

To Chairperson of the Academic Committee,
Approved by the Rector of the Medical University
"Prof. Dr. Paraskev Stoyanov" – Varna

REVIEW

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, UMHAT "Queen Joanna", Member of the Academic Committee, according to Order No. R-109-150/13.03.2025 of the Rector of the Medical University "Prof. Dr. Paraskev Stoyanov" – Varna, and Minutes of the Committee Meeting No. 1/20.03.2025

On

the dissertation submitted for the award of the educational and scientific degree "Doctor" in Higher Education Area 7. Health and Sports, Professional Field 7.1. Medicine, Doctoral Program: Pediatrics

By

Dr. Hristina Yaneva Hristozova, Full-time PhD student at the Department of Pediatrics, Faculty of Medicine, Medical University – Varna

Titled:

"Quality of life after treatment of malignant hemopathies and solid tumors in childhood"

Scientific Supervisors: Prof. Valeria Ignatova Kaleva, MD, PhD

And

Prof. Paraskeva Mancheva Draganova, MD, DSc

1. General Overview of the Procedure

The submitted set of materials by PhD student Dr. Hristina Hristozova, in both paper and electronic formats, complies with Article 70, Paragraph 1 of Section I "Acquisition of the Educational and Scientific Degree 'Doctor' and the Scientific Degree 'Doctor of Sciences'" from the Regulations for the Development of Academic Staff at the Medical University – Varna. The set includes the following documents: – Application to the Rector of MU–Varna for initiating the dissertation defense procedure – European-format CV signed by the doctoral candidate – Notarized copy of the medical degree diploma – Orders for enrollment in the PhD program, temporary leave, reinstatement, and completion with the right to defend – Order for an examination under the individual study plan and the corresponding protocol for passing the specialty doctoral minimum – Protocol from the Departmental Council meeting regarding the preliminary discussion of the dissertation and decisions to initiate the procedure and appoint the academic committee – Dissertation – Abstract – List of scientific publications related to the dissertation topic – Copies of the publications – List of participations in scientific forums – List of identified citations – Declaration of authenticity and accuracy of the submitted documents. The doctoral candidate has included three scientific publications related to

the dissertation topic—one full-text article indexed in Scopus (Pediatria, 2020, vol. LX, Supplementum: 15–17) and two conference abstracts presented at national scientific forums.

2. Candidate's Biographical Data

Dr. Hristina Hristozova is an experienced pediatrician and pediatric hemato-oncologist with more than 25 years of expertise in clinical diagnostics, treatment, and academic teaching. She graduated with distinction from the Medical University – Varna in 1994. Since then, she has worked continuously at UMHAT "St. Marina" – Varna and, since 2005, has served as an assistant professor in the Department of Pediatrics and Clinical Medical Sciences at MU – Varna.

Dr. Hristozova holds three clinical specialties: Pediatrics (2001), Oncology (2006), and Pediatric Clinical Hematology and Oncology (2009). In 2014, she completed a Master's degree in Public Health and Healthcare Management at MU – Pleven. Her career is closely tied to the education of both Bulgarian and international students, alongside her clinical and research activities in pediatric hemato-oncology.

She has completed certified training in Good Clinical Practice (GCP, E6 R2, 2023) and has practical experience as a sub-investigator in phase II clinical trials for pediatric oncology indications.

Dr. Hristozova is a member of multiple professional societies, including the Bulgarian Medical Association, the Bulgarian Pediatric Association, the Bulgarian Society of Hematology, the Bulgarian Medical Society of Pediatric Hematology and Oncology, and the international organization SIOPE (European Society for Paediatric Oncology).

In 2020, Dr. Hristozova was enrolled as a full-time PhD student in the Department of Pediatrics at the Medical University – Varna under Order No. R-109-22/30.01.2020.

3. General Structure of the Dissertation

The dissertation of Dr. Hristina Hristozova consists of 140 pages and includes 27 figures, 19 tables, and 2 appendices. The bibliography comprises 235 sources—227 in Latin script, 5 in Cyrillic, and 3 online references. The content is well structured and includes a literature review, formulated hypothesis, objectives and tasks, detailed materials and methods section, results, discussion, conclusions, contributions, and a final summary.

4. Relevance and Significance of the Topic in Scientific and Applied Research Terms. Degree and Scope of Relevance of the Problem and the Specific Tasks Developed in the Dissertation.

The topic of the dissertation—"Quality of life after treatment of malignant hemopathies and solid tumors in childhood"—is particularly relevant in the context of contemporary pediatric hemato-oncology. Advances in treatment over recent decades have significantly increased survival rates, which in turn raises the necessity of systematic evaluation and enhancement of survivors' quality of life.

From a scientific standpoint, the dissertation focuses on the multidimensional nature of quality of life, including physical, emotional, social, and psychological aspects. In applied terms, the work addresses the development of effective tools and frameworks for assessing and supporting childhood cancer survivors. Neglected aspects of post-treatment quality of life may lead to under recognition of chronic physical, cognitive, and psychosocial effects that hinder long-term adaptation. A lack of structured evaluation and intervention could compromise therapeutic outcomes and reduce survivors' chances for fulfilling lives.

This dissertation is of clear practical value, offering data on the influence of medical and social factors on quality of life and potentially informing targeted interventions and healthcare policy.

5. Knowledge of the Problem

Dr. Hristozova's dissertation reflects a thorough understanding of the complex issues surrounding quality of life in pediatric cancer survivors. The author presents an extensive and well-organized literature review that traces the evolution of the concept of quality of life and its integration into pediatric hemato-oncology.

Contemporary models and tools for measuring quality of life in children and adolescents are explored, incorporating interdisciplinary perspectives across medicine, psychology, and social science. Particular attention is paid to specific factors influencing post-treatment quality of life, such as residual physical impairments, neurocognitive deficits, psychological well-being, and the role of family and social support systems.

The author emphasizes the importance of validated and culturally adapted questionnaires for the Bulgarian population. This in-depth analysis reflects a strong personal engagement with the topic and the ability to apply theory to practical clinical evaluation.

6. Objectives and tasks

The objectives and tasks presented in the dissertation logically stem from the analysis of contemporary scientific literature and current clinical practice needs. The primary aim is to assess the quality of life in children and adolescents after completing treatment for hemato-oncological diseases by analyzing the influencing factors.

The six specific tasks are clearly defined, feasible, and focused on evaluating clinical, psychological, and social aspects to identify key predictors of reduced or preserved quality of life. The structure of the tasks demonstrates a thorough understanding of the complexity of the research subject and a commitment to developing a practical framework for interdisciplinary assessment.

7. Methodology of the Study

The methodology of the dissertation research is thoroughly developed and meets contemporary standards for medical and socio-psychological studies. A quantitative approach has been employed, incorporating standardized questionnaires, statistical data processing, and classification systems tailored to the age and clinical profile of the participants.

A total of 112 children and adolescents with malignant hematologic diseases or solid tumors, diagnosed and treated during childhood at the Clinic of Pediatric Clinical Hematology and Oncology (CPCHO) of University Hospital "St. Marina" EAD – Varna, were studied during the period 2000–2021. Upon reaching the age of 18, they were continuously monitored at the CPCHO outpatient dispensary. The study commenced following approval by the Research Ethics Committee (REC) at the Medical University of Varna (No. 91/27.02.2020) and was conducted over a two-year period (March 2020 – February 2022). The inclusion and exclusion criteria for participants, along with the ethical considerations, are precisely described. Informed consent was obtained from both the parents and the participants, ensuring the reliability, validity, and reproducibility of the results achieved through the selected methodology.

The prospective design was combined with retrospective information regarding the course of the disease and therapeutic approaches.

The methods used included documentary analysis, a sociological approach using the WHOQOL-BREF 26 Generic Quality of Life Questionnaire (developed by the WHO), surveys, as well as clinical and laboratory methods. To assess quality of life, validated international tools adapted for the Bulgarian population were used – including the PedsQL 4.0 Generic Core Scale and the PedsQL Cancer Module. Parent surveys were also used as an additional source of information. The statistical analysis included both descriptive and inferential analyses, as well as significance and correlation tests.

8. Results and Discussion

The presented results are consistently structured, logically substantiated, and supported by appropriate statistical methods. The data are clearly illustrated through relevant graphical and tabular formats: 27 figures and 19 tables are included, effectively visualizing key correlations and enhancing the understanding of the examined relationships.

Despite the relatively short selected period (2000–2021), which covers the antitumor treatment of the patient group, the duration of dispensary follow-up of the study participants averaged 10.24 ± 5.35 years, with some individuals being followed for as long as 21 years. Notably, nearly 20% of the participants fall into the group observed up to the fifth year following treatment, allowing for the analysis of patients with recent treatment experience and fresh impressions at the time of the survey. On the other hand, as noted by the PhD candidate, the relatively young age of the patients may be a factor for the absence of fully manifested long-term side effects from the treatments received. The most frequently observed complications are documented, falling within the expected spectrum and aligning with those most commonly cited in the literature.

A critical limitation of the dispensary follow-up has also been acknowledged—namely, the lack of early subclinical damage assessments such as lipid profiling, echocardiography, bone density measurements, and body composition analysis. These omissions are attributed to objective administrative and organizational constraints.

The dissertation explores the influence of various medical, social, and psycho-emotional factors on quality of life, which adds depth and multidimensionality to the analysis. The author has formulated conclusions with clear practical and applied relevance, including recommendations for clinical assessment and long-term support of childhood cancer survivors.

The discussion section is well-argued and coherent, demonstrating the author's capacity for critical synthesis of the results. The candidate compares her findings with up-to-date publications in international literature, identifying both shared trends and divergences, and provides logical interpretations rooted in the clinical context. This approach highlights her in-depth understanding of the subject and adds value to the scientific interpretation of the data.

The dissertation reflects professionalism, research maturity, and an ability for critical analysis. The gathered experience, the conducted research, the obtained results, and the resulting conclusions have direct applicability in clinical practice. The candidate outlines evidence-based recommendations for modern, comprehensive follow-up care of long-term survivors of childhood cancer, aimed at achieving and maintaining an optimal quality of life.

9. Characteristics and Evaluation of the Dissertation and Its Contributions

The dissertation of Dr. Hristina Hristozova is distinguished by the coherence and consistency of its exposition, as well as by a high professional standard in the applied research approach. The concept of quality of life as both a clinical and social category subject to objective evaluation is clearly articulated.

The work combines theoretical analysis with clinical practice and presents contributions that are both original and confirmatory in nature. The author demonstrates skill in critically interpreting data, systematizing observations, and proposing practically applicable solutions. The doctoral candidate's commentary and conclusions reflect a deep understanding of the mechanisms through which various factors affect the quality of life in patients with oncohematological diseases.

The accumulated experience, conducted research, and derived conclusions have direct applicability in clinical practice and will contribute to improving the quality of life of children and adolescents following treatment for malignant diseases.

The obtained results and their analysis form the foundation for contributions of both theoretical and clinical-practical significance.

The contributions are clearly defined, with the following standing out:

- adaptation and application of internationally validated instruments for quality of life assessment in a Bulgarian pediatric oncohematology population;
- analysis of specific predictors influencing quality of life after treatment;
- development of risk group profiles in need of targeted intervention;
- proposals for including quality of life indicators in the long-term monitoring and follow-up of pediatric oncology patients.

These contributions align with contemporary approaches in personalized medicine and multidisciplinary care, and they have the potential to be further developed in future research and practice.

10. Evaluation of the Publications and the Doctoral Candidate's Individual Contribution

Dr. Hristina Hristozova has submitted three scientific publications related to the topic of her dissertation. One of these has been published in a peer-reviewed scientific journal (*Pediatrics*, 2020, Volume LX, Supplementum: 15–17), while the other two were presented as conference abstracts at national scientific forums.

The topics of the publications align with the main focuses of the dissertation, and their content reflects the originality, scientific rigor, and clinical relevance of the research. The doctoral candidate is the first author on all the submitted publications, which affirms her leading role in conducting the research, analyzing the results, and formulating the conclusions.

The publications demonstrate a high level of engagement, an analytical approach, and the ability to think across disciplines. The results and discussions presented in the articles support the key findings of the dissertation and highlight its value to both the scientific community and clinical practice. They align with modern trends in personalized medicine and multidisciplinary care and have the potential to be further developed in future research and clinical applications.

11. Abstract

The abstract accurately reflects the main content and structure of the dissertation. It has been prepared in accordance with the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria and the relevant regulations of the Medical University – Varna. It covers all the essential elements of the dissertation research—introduction, objectives and tasks, methodology, results, conclusions, and contributions.

The text is clear and well-organized. It presents adequate information on the methods used and the results obtained, allowing for a quick orientation to the essence of the work. The exposition is con-

cise yet sufficiently informative to convey the significance of the research and its contribution. The summarized data correspond to the content of the dissertation and emphasize both its clinical and scientific value.

Conclusion

The presented dissertation by Dr. Hristina Hristozova is the result of in-depth research activity that combines clinical expertise, scientific rigor, and a humanistic focus on the patient. The work is timely, well-argued, and structured, with high practical relevance for the field of pediatric hemato-oncology.

The study demonstrates the doctoral candidate's ability for independent scientific thinking, analytical precision, and the application of appropriate methodology. The results obtained carry both clinical and scientific contributions, and the conclusions and recommendations formulated have the potential to improve long-term support for children who have survived malignant diseases.

Based on the comprehensive assessment of the content, methodology, and contributions of the dissertation, I recommend that the esteemed academic committee confer upon Dr. Hristina Hristozova the educational and scientific degree of "Doctor" in the professional field of Medicine, scientific specialty Pediatrics.

May 19, 2025

Reviewer:

Assoc. Prof. Maya Nikolova Yordanova, MD, PhD

Заличено на основание чл. 5, §1, б. „В“ от Регламент (ЕС) 2016/679
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