REVIEW

by Prof. Juliana Krumova Marinova, MD, PhD

for the presented doctoral thesis ***"Quality of life after treatment of malignant hematopathies and solid tumors in childhood"***

by Hristina Yaneva Hristozova, MD,

doctoral student in full-time study in the doctoral program "Pediatrics" (enrolled with Order No. R-109-22/30.01.2020), professional direction 7.1 "Medicine", field of higher education 7. Health and Sports with scientific supervisors - Prof. Valeria Ignatova Kaleva, MD, PhD and Prof. Dr. Paraskeva Mancheva Draganova, MD, DSc.

Based on Protocol No. 1/20.03.2025 from a meeting of the Scientific Jury, appointed by Order No. R 109-150/13.03.2025 of the Rector of the Medical University "Prof. Paraskev Stoyanov" - Varna, I have been assigned to prepare a review. The review is prepared on the basis of the documents submitted under the procedure, which are in full compliance with the requirements and are excellently arranged.

Doctoral student's career profile:

Hristina Yaneva Hristozova completed her secondary education at the Second Mathematical High School "Dr. Petar Beron", Varna. In 1994, she graduated with honors from the Faculty of Medicine at the Medical University of Varna. She successively acquired a specialty in Pediatrics (2001), Oncology (2006) and Pediatric Clinical Hematology (2009). In the system of continuing education, she has acquired qualifications in Abdominal Ultrasound, Palliative Care and Stem Cell Transplantation. In 2014, she completed a specialization in the Pediatric Oncology Clinic of the Children's Hospital "St. Anna", Vienna. In 2014, she acquired the master"s degree in "Public Health and Health Management" at the Medical University of Pleven.

Since 1995 worked successively at the First Children's Clinic and the Children's Emergency Center, and since 2001 she has been part of the team of the Clinic of Pediatric Clinical Hematology and Oncology of the University Hospital "St. Marina" - Varna. In 2005 she won a competition for an assistant professor in pediatric diseases at the Department of Pediatrics of the Faculty of Medicine, and since 2006 she has been appointed as an assistant professor at the Department of Clinical Medical Sciences, Faculty of Dental Medicine of the Medical University - Varna.

Dr. Hristozova has scientific interests in the field of treatment of childhood malignant diseases and quality of life after treatment of childhood malignant diseases. She has 20 publications and over 90 participations in scientific forums, she is a co-author of a clinical guideline "Behavior in Neuroblastoma in Children".

She is a member of the Bulgarian Medical Union, Bulgarian Pediatric Association (BPA), Bulgarian Society of Hematology, Bulgarian Medical Society of Pediatric Hematology and Oncology and the European Society of Pediatric Oncology (SIOPE).

Speaks Russian and English.

General description of the dissertation: The dissertation contains 140 pages, structured in three main chapters, illustrated with 19 tables and 27 figures, two appendices. The bibliographic list includes 235 literary sources, of which 5 are in Cyrillic, 227 in Latin and 3 internet sources. The dissertation was discussed and directed for public defense by the departmental council of the Department of Pediatrics at the Medical University - Varna on 27.02.2025.

Relevance and significance of the topic of the dissertation: "Quality of life after treatment of malignant hematopathies and solid tumors in childhood": In full accordance with the professional profile of the doctoral student, the dissertation focuses on the assessment of the quality of life (QoL) of those monitored in the Clinics of Pediatric Clinical Hematology and Oncology and the identification of the factors that influence it in support of the timely identification of risks in survivors of childhood cancer (CCS) and the development and implementation of appropriate, person-oriented, health and psychosocial interventions to improve their well-being. Dr. Hristozova argues the relevance of the topic in the introduction: scientific research confirms that subgroups with significant differences in QoL are formed among the CCS population, related to the type of malignant disease, age at diagnosis, type of treatment, demographic characteristics of individuals, as well as differences in individual countries related to features of treatment and follow-up long-term care. Quality of life assessment is a mandatory element of follow-up care for survivors and is integrated into long-term follow-up programs in countries with successful practices in the treatment of childhood oncological diseases. Quality of life assessment and identification of factors related to the disease, the treatment received and the demographic characteristics of the patients would allow for the adaptation of the follow-up care model in order to achieve optimal quality of life for survivors of childhood malignant diseases.

Chapter One. A 45-page literature review was structured in 4 sections: 1. Health, quality of life and health-related quality of life. Quality of life measurement tools. Generic and cancer-specific questionnaires; 2. Quality of life after childhood malignant disease – problem statement, areas and determinants; 3. Role of follow-up of childhood malignant disease survivors; 4. Summary of the literature review and prerequisites for the study. The literature sources used are scientific publications, mainly by foreign researchers, cited in good faith by the doctoral student. The review is written in clear and accessible language and reflects a thorough knowledge of the issues discussed and a skillful use of scientific terminology.

The manner of presenting the literature review demonstrates the author's ability to analytically present scientific information and to argue the relevance and significance of the dissertation topic, as well as the approach of his own scientific research.

Chapter Two. Purpose, tasks, material and methods of the study: are presented precisely on 6 pages of the dissertation. The research hypothesis is presented: “The quality of life of patients undergoing follow-up, survivors of malignant hematopathies and solid tumors in childhood, correlates with demographic characteristics, type and risk group of the disease, therapeutic modality and late post-therapeutic consequences”.

The goal is “To assess the quality of life in patients who have undergone treatment for malignant hematopathies and solid tumors in childhood, and to study the factors that influence it”. The research tasks are presented in 4 points, directly related to achieving the goal, clearly formulated as follows: 1. To study the available scientific literature on the quality of life in patients who have undergone treatment for malignant hematopathies and solid tumors in childhood; 2. To assess the quality of life in patients who have undergone treatment for malignant hematopathies and solid tumors in childhood with appropriate methods; 3. To compare the quality of life of individuals treated for malignant hematopathies with the quality of life of individuals treated for solid tumors; 4. To establish indicators related to the demographic characteristics of the patients, the malignant disease and the treatment provided and clinical data from the dispensary observation, affecting the quality of life of the survivors.

A consistent and in-depth description of the material and methodology applied in the scientific study follows. They are clearly justified and adequate, respectively to the set goals and objectives and are described in detail. Selection of participants: The study included patients with malignant hematopathies or solid tumors, diagnosed and treated in childhood at the Clinic of Pediatric Clinical Hematology and Oncology (CPCHO) of the University Hospital "St. Marina" – Varna in the period 2000-2021, who have reached the age of 18 and are continuously monitored at the clinic. The study was conducted after receiving approval from the Research Ethics Committee at the Medical University - Varna (№91/27.02.2020) and was carried out for 2 years in the period March 2020 - February 2022 based on the CPCHO.

The inclusion and exclusion criteria for the study are presented. Inclusion criteria are: - age over 18 years; treatment (chemotherapy, radiotherapy, surgery) for malignant hemopathy or solid tumor in childhood; registration for long-term follow-up at the CPCHO; absence of relapse or secondary neoplasia, with active treatment during the study period; absence of accompanying severe chronic disease with mental impairment; signed Declaration of informed consent to participate in the study. Exclusion criteria are: age under 18 years; diagnosed recurrence or secondary neoplasia, with active treatment during the study period; diagnosed severe chronic disease with mental impairment; persons who did not sign a Declaration of Informed Consent to participate in the study. The monitoring body is the doctoral student himself. Of the patients diagnosed and successfully completed treatment for malignant hematopathies and solid tumors in childhood at the CPCHO during the period 2000-2021, at the time of the study, 159 were over 18 years of age, of whom 91 were registered for follow-up and were determined as potential participants, of whom 52 met the inclusion criteria: 25 men and 27 women.

The methods applied are presented below: 1. Documentary method – the data from the participants’ medical records were retrospectively studied: “History of illness” and “Outpatient list”; 2. Sociological methods: the applied instruments are described in detail: 2.1 - Generic questionnaire for assessing the quality of life of the World Health Organization (WHO) – WHOQOL-BREF 26. The questionnaire is described in detail in the four areas: “physical”, “psychological”, relationships”, “environment” and one question related to the self-assessment of QoL and general health. The reasons for choosing WHOQOL-BREF26 in the own study are presented in 5 points: - suitable for research in polymorbid patients; - has good reliability, successfully tested in 23 countries with different cultural characteristics and socio-economic development; - validated for Bulgaria by V. Petkov in 1999; - successfully applied in studies by Bulgarian authors; the questions are asked clearly and understandably, filling it out takes little time. 2.2. Questionnaire for qualitative data on the demographic and social characteristics of the participants, described in detail by the doctoral student. 3. Clinical and laboratory methods: clinical examination; anthropometric measurements; laboratory tests. 4. Statistical methods for data processing and analysis - methods of descriptive and analytical statistics (correlation analysis, one-factor analysis of variance ANOVA - post hoc Tukey HSD), presented in detail. Statistical data processing was carried out with the IBM SPSS Statistics 20 software product.

The tools in the scientific study are applied to the dissertation work. In summary: The chosen approach allows to achieve the set goal by obtaining an adequate answer to the tasks solved in the dissertation work. The applied methodology is described by Dr. Hristozova in detail and with skill.

Chapter Three. Results and Discussion. This part of the dissertation covers 58 pages, precisely arranged and illustrated, structured in two sections: 1. The sections of the results and discussion fully correspond to the tasks set in the dissertation work. The results are consistently and analytically presented, illustrated with tables and colored figures, as follows: 1. Demographic data for the participants; 2. Data on the malignant disease in childhood and the treatment performed; 3. Data from the follou-up observation of the participants; 4. Results from the assessment of QoL with the WHOQOL-BREF 26 questionnaire; 5. Correlation analysis. The discussion of the results follows the same sequence of their presentation, extremely thorough and conscientious, in the context of the own study and compared with those from studies conducted by other researchers. The two sections of this part of the dissertation reflect Dr. Hristozova's ability to handle data from the scientific study, to apply appropriate methods of analysis and to interpret in depth. Summary: This part of the dissertation deserves special attention and high praise for its adequate structuring, logical coherence and consistency of presentation.

Conclusions, contributions, conclusion. The conclusions are presented in 9 points, skillfully formulated and directly related to the research goal and tasks: 1. In general, for all participants who survived malignant hemopathies and solid tumors in childhood, the highest average score of QoL was for the "Physical" area, and the lowest for the "Psychological" area; 2. The type of malignant disease moderately influences the assessment of QoL in the "Psychological", "Relationships" and "Environment" areas and extremely weakly the assessment of QoL in the "Physical" area; 3. No correlation was found between the disease group (malignant hemopathy or solid tumor) and the QoL of the survivors; 4. The assessment of QoL of the survivors in the socio-demographic status module is most strongly influenced by "Occupation" and "Marital status". Gender, age and education, as factor variables, have a negligible impact on QoL assessments; 5. Of the factors related to the experienced illness, the strongest relationship is between "Risk group" and the assessment of QoL in the "Physical" area; 6. The diagnostic group, the type of medications administered, CNS radiotherapy performed and the duration of treatment have a weak impact on the assessment of QoL; 7. The presence of scars and body asymmetry negatively affects the assessment of QoL in the "Psychological" area; 8. A moderate relationship is established between the BMI group and the assessment of QoL in the "Physical" area and a negligible relationship with the assessment in the "Psychological", "Relationships" and "Environment" areas; 9. After treatment of malignant hematopathies and solid tumors in childhood, the number of patients with chronic diseases progressively increases.

The contributions are presented in two groups: contributions of a scientific-theoretical nature and contributions of a scientific-applied nature. The contributions of a scientific and theoretical nature are reduced to 3: 1. For the first time in Bulgaria, the QoL of persons over 18 years of age who have survived treatment for malignant hematopathies and solid tumors in childhood has been assessed; 2. The reliability of the WHOQOL_BREF questionnaire has been established as a tool for quantitative assessment of QoL in patients who have survived treatment for malignant hematopathies and solid tumors in childhood; 3. Indicators related to the demographic characteristics of the patients, the malignant disease and the treatment performed and clinical data from the dispensary observation have been established, which correlate with the quality of life of the survivors.

The contributions of a scientific and applied nature are presented in 3 points: 1. An algorithm for collecting data - demographic and clinical - has been developed, which are related to QoL in survivors of treatment for malignant hematopathies and solid tumors in childhood; 2. The WHOQOL_BREF questionnaire was successfully applied in the studied group of patients and can be used in the future in routine clinical practice and in scientific research as a tool for quantitative assessment of QoL in adult patients who have survived treatment for malignant hematopathies and solid tumors in childhood; 3. The established indicators affecting the quality of life of survivors of treatment for malignant hematopathies and solid tumors in childhood can be used for timely identification of patients at risk and taking appropriate measures for comprehensive care during their follow-up.

The conclusion of the dissertation is its maximum synthesis and contains 4 recommendations: 1. Quality of life assessment should become a mandatory part of the long-term follow-up of survivors of malignant hematopathies and solid tumors in childhood. Its implementation by filling out a self-assessment questionnaire takes little time and resources. 2. It is necessary, upon completion of treatment and transition to follow-up, for each survivor to receive a summary of the treatment performed and the complications obtained and an individual follow-up plan, according to the risks of late effects. These data should be available both to the medical team that follows him, and to the general practitioner and the various specialists with whom the patient has contact, which is easily feasible in the conditions of modern electronic healthcare. 3. Due to the specific needs of survivors and the peculiarities of the late consequences of treatment, follow-up should gradually move from pediatric oncohematology clinics to centers for monitoring adults who have survived long-term cancer diseases. 4. It is necessary that the team monitoring survivors of malignant hematopathies and solid tumors in childhood include both oncologists and specialists from other fields, as well as a psychologist with appropriate experience and a social worker. Monitoring according to this model would ensure adequacy of care and achievement and maintenance of optimal QoL of long-term survivors of childhood cancer.

Abstract and scientific asset in connection with the dissertation work: The abstract is written on 76 pages, is structured according to the requirements and reflects the main results achieved in the dissertation. It contains a list of publications and participation in scientific forums in accordance with the requirements of the Regulations of the Medical University - Varna. Comprehensive assessment: I give a high positive assessment of the dissertation presented by Dr. Hristozova. I congratulate the doctoral student and the scientific supervisors for the choice of the topic, the applied approach of the scientific research and the results obtained therein, confirming the need for integrated care for patients who have experienced childhood cancer, to achieve optimal quality of life in their specific circumstances.

CONCLUSION

The dissertation contains scientific-theoretical, methodological and applied results, which represent an original contribution to science and meet all the requirements of the Act on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for the Implementation and the Regulations of MU - Varna. The presented materials and dissertation results fully comply with the requirements of the Regulations of Medical University - Varna. The dissertation shows that the doctoral student Hristina Yaneva Hristozova, MD, possesses in-depth theoretical knowledge and professional skills and demonstrates qualities for independent conduct of scientific research.

This gives me reason to confidently confirm my positive assessment of the conducted research, presented by the above-reviewed dissertation, abstract, achieved results, contributions and scientific assets.

I propose to the esteemed scientific jury to award the educational and scientific degree "Doctor of philosophy" to Hristina Yaneva Hristozova, MD in the doctoral program "Pediatrics", professional direction 7.1 "Medicine", field of higher education 7. Health and Sports.

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Stara Zagora Prof. Juliana Krumova Marinova, MD, PhD