

OPINION

from Assoc. prof. Dr. Veselin Georgiev Popov, PhD
Department of Clinical Oncology, Faculty of Medicine,
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Subject: dissertation for the award of educational and scientific degree "Doctor" Professional field – 7.1. Medicine, Doctoral program „Clinical laboratory“

PhD student: Dr. Snezhana Stoyanova Stoencheva

Form of doctoral studies: PhD student in independent training, Department of clinical laboratory, Faculty of Pharmacy, MU- Plovdiv

Topic: „Clinical-laboratory evaluation of coagulation and fibrinolysis in patients with malignant diseases“

Scientific supervisors: Assoc. prof. Dr. Tanya Deneva, PhD

Prof. Dr. Zhanet Grudeva-Popova, PhD

The opinion has been prepared on the basis of Order № P-819/03.04.2023 of the Rector of MU-Plovdiv, in connection with the procedure for awarding of educational and scientific degree "Doctor" in scientific specialty „Clinical laboratory“, and in implementation of the Law on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for its implementation and the Regulations of MU-Plovdiv.

1. General presentation of the procedure and PhD student (doctoral candidate)

The presented set of materials on paper/electronic media is in accordance with Art. 70 (1) of I. Section. Acquisition of educational and scientific degree "DOCTOR" and scientific degree "DOCTOR OF SCIENCES" at MU-Plovdiv; Regulations of MU-Plovdiv dated 28.01.2021 and includes the following documents:

- application to the Rector of MU-Plovdiv for disclosure of the procedure for the defense of a dissertation work
- autobiography in European format with the doctoral student's signature
- a notarized copy of a higher education diploma
- orders for enrollment in doctoral studies, interruption of studies (due to maternity) and for continuation of studies; for deduction with right of defense
- an order for conducting an exam from the individual plan and a corresponding protocol for a passed exam or doctoral minimum in the specialty

- protocol of the departmental council for preliminary discussion of the pre-dissertation work and the decisions taken for the disclosure of the procedure and for the composition of the scientific jury
- dissertation work
- abstract
- a list of scientific publications on the topic of the dissertation
- copies of scientific publications
- list of participations in scientific forums
- list of noticed citations
- declaration of originality and authenticity of the attached documents
- other documents related to the course of the procedure

The doctoral candidate has presented three publications.

Dr. Snezhana Stoyanova Stoencheva graduated with a Master's degree Medicine at MU-Plovdiv in 2006. She started specializing in clinical laboratory at the Medical University of Plovdiv in 2009. Since 2012, she has been employed as a specialist doctor in the Central Clinical Laboratory, UMBAL "St. Georgi" EAD, Plovdiv. She obtained a specialty in clinical laboratory in 2014. After winning a competition in 2015, Dr. Stoencheva was appointed to the position of assistant in the Department of Clinical Laboratory of the MU - Plovdiv. From June 2021, she is a doctoral student of independent training at the Department of Clinical Laboratory of the MU - Plovdiv.

2. Actuality of the topic

Malignant diseases are a large part in human pathology. A common complication in patients with malignant pathology is thrombosis. The problem of prevention, diagnosis and treatment of thrombotic complications in cancer patients is particularly relevant. The tendency in modern medicine is the use of certain markers in different clinical conditions, which often involves a complex approach with a panel of specific tests. The active follow-up of patients with malignancy and assessment of the need for antithrombotic prophylaxis would contribute to increase the quality of life in these patients. Therefore, the clinical-laboratory evaluation of alterations in hemostasis parameters in various cancer pathology would be useful in clarifying the problems related to thrombotic changes in these patients.

3. Knowledge of the problem

The PhD student shows in-depth knowledge in the field, which is evident from the prepared literature review with a volume of 27 pages. She uses professional terminology

correctly, analyzes and systematizes the information in a very good pattern. The very targeting of this current topic shows knowledge of the problem related to thrombotic complications in patients with malignant diseases, their prevention and the choice of antithrombotic therapy.

4. Research methodology

The clinical, laboratory and statistical methods used in the study were selected appropriately to achieve the set aim. A sufficient number of patients (185) were examined to fulfill the set tasks.

5. Characteristics and evaluation of dissertation and contributions

The dissertation "Clinical-laboratory evaluation of coagulation and fibrinolysis in patients with malignant diseases" is a well-planned, designed and conducted scientific study. It is written on 136 pages and contains 71 figures and 24 tables. The dissertation is structured as follows: introduction – 2 pages, literature review – 27 pages, aim and tasks – 1 page, material and methods – 14 pages, results – 54 pages, discussion – 7 pages, conclusions and contributions – 2 pages, bibliography - 21 pages. At the beginning there is a table of contents and a list of abbreviations.

The introduction outlines the significance of the research problem. **The literature review** is written on 27 pages and is based on 252 authors, 3 of the publications are in Cyrillic and 249 in Latin, 110 were published in the last 10 years. In the literature review, the modern understanding of hemostasis, the mechanisms leading to changes in the coagulation and fibrinolysis systems in patients with malignant diseases are explained in details. The role of hemostasis in angiogenesis and the close relationship between it, coagulation and the progression of the tumor process are thoroughly presented.

The aim of the dissertation was formulated on the basis of a detailed review of the literature on the problem related to changes in laboratory parameters of coagulation and fibrinolysis (fibrinogen, thrombin-antithrombin complex, tissue factor, prothrombin fragment 1+2, Antithrombin III, D-dimer, tissue plasminogen activator) in patients with breast cancer, lung cancer and non-Hodgkin's lymphoma. The tasks are clearly formulated and are sufficient for the fulfillment of the set goal.

The Material and Methods section is detailed and well structured. The clinical material includes 185 individuals aged between 18-70 years, divided into three patient groups: breast cancer (n=38), lung cancer (n=42) and non-Hodgkin's lymphoma (NHL) (n=40) and 65 clinically healthy volunteers. Clinically healthy subjects were used as a control group

comparable in sex and age to the patients groups. The clinical, laboratory and statistical methods used are selected appropriately to achieve the set goal.

The results are clearly presented in tables, figures and graphs. The obtained data support the hypothesis of the relationship between carcinogenesis and blood coagulation disorders. Higher levels of TF, thrombin-antithrombin complex, prothrombin fragment 1+2, and lower AT III activity were found in patients with malignant diseases compared to healthy controls. Standard screening hemostasis tests (aPTT, PT, TT) appear to be insufficiently informative about changes in the hemostasis system in these patients. D-dimer, TAT and F1+2 achieved high criteria scores for diagnostic reliability assessed by ROC analysis and can be used as indicators to differentiate patients at increased risk of thrombotic complications. In the discussion section, the results of the study are critically analyzed, compared to those of other authors.

There are seven **conclusions**, which are a logical consequence from the obtained results and support the hypothesis of a prothrombotic state in patients with malignant diseases.

Dr. Snezhana Stoencheva has indicated 5 contributions, which are theoretically and scientifically applied. Markers of coagulation activation, thrombin-antithrombin complex (TAT) and prothrombin fragment F1+2, and their diagnostic reliability in patients with malignancy are evaluated for the first time in our country.

6. Assessment of the publications and contributions of the PhD student (doctoral candidate)

The doctoral candidate has presented three articles in connection with the dissertation work - one of which is in a refereed journal with an impact factor that fulfills the quantitative criteria laid down in the Regulations of the MU-Plovdiv. Dr. Snezhana Stoencheva has participated in 7 forums, and she is the first author in 4 of them.

7. Critical remarks and recommendations

I do not have any critical remarks and recommendations.

8. Abstract

The abstract is prepared according to the requirements, with illustrative material and sufficient volume to fully reflect the main results achieved in the dissertation.

CONCLUSION

I believe that Dr. Snezhana Stoyanova Stoencheva's dissertation work is up-to-date, correctly structured, with accurate methodology and reliable results. It contains scientific and

applied results with an original contribution and meets all the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for its implementation and the Regulations of MU-Plovdiv.

The dissertation shows that the doctoral candidate has the necessary knowledge and professional skills in the scientific specialty "Clinical Laboratory", showing qualities and skills for independent research.

Due to the above, I confidently give my **positive assessment of the research**, presented by the dissertation work, abstract, achieved results and contributions, and I propose to the esteemed scientific jury **to award the educational and scientific degree "Doctor"** to Dr. Snezhana Stoyanova Stoencheva in a doctoral program " Clinical Laboratory".

Prepared the opinion: Assoc. prof. Dr. Veselin Popov, PhD

