

Review
from assoc. Prof. Ivanka Nenova - Chilova, MD, PhD
Department of Clinical Oncology
Medical University, Plovdiv
of a dissertation awarding the educational and scientific degree “Doctor”

Field of higher education 7. “ Healthcare and sport”

Professional direction 7.1. Medicine

Doctoral program „Clinical Laboratory“.

Author: Snezhana Stoyanova Stoencheva

Form of doctoral study: Independent preparation

Department of Clinical Laboratory, Faculty of Pharmacy

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

Research supervisor: assoc. Prof. Tanya Ivanova Denevap, MD, PhD ,

Department of Clinical Laboratory, Faculty of Pharmacy and

Prof. Zhanet Grudeva-Popova, MD, PhD,

Department of Clinical Oncology, Faculty of Medicine.

1. General presentation of the procedure and the 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 at MU Plovdiv; Regulations of MU Plovdiv dated 28. 01. 2021 and includes the following documents:

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

- ❖ minutes of the departmental council for a preliminary discussion of the pre - dissertation work and the decisions made for the disclosure of the procedure and the composition of the scientific jury
- ❖ dissertation work
- ❖ abstract
- ❖ 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 presented set of materials is well organized and in the required order. The doctoral candidate has submitted 3 publications related to the dissertation work. They are included in journals referred to and indexed in an international database. The scientific articles are presented in national and international forums.

2. Brief biographical data of the doctoral candidate

Doctor Snezhana Stoyanova Stoencheva completed her medical degree in 2006 in Medical University Plovdiv. She was appointed for specialization in Clinical laboratory in MU Plovdiv. She has been working as a doctor in UMHAT St. Georgi, Plovdiv, Central Clinical Laboratory since 2012. Doctor Stoencheva acquired a specialty of Clinical Laboratory in 2014. After successfully passing an exam, she has been appointed to the position of “assistant” in the Department of Clinical laboratory. She has been a doctoral student on a self-study basis in the Department of Clinical laboratory since 2021. Doctor Stoencheva is a member of the Bulgarian committee of clinical laboratory.

3. Relevance of the topic

Thrombotic complications can change the course of a malignancy and limit the opportunities for antitumor therapy. The goal of this dissertation work is an evaluation of coagulation markers in relation to their diagnostic reliance for an early assessment of the thrombotic risk and their prognostic value for screening of high - risk patients with high potential for metastases.

From a practical point of view an attempt is being made for

- 1) creation of an algorithm for an active follow - up of patients with malignancies and thrombophilic risk
- 2) analysis for the need for antithrombotic prophylaxis in these patients with the goal of life quality enhancement

This information defines the dissertation work as highly relevant in scientific and scientific applied aspects.

4. Knowing the problem

The doctoral candidate has studied the theoretical basis of the hemostasis processes and their connection with oncogenesis. The presented conceptions include a modern overview of tissue factor, thrombin, fibrinogen, components of the fibrinolytic system in the process of tumor angiogenesis and the associated metastasizing.

5. Research methodology

The research is approved by the Commission of Scientific Ethics in MU Plovdiv. A sufficient number of 185 patients have been studied to achieve the set goals and objectives. The patients are divided in 3 groups according to their malignancy - carcinoma of the breast, lung and lymphomas. The including and excluding criteria are well thought in order to give a maximally accurate assessment of the parameters. The methods used for collecting scientific information include a questionnaire method, clinical diagnostic and instrumental methods and clinical laboratory tests. The statistical analysis is done with parametric and nonparametric statistical methods, descriptive analysis, methods for assessment of diagnostic sensitivity and specifics, graphical analysis and frequency tables.

6. Characterisation and evaluation of the dissertation work

The presented for opinion scientific work includes 136 standard pages, 71 figures and 24 tables. The main text includes a title page, contents, a list of used abbreviations - total 6 pages; introduction 2 pages, literary overview - 25 pages; goal and tasks - 1 page, materials and methods - 14 pages; results 57 pages, discussion - 7 pages; conclusions and contributions 2 pages, publications and participation in scientific forums 2 pages. The bibliography is 19 pages and it consists of 252 literary sources. 3 of the literary sources are in Cyrillic alphabet and 249 are in Latin alphabet. 31 sources are published within the last 5 years.

Modern data about the biological role of hemostasis factors and their role in tumor angiogenesis, cell migration and metastasising are analyzed in detail in the *literary overview*. The activation of coagulation and fibrinolytic systems are highlighted to contribute to tumor progression and metastasis. Routinely used tests have limited capabilities to provide information about hypercoagulability. Highly specialized hemostasis parameters are demanded. The accent is put on the contradictions about the necessity of an anticoagulant treatment in the course of antitumor therapy.

The goal is correctly and precisely formulated and corresponds to the gist of the dissertation work.

The 5 tasks correspond to the aimed goal.

The study is defined as perspective, controlled and longitudinal.

The material and methods are correctly and precisely chosen to do the aimed goal and task.

Clinical laboratory methods for measurement of specific parameters of coagulation and fibrinolysis are precisely described.

Modern methods of statistical analysis are used for statistical processing.

The material and used methods allow formulation of precise and valid conclusions and to outline the contributions of the dissertation work.

In chapter "*Results*" doctor Stoencheva presents her own data from the research that included 120 patients divided in 3 groups according to their nosology - lung cancer, breast

cancer, Non Hodgkin lymphoma and a control group of 65 healthy people. The tendency of elevated tissue factor, D - dimer, thrombin - antithrombin complex, prothrombin fragment 1 + 2, fibrinogen and t-PA are common in the three groups with malignancy in comparison with the control groups - indication for activated coagulation and fibrinolysis. The increased thrombogenic risk in malignancies correlates with an advanced clinical stage of the tumor. These coagulation parameters decrease in the course of antitumor treatment because of the positive effect of antitumor therapy. The concentration of antithrombin III, which is a natural coagulation inhibitor, has a tendency to increase or normalize in the course of treatment. The D-dimer test followed by TAT and F1+2 shows the highest values for diagnostic sensitivity and specificity in all three patient groups. The correlation between hypercoagulability in malignancies and the processes of tumor angiogenesis (especially tissue factor) and metastasis (thrombin - antithrombin complex) is emphasized.

The description of the results corresponds to the set objectives and is supported by a lot of graphics and tables.

The exposition is with a precise scientific style.

The seven *conclusions* correspond to the objectives. The conclusions confirm the existence of thrombophilia as a problem in clinical practice while demonstrating coherent and complex change in the correlations between the hemostasis and fibrinolytic factors, induced by the tumor. In contrast with standard screening hemostasis tests (aPTT, PT, TT) specialized tests like TAT, D - dimer and F1+2 are evaluated with high diagnostic reliability. The effect of cytotoxic therapy is objectified by a characteristic dynamics (suppression) of specialized coagulation tests and a favorable influence on the prothrombotic state.

7. Contributions and significance for science and practice

The presented for review dissertation work finishes with 5 contributions - 3 of them with original character (used for the first time in Bulgaria) and 2 with confirmative character. The confirmative theoretical contribution is a proof of correlation between coagulation disturbances and malignancies.

The confirmative practical contribution is the availability to use certain parameters of coagulation and fibrinolysis for evaluation of thrombotic risk in malignancies.

The original contributions include introduction of TAT, prothrombin fragment 1+2, t-PA for assessment of thrombophylic risk in malignancies. The dynamics of coagulation and fibrinolysis parameters in the course of antitumor treatment is tested for the first time in this country, which gives an opportunity for assessment of changes in thrombogenic risk in the course of treatment.

8. Evaluation of publication and contributions of the doctoral candidate

There are 3 publications in English in foreign journals that are referred and indexed in an international database. One of these journals has an impact factor. The doctoral candidate is a first author in all three publications.

In addition, there is a list of 3 participations in national and 4 in international scientific forums, in four of which doctor Stoencheva is a first author.

9. Personal participation of the doctoral candidate

I appreciate the participation of the doctoral candidate as highly independent in the research conduction, result analysis and conclusion formulation.

10. Author's abstract

The author's abstract is 55 pages. It summarizes the structure of the dissertation work very well. The goal and tasks are clearly and specifically presented. The results are visualized with 49 figures and 20 tables. The author's abstract includes the most important studies, conclusions and contributions of the dissertation work. It is made according to the requirements of the relevant regulations and reflects the main results achieved in the dissertation.

11. Critical remarks and recommendations

There are not any critical remarks. The recommendations coincide with the recommendations for future use of the dissertation contributions and results.

12. Personal impressions

I know doctor Stoencheva as a specialist and a lecturer who is precise and disciplined in her scientific and research work. An additional list of 10 publications, half of which have an impact factor, supports my opinion. The published works are quoted 13 times in medical literature.

13. Recommendation of future use of the dissertation contributions and results

The treatment process of newly diagnosed malignancies starts with an assessment of prognostic risk and why not with thrombophylic risk which creates a basis for an individualized approach in selecting therapy, the so-called personalized treatment. The analyzed laboratory parameters can be used for assessment of the metastatic potential and the effect of antitumor treatment in the individual patient. In this direction, prospects for research are suggested also for other malignancies, as well as for patient groups with different age characteristics. The dissertation work results can be the necessary theoretical basis for attempts in creating a standard for prophylaxis of thrombotic complications in oncological patients.

14. Conclusion

In my opinion, the dissertation work contains scientific and practical results that are contributions to science. It meets all the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria (LDSASRB), the Regulations for the Implementation of LDSASRB, and the Regulations of the Medical University of Plovdiv. The dissertation work shows that the doctoral candidate doctor Snezhana Stoyanova Stoencheva has deep theoretical knowledge and professional skills in the specialty of Clinical laboratory, as she demonstrates qualities and skills for independent conduction of scientific research. Therefore, I confidently give my positive assessment of the conducted research, presented in the reviewed above dissertation work, author's abstract, achieved results and contributions. I propose to the honorable scientific jury to award the educational and scientific degree "doctor" to Snezhana Stoencheva in the doctoral program in "Clinical laboratory"

28.04.2023

Reviewer:

(assoc. prof. Ivanka Nenova - Chilova, MD, PhD)


Заличено на основание
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