

REVIEW

of the doctoral dissertation submitted by

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Second Department of Internal Medicine

entitled

"Risk Factors and Clinical Follow-up of Patients with Upper Gastrointestinal Bleeding"

submitted for the award of the educational and scientific degree

Doctor (PhD)

Reviewer

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I. Significance and Relevance of the Research Topic

The subject of Dr. Aleksandar Yordanov's doctoral dissertation addresses an important and highly relevant issue in contemporary medical science and gastroenterology, namely upper gastrointestinal bleeding.

This clinical syndrome results from a wide spectrum of underlying conditions, many of which progress rapidly as medical emergencies and pose a substantial threat to patients' lives. Prior to establishing the definitive diagnosis, upper gastrointestinal bleeding is generally classified as variceal, non-variceal, or post-procedural. Several aspects of patient management, particularly the optimal timing of blood transfusion and the early maintenance of adequate haemodynamic stability, remain incompletely defined. Following oesophagogastroduodenoscopy and identification of the bleeding source, various endoscopic haemostatic techniques may be employed.

Against this background, Dr. Yordanov's study is both timely and scientifically valuable, as it presents an evidence-based management approach while simultaneously evaluating the risk factors associated with both variceal and non-variceal bleeding, assessing the prognostic performance of the most widely used clinical scoring systems and comparing their predictive accuracy, as well as analysing the incidence, causes, and risk factors for in-hospital mortality among these patients.

II. Technical Characteristics of the Dissertation

The dissertation comprises 231 pages, structured as follows: Introduction - 1 page, Literature Review - 47 pages, Aim and Objectives - 1 page, Materials and Methods - 8 pages, Results and Discussion - 148 pages, Conclusions and Scientific Contributions - 2 pages, Final Conclusions - 1 page, References - 16 pages

The dissertation is illustrated with 149 tables, 76 figures, and additional photographic material documenting the performed investigations.

The proportional balance between the individual sections has been appropriately maintained. The dissertation is written in clear and grammatically correct academic language, with accurate and consistent use of medical terminology.

III. Critical Evaluation of the Dissertation

1. Literature Review

The literature review constitutes approximately 18% of the dissertation. It opens with an overview of the research topic and is structured into two main sections.

The first section is devoted to non-variceal upper gastrointestinal bleeding (NVUGIB). It provides a comprehensive review of the epidemiology of non-variceal bleeding and discusses the major risk factors, including *Helicobacter pylori* infection, the use of high-risk medications such as acetylsalicylic acid and other non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulants, antiplatelet agents, and other relevant pharmacological factors. The review subsequently addresses the aetiology and pathogenesis of non-variceal bleeding and outlines the currently accepted management algorithm for these patients, including pre-endoscopic management, risk stratification using the principal clinical scoring systems, and pharmacological treatment. Particular attention is given to the various endoscopic haemostatic techniques, including injection therapy, thermal modalities, mechanical methods, and topical haemostatic agents. The section concludes with a discussion of post-endoscopic management strategies following emergency endoscopy.

The second section focuses on variceal upper gastrointestinal bleeding. It systematically reviews the epidemiology, risk factors, and primary prevention of variceal bleeding. The author further presents the contemporary management algorithm for patients with variceal haemorrhage, encompassing pre-endoscopic management and risk stratification based on the currently available scoring systems. Endoscopic haemostatic techniques for oesophageal and gastric variceal bleeding are discussed in detail, and the section concludes with an overview of the available interventional therapeutic approaches.

A notable strength of the dissertation is the quality of the literature review, which clearly reflects the author's critical thinking, independent scientific judgement, and analytical approach to the reviewed evidence. Furthermore, it provides a well-founded rationale for the selection of the dissertation's aim and research objectives.

2. Aim and Objectives

The overall aim of the dissertation is clearly and concisely formulated: to analyse the clinical, laboratory, endoscopic, and therapeutic characteristics of patients presenting with acute upper gastrointestinal bleeding in order to identify the risk factors associated with severe clinical course, recurrent bleeding, and adverse outcomes.

To accomplish this aim, Dr. Yordanov has formulated seven specific research objectives. Both the overall aim and the seven objectives are well defined and logically structured. There is a strong conceptual relationship between the stated aim and the individual objectives, while the latter are appropriately sequenced to facilitate the achievement of the study objectives and the formulation of evidence-based conclusions.

3. Materials and Methods

The dissertation is designed as a retrospective, observational, single-centre cohort study. The study population comprised 209 patients admitted between February 2021 and March 2024, including 138 men (66.0%) and 71 women (34.0%). The inclusion and exclusion criteria are clearly defined. The methodology is described in a comprehensive and systematic manner. The diagnostic work-up includes medical history, physical examination, laboratory investigations, assessment of liver function, and evaluation of portal hypertension. The dissertation also presents the pre-endoscopic and post-endoscopic clinical scoring systems employed for risk stratification. The endoscopic protocol and the various endoscopic haemostatic techniques applied during the study are described in sufficient detail. The statistical analysis is based on both descriptive and inferential statistical methods. Appropriate, well-selected, and informative statistical techniques have been employed to ensure a reliable evaluation and interpretation of the study findings.

4. Original Research Findings

The original research findings constitute approximately 70% of the dissertation and are presented in seven chapters, each comprising several subsections.

The first chapter describes the characteristics of the study population. It systematically presents the demographic profile, clinical presentation at admission, laboratory findings, coagulation status, biochemical parameters, comorbidities, use of high-risk medications, emergency upper gastrointestinal endoscopy, and endoscopic findings. Non-variceal bleeding was identified in 190 patients (90.9%), whereas 19 patients (9.1%) presented with variceal bleeding. Of particular interest is the finding of portal hypertensive gastropathy in 17 patients (8.9%) within the non-variceal bleeding group. The chapter concludes with the clinical follow-up and treatment outcomes. Endoscopic haemostasis was performed in 79 patients (37.8%), while the initial haemostatic intervention was unsuccessful in 15 patients (18.8%). Rebleeding occurred in 58 patients (27.8%), and repeat endoscopic haemostasis was required in 46 patients (22.0%). The overall in-hospital mortality rate was 28.2% (59 of 209 patients).

The second chapter focuses on the risk factors associated with severe non-variceal upper gastrointestinal bleeding. Criteria defining severe bleeding are clearly established, with 115 of the 190 patients (60.5%) meeting these criteria. The demographic and clinical characteristics, laboratory and biochemical parameters, coagulation profile, comorbidities, risk factors, and endoscopic findings are subsequently compared between patients with severe and non-severe bleeding. A multivariable logistic regression analysis was performed to identify independent predictors of severe non-variceal bleeding using three sequential models:

a model including categorical variables, a model including continuous variables, and a combined model incorporating both types of variables. Comparative evaluation of these models demonstrates a progressive improvement in their predictive performance.

The third chapter evaluates the risk factors associated with severe clinical presentation in patients with variceal bleeding secondary to chronic liver disease. Liver cirrhosis was diagnosed in 41 patients (19.6%), of whom 19 patients (46.3%) presented with variceal bleeding and 22 patients (53.7%) with non-variceal bleeding. Their demographic and clinical characteristics, laboratory and biochemical findings, coagulation profile, comorbidities, non-invasive liver fibrosis scores, risk factors, and endoscopic findings are comprehensively presented. Logistic regression analysis was performed to identify independent predictors of variceal bleeding among patients with liver cirrhosis. Although no statistically significant independent predictors were identified, important trends were observed regarding the presence of oesophageal varices, higher MELD scores, thrombocytopenia, hyperbilirubinaemia, and coagulation abnormalities.

The fourth chapter evaluates the prognostic performance of clinical risk scoring systems in patients presenting with acute upper gastrointestinal bleeding. A descriptive analysis is provided for nine prognostic scoring systems, together with an assessment of their predictive value regarding in-hospital mortality, recurrent bleeding, the need for endoscopic haemostasis, surgical intervention, and blood transfusion.

The fifth chapter presents a comparative analysis of these scoring systems with respect to their prognostic accuracy in predicting adverse clinical outcomes and the need for therapeutic intervention in patients with both non-variceal and variceal bleeding. The chapter concludes with a comprehensive discussion of the strengths and limitations of each scoring system in relation to the respective clinical outcomes.

The sixth chapter examines episodes of recurrent bleeding during hospitalization. The incidence and timing of rebleeding are analysed together with the associated clinical and laboratory parameters, comorbidities, high-risk medications, and endoscopic findings. Independent risk factors and predictors of recurrent bleeding are identified and discussed.

The seventh and final chapter addresses in-hospital mortality and the factors associated with fatal outcome. The analysis demonstrates that demographic characteristics are not independently associated with mortality. In contrast, low systolic arterial pressure and respiratory failure are identified as significant clinical determinants. Particular emphasis is placed on haemodynamic instability, including hypotension, tachycardia, and an elevated shock index. Comorbid conditions also play an important role, especially liver cirrhosis and increasing MELD score, previous pulmonary embolism, pneumonia, and recent surgical intervention. Among the treatment-related factors, parenteral administration of direct anticoagulants and the use of antisecretory therapy were found to be associated with increased mortality. Additional determinants of in-hospital mortality include the requirement for blood transfusion and the occurrence of recurrent bleeding.

5. Conclusions

The dissertation presents nine conclusions, all of which are precise, scientifically sound, and logically derived from the obtained results. Each conclusion is appropriately formulated and provides relevant and meaningful information. Collectively, they accurately

summarize the principal findings of the study and fully correspond to the stated aim and research objectives.

6. References

The bibliography comprises 266 references, including 4 publications in Cyrillic and 262 publications in Latin script. More than two-thirds of the cited literature has been published within the past ten years.

All cited references are directly relevant to the research topic and have been appropriately incorporated in accordance with the objectives and scope of the dissertation.

Overall, this critical evaluation demonstrates that the dissertation represents a substantial scientific contribution by a young researcher with well-developed clinical reasoning, who has successfully combined sound practical expertise with the ability to propose original evidence-based approaches derived from the study findings.

IV. Scientific Merit of the Dissertation

The dissertation includes ten original scientific contributions, all of which I fully acknowledge. These contributions are predominantly of clinical and applied significance.

In my opinion, the fourth, fifth, and eighth contributions are of particular importance:

Contribution 4. For the first time in a Bulgarian patient cohort, the differential prognostic performance of the Glasgow-Blatchford Score (GBS), AIMS65, ABC, CANUKA, MAP(ASH), Rockall (pre-endoscopic and complete), PNED, and CSMCPI has been evaluated with respect to the principal clinical endpoints, including in-hospital mortality, recurrent bleeding, and the need for therapeutic intervention.

Contribution 5. For the first time in a Bulgarian clinical cohort, a comprehensive comparative analysis of nine prognostic scoring systems has been performed in routine hospital practice, thereby defining their respective strengths and limitations in predicting major adverse outcomes and the need for therapeutic intervention in patients with upper gastrointestinal bleeding.

Contribution 8. A comprehensive analysis has been conducted of the incidence, associated factors, and independent predictors of in-hospital mortality among patients with acute upper gastrointestinal bleeding, thereby providing a more precise characterization of the risk profile of patients with the most unfavourable clinical course.

With regard to the tenth contribution, I would recommend the future development of a local clinical management algorithm for patients with upper gastrointestinal bleeding. Had such an algorithm been developed within the framework of the present dissertation, it would have represented an additional significant clinical and applied contribution.

V. Publications

In connection with the dissertation, Dr. Yordanov has published five scientific articles in Bulgarian peer-reviewed medical journals and has presented two papers at Bulgarian

scientific conferences, which fully satisfy the requirements for the award of the educational and scientific degree of Doctor (PhD).

Final Assessment

The dissertation submitted by Dr. Aleksandar Yordanov is the result of extensive and systematic scientific research. It contains several original scientific and clinically applicable contributions. In terms of its scientific significance, topicality, methodological quality, and originality, the dissertation fully meets the requirements established by the current regulations for the award of the educational and scientific degree Doctor (PhD).

In view of these merits, I confidently provide a positive evaluation of Dr. Aleksandar Valeriev Yordanov's dissertation and recommend that he be awarded the educational and scientific degree Doctor (PhD).

15 June 2026

Reviewer:

**Заличено на основание чл. 5,
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