prognostic value and applicability are demonstrated as early as the initial assessment for early risk stratification.

A particular merit of the work is the comparison between the individual scoring systems with respect to their prognostic effectiveness for unfavorable outcomes and the need for intervention. Comparing the AUCs, the author outlines the strongest predictors of in-hospital mortality, recurrence, the need for endoscopic hemostasis, the need for surgical or interventional treatment, and the need for blood transfusions in non-variceal and variceal bleeding.

The recurrence of bleeding during the hospital stay is examined separately, with its significance for the patient's outcome being emphasized. The laboratory profile of patients

with recurrence is outlined in detail – more pronounced anemia, low fibrinogen values, hypoalbuminemia, thrombocytopenia, and others. The association with comorbidities, the use of high-risk medications, and the correlation with the endoscopic finding are specified. In-hospital mortality and the factors associated with it are analyzed in detail. It is demonstrated that hemodynamic instability and severe blood loss on admission are markedly associated with both the risk of recurrence and fatal outcome. Patients with a fatal outcome are characterized by severe anemia on admission, higher serum creatinine, hepatic dysfunction, hypoproteinemia, hypoalbuminemia, and comorbidities. The medications associated with an increased risk of fatal outcome are also examined, as are the endoscopic findings, with emphasis on the increased association with the detection of active bleeding during endoscopy and the need for endoscopic hemostasis. The strong association with pneumonia, COVID-19, and respiratory failure is emphasized.

In-hospital mortality is analyzed in exceptional detail, and important conclusions of significance for everyday clinical practice are drawn. A complex interplay is established between the severity of the endoscopically identified lesion, the presence of recurrent bleeding, hemodynamic instability on admission, underlying organ failure, the use of certain medications, and other factors, which emphasizes the need for early identification of high-risk patients and aggressive therapeutic management in this group.

In conclusion, the author emphasizes that acute upper gastrointestinal bleeding is not losing its relevance and that, despite the progress in diagnostic and therapeutic capabilities, mortality continues to be high. The population of hospitalized patients with bleeding consists mainly of elderly and multimorbid patients, often taking high-risk medications. It is emphasized that, beyond the severity of the endoscopically identified bleeding source and the need for endoscopic hemostasis, the outcome is determined by a complex interplay between the etiology of the bleeding, the patient's general condition, comorbidity, and the presence and degree of organ dysfunction. The absence of a universal score, the need for an individualized approach, and the key role of the early identification of risk factors are emphasized.

Conclusions: The author formulates 9 conclusions. Of the greatest practical significance is the following: patients with acute upper GI bleeding requiring hospitalization are most often of advanced age and with an increased frequency of comorbidities, which, together with hemodynamic instability on admission, significantly increases the risk of an unfavorable outcome. The risk of severe course, recurrence, and death is determined by a complex

interplay between the severity of the endoscopic finding, the need for endoscopic hemostasis, the patient's general condition, the comorbidities, and the laboratory abnormalities. The established scoring systems, although validated in large-scale studies, show differing prognostic effectiveness. It is demonstrated that a universal score is lacking and that the choice of prognostic model is predetermined by the specific clinical scenario. The early identification of risk factors and the targeting of therapeutic efforts upon recognition of specific predictors of an unfavorable outcome are of importance for improving the prognosis.

Contributions: The author formulates 10 contributions. A particular merit is the fact that a comparatively large cohort of hospitalized patients with upper GI bleeding in real hospital practice has been analyzed. Risk factors for severe course, recurrences, and fatal outcome have been analyzed and identified. For the first time in the country, the prognostic value of several scoring systems has been assessed and compared, with their advantages and disadvantages in real clinical practice highlighted. The differing prognostic value of the individual scoring systems has been defined and, on this basis, the need for individualizing the approach in these patients. The results are significant and can be used to optimize everyday clinical practice.

Discussion: The dissertation presented is fully complete and well structured. The topic is relevant and clinically significant. Acute upper GI bleeding is a frequent emergency condition with high morbidity and mortality, and precise risk stratification continues to be a subject of debate. The work is large-scale and ambitious. The seven tasks cover the entire chain – from the characteristics of the cohort to the outcome of the bleeding. Undoubtedly the strongest aspect is the direct comparison between nine validated scoring systems across five endpoints and by etiology. This outlines the indisputable contribution of the work to Bulgarian science and practice. The methodological toolkit is adequate. The endoscopic data are presented using the generally accepted classifications and terminology. The conclusion is clinically sound, does not overstate the data, and conveys a useful and applicable message. The conclusions and contributions are well and concisely formulated, and the bibliography is extensive and contemporary.

Of course, the work also has some weaknesses, which in no way diminish its significance. The main limitations are statistical – unstable multivariate models, the lack of a formal AUC comparison, and selection bias – and for the most part are correctable through reanalysis and/or refinement of the formulations, without compromising the foundation of the work. Another weakness is the retrospective design and the small number of patients with variceal

bleeding, which makes the comparisons between the two groups irrelevant. Notwithstanding this, the work is significant, well structured, and with real contributions to clinical practice.

Final conclusion: Considering the aptly chosen and, for Bulgaria, highly relevant topic of the dissertation, the corresponding aim and tasks, the rich and current bibliography, the large number of patients processed and followed up who were included in the study, the conclusions useful for practice, and the indisputable contributions of the work, I call upon the esteemed Scientific Jury to vote "in favor" of awarding the educational and scientific degree "Doctor" to Dr. Aleksandar Yordanov.

18.06.2026Respectfully: .

Sofia/Prof. P. Karagyozov, FASGE/