

TO

The Chair of the Scientific Jury

STATEMENT

by Assoc. Prof. Maya Nikolova Yordanova, MD, PhD, Department of Pediatrics, Medical University – Sofia, Head of the Oncology Unit at the Clinic of Pediatric Clinical Hematology and Oncology, University Hospital "Tsaritsa Yoanna"

In accordance with Order No. R-616/11.02.2025, issued by the Vice-Rector for Research and Innovation of the Medical University of Plovdiv, for participation in the Scientific Jury, approved by a decision of the Faculty Council of the Faculty of Medicine at the Medical University of Plovdiv (Protocol No. 1/22.01.2025),

regarding

the dissertation submitted for the award of the educational and scientific degree "**Doctor**"

in Professional Field 7.1. Medicine, Doctoral Program in Pediatrics, Code 03.01.50,

by

Dr. Petya Petkova Markova, a full-time doctoral student

at the Department of Pediatrics "Prof. Dr. Ivan Andreev," Faculty of Medicine, Medical University of Plovdiv,

on the topic:

"Monitoring Renal Function in Children Undergoing Chemotherapy"

Scientific Supervisors:

Prof. Dr. Mariya Spasova, MD, PhD, Head of the Department of Pediatrics "Prof. Dr. Ivan Andreev," Medical University of Plovdiv,

and

Prof. Dr. Polina Miteva-Shumnalieva, MD, PhD, Faculty of Public Health, Medical University of Sofia.

1. General Overview of the Procedure

The submitted set of materials by the doctoral candidate, Dr. Markova, in both printed and electronic format, complies with Article 70 (1) of Section I: Acquisition of the Educational and Scientific Degree "Doctor" and the Scientific Degree "Doctor of Science" at the Medical

University of Plovdiv, as per the Regulations of the Medical University of Plovdiv dated 28.01.2021. The materials include the following documents:

- Application to the Rector of the Medical University of Plovdiv for initiating the dissertation defense procedure
- Curriculum vitae in European format, signed by the doctoral candidate
- Notarized copy of the diploma for higher education
- Orders for enrollment in the doctoral program, interruption of studies (due to maternity leave), continuation of studies, and discharge with the right to defense
- Order for conducting an examination from the individual study plan and the corresponding protocol for the successfully passed examination or doctoral minimum in the specialty
- Protocol from the Departmental Council on the preliminary discussion of the dissertation and the decisions taken regarding the initiation of the procedure and the composition of the scientific jury
- Dissertation thesis
- Dissertation abstract
- List of scientific publications related to the dissertation topic
- Copies of the scientific publications
- List of participation in scientific forums
- List of citations recorded
- Declaration of originality and authenticity of the submitted documents
- Other documents related to the course of the procedure

The doctoral candidate has submitted three full-text scientific publications related to the dissertation topic, one of which is indexed in Scopus (Pediatrics Journal, Issue 3 / 2019). Additionally, three presentations were delivered at national conferences and one at an international forum (56th ESPN Congress, Valencia, Spain; September 2024). The candidate is also a participant in a scientific project related to the research topic (NO-07/2021, "Investigation of Urinary NGAL as a Marker of Renal Damage in Pediatric Oncology Patients Undergoing Chemotherapy").

2. Biographical Overview of the Doctoral Candidate

Dr. Petya Markova is an experienced pediatrician with nearly 18 years of clinical practice in the field of pediatric disease diagnosis and treatment, with the last eight years specifically dedicated to pediatric nephrology. She graduated with honors in Medicine from the Medical University of Plovdiv in 2006, successfully obtained her specialization in Pediatrics in 2014, and in 2016 completed a second specialization in Pediatric Nephrology and Hemodialysis.

The candidate has provided certificates of professional competence for three specialized diagnostic and therapeutic skills: placement of central venous access devices (2012), abdominal ultrasound (2013), and performing percutaneous renal biopsy.

In addition to her second specialization, the doctoral candidate has successfully completed international training in pediatric nephrology through the IPNA - Master for Junior Classes program, following a three-year modular training course.

Dr. Petya Markova is actively involved in all diagnostic, therapeutic, teaching, and research activities within the Department of Pediatrics at the Medical University of Plovdiv. In 2021, she was officially enrolled as a full-time doctoral student in the Department of Pediatrics by Order No. R-2374/17.12.2021.

3. General Structure of the Dissertation

The dissertation consists of 167 pages, structured as follows: a four-page section including the title page, table of contents, and list of abbreviations; a 48-page review of the existing medical literature on the topic, followed by the formulation of the research objectives and tasks.

The materials and methods of the study are thoroughly described over six pages, detailing the study design, including retrospective, cross-sectional, and prospective patient groups with corresponding selection criteria, as well as the clinical, imaging, laboratory, and functional parameters for follow-up. The statistical methods used for evaluation are also outlined.

The results of the author's clinical research span 71 pages and are presented in alignment with the research objectives, integrating discussion and conclusions for each task. A clinical-diagnostic algorithm for monitoring renal function in children undergoing chemotherapy has been developed.

The study's conclusions and contributions are summarized over two pages. The dissertation also includes a list of related publications, conference presentations, and the research project associated with the dissertation topic.

The references cited and discussed comprise works from 247 author groups, predominantly from recent years, and are listed over 28 pages. The dissertation features 29 tables, 63 figures, and one appendix.

4. Relevance of the Topic in Scientific and Applied Research. Degree and Levels of Relevance of the Problem and the Specific Research Objectives Addressed in the Dissertation

The significant advancements in the treatment of pediatric oncological and hematological diseases are associated with the combined use of chemotherapeutic, targeted, and immunological agents, each with a diverse spectrum of side effects, including renal complications. Renal function plays a crucial role in the excretion of both administered medications and tumor breakdown products, as well as additional therapeutic agents used in recovery. A large proportion of chemotherapeutic agents, as well as supportive and anti-infective medications, exhibit nephrotoxic effects.

Understanding, investigating, and monitoring the impact of these primary therapeutic combinations and the course of the recovery period concerning renal function are of critical

importance to the overall therapeutic process. The identification and evaluation of risk factors for acute kidney injury (AKI) and chronic kidney disease (CKD) in patients undergoing treatment for malignant diseases remain subjects of extensive discussion and research by pediatric medical teams worldwide.

The potential long-term consequences of impaired renal function present an ongoing morbidity risk for the growing population of pediatric cancer survivors. Timely diagnosis of renal impairment and the development of a pragmatic algorithm for monitoring and adapting treatment based on renal function have an immediate scientific and practical significance.

5. Understanding of the Problem

Dr. Markova's dissertation demonstrates a thorough and in-depth understanding of the research problem. The structuring of the research objectives, the organization of the studies, the presentation of the results, and their interpretation reflect her strong research skills, ability to conduct scientific investigations, and critical analysis of the obtained findings.

literature review encompasses a comprehensive collection of available research on the topic, providing a comprehensive historical perspective on the study of acute kidney injury (AKI) in children and current concepts in the field. It covers a broad spectrum of causes, risk factors, mechanisms of kidney damage, classification systems, clinical manifestations, and differential diagnostic approaches.

Within this context, three groups of biochemical markers for the early diagnosis of kidney injury—associated with nephrotoxicity and ischemia are discussed:

- Inflammatory and pro-inflammatory cytokines: Neutrophil gelatinase-associated lipocalin (NGAL), interleukins IL-6 and IL-18.
- Biomarkers of cellular injury: Kidney injury molecule-1 (KIM-1), Liver fatty acid-binding protein (L-FABP), Sodium/hydrogen exchanger-3 (NHE-3).
- Cell cycle markers: Urinary tissue inhibitor of metalloproteinases-2 (TIMP-2), Insulin-like growth factor-binding protein 7 (IGFBP-7).

The significance of NGAL is particularly emphasized and analyzed in greater depth. The dissertation details the pathophysiological mechanisms and assessment methods of AKI in pediatric onco-hematological patients. It also provides a comprehensive review of the nephrotoxic potential of various chemotherapeutic agents and the most commonly used conventional combination treatment regimens.

Furthermore, the fundamental mechanisms of drug-induced nephrotoxicity are described in detail. A separate discussion is dedicated to tumor lysis syndrome (TLS) and its distinct risk for kidney injury. The dissertation compares classical markers for monitoring kidney function and damage, assessing their applicability in dynamic monitoring during chemotherapy.

6. Objectives and Tasks

Based on the literature review, the selected topic and research objective of the dissertation were formulated. The topic of monitoring renal function in children undergoing chemotherapy is motivated by unresolved issues related to the nephrotoxicity of the antitumor treatments applied in pediatrics. The six research tasks, associated with the realization of the study, are logical, well-defined, and directed toward achieving the main research goal.

7. Research Methodology

Dr. Markova conducted research on a total of 281 children, including a retrospective study of 213 children, a cross-sectional study of 40 children currently undergoing chemotherapy with nephrotoxic potential, and a prospective study of 28 patients who had completed treatment at least a year prior, aimed at monitoring and evaluating potential chronic kidney disease. The study was approved by the Ethics Committee of the Medical University of Plovdiv (Protocol No. 6/07.10.2021). The patient group is significant and provides a reliable basis for assessing the results.

A comprehensive set of monitoring methods was employed, including clinical, imaging, laboratory, and functional parameters, all of which facilitated the achievement of the research objectives. The classifications used to evaluate AKI and CKD were carefully described.

Descriptive and inferential statistical methods were applied to assess the results, in line with current standards for data processing and scientific analysis—comprising comparative and correlational techniques.

9. Results and Discussion

The obtained data are reliable and presented adequately, including through graphical representation. The discussion following the results of each task contributes to the clarity and organization of the conclusions drawn.

The results indicate kidney damage rates comparable to global statistics in response to antineoplastic therapy. Nephrotoxicity from chemotherapy agents has been confirmed as the leading cause in all episodes of acute kidney injury (AKI). Other factors, such as infections, sepsis, tumor lysis syndrome, and renal infiltration, contribute to a lesser extent, though it should be noted that, apart from infections, the other factors are relatively rare. The age-related frequency largely reflects the incidence of malignant diseases (higher during school age). More severe AKI was observed in the cohort of patients with solid tumors, which is likely related to a higher-risk stage of the disease and the need for more intensive therapy. Attention should be drawn to the novel studies in Bulgaria aiming to validate a more sensitive biomarker (uNGAL) for subclinical kidney involvement, offering a potential early diagnostic tool for AKI. The reasons for the lack of satisfactory indicator results have been critically discussed, along with the exploration of opportunities for further refinement.

The conclusions regarding the recommended monitoring of kidney function using eGFR calculation based on the Schwartz formula, corrected for body surface area, are of practical value. Furthermore, the conclusion that tubulopathy is the primary pathogenic mechanism for AKI caused by drug-induced nephrotoxicity, and that markers for it can be used for early diagnosis of drug-induced nephrotoxicity in pediatric oncology, is significant.

The candidate's commentary reflects a deep understanding of the mechanisms of kidney involvement during antineoplastic therapy. The presentation and discussion of the results showcase professional attitude and competence, underpinned by extensive professional experience and clinical critical thinking. The results are examined and compared in the context of existing data from both Bulgarian and international studies. The conclusions align with the findings and demonstrate skills in synthesizing and critically summarizing data.

The obtained results are of both theoretical and clinical-applied significance. The accumulated experience, research, and ensuing conclusions have direct application in clinical practice. The aspects discussed and the candidate's conclusions reflect a clear understanding of the mechanisms of kidney damage during antineoplastic therapy.

8.Characteristics and Evaluation of the Dissertation and Contributions

The presentation and discussion of the research results demonstrate a high level of professionalism and competence on the part of the doctoral candidate, as well as a profound understanding of the subject matter. It is evident that the candidate possesses the ability for critical analysis and synthesis, complemented by sufficient professional experience and clinical maturity.

The candidate's own results are compared within the context of existing data from both Bulgarian and international studies. The conclusions align with the obtained results and demonstrate the ability to synthesize and critically summarize the data.

As a result of the study, ten conclusions were drawn, and five contributions were highlighted. Two of these contributions are original to Bulgaria, two are confirmatory, and one is original—a developed algorithm for monitoring kidney function in children undergoing chemotherapy. This algorithm offers possibilities for differentiated calculation of doses for specific nephrotoxic cytostatic drugs.

The obtained results have both theoretical and clinical-applied significance. The collected experience, research, and conclusions have immediate application in clinical practice. The topic will remain relevant and will likely be the subject of ongoing research aimed at developing an optimal diagnostic algorithm

9.Evaluation of the Publications and the Doctoral Candidate's Personal Contribution

The doctoral candidate has submitted three full-text scientific publications related to the topic of the dissertation, one of which is indexed in Scopus (Pediatrics, issue 3/2019), along with three national presentations and one international presentation (56th ESPN Congress, Valencia, Spain; September 2024). The candidate is also involved in a scientific project related to the topic of the

study (NO-07/2021, titled “Investigation of NGAL in urine as a marker of kidney damage in pediatric oncology patients undergoing chemotherapy”). The doctoral candidate’s role as the first author reflects her personal contribution to the research, summaries, and discussion of the results.

The work requires some final editorial revisions, but I have no substantial comments

10. Abstract

The abstract covers the individual chapters of the dissertation and reflects the scientific work of the doctoral candidate. It has been prepared according to the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria and reflects the main results achieved in the dissertation.

CONCLUSION

The dissertation submitted for review by Dr. Petya Petkova Markova represents a study on kidney function in children undergoing chemotherapy, based on retrospective, cross-sectional, and prospective research using a wide range of methods. The work includes scientific, applied, and practical results, which provide an original contribution to pediatric science and pediatric nephrology. They meet all the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria (ZRASRB), the regulations for the application of ZRASRB, and the regulations of the Medical University of Plovdiv. The presented materials and dissertation results fully comply with the specific requirements adopted by the regulations of the Medical University of Plovdiv for the application of ZRASRB.

The dissertation demonstrates the doctoral candidate Dr. Petya Petkova Markova’s in-depth theoretical knowledge and professional pediatric training, as well as her qualities and skills for independently conducting scientific research.

In view of the above qualities of the scientific work, I confidently give my positive evaluation of the conducted research, as presented in the reviewed dissertation, abstract, achieved results, and contributions. I recommend that the esteemed scientific jury award the educational and scientific degree of ‘Doctor’ to Dr. Petya Petkova Markova in the doctoral program in “Pediatrics.”

Заличено на основание
Чл.5 §1, б. “В” Регламент (ЕС)2016/679

17.03.25

Prepared the statement:

Assoc. Prof. Maya Nikolova Yordanova, PhD

