REVIEW

by Prof. Dr. Silva Peteva Andonova-Atanasova, MD, PhD, DSc
Member of the Scientific Jury
Executive Director of UMHAT „Sveta Marina" EAD - Varna, Bulgaria
Head of the Department of „Neurology and Neurosciences"
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Regarding a dissertation, submitted for the award of the educational and scientific degree **„doctor"**
in the field of higher education
7. Health and Sports, professional field
7.1. Medicine, specialty „Neurology"

by **Dr. Paola Nikolay Kulicheva**, full-time PhD student

Dissertation title:
„Predictive Factors for Fatal Outcome in Patients with Ischemic Stroke in Young and Middle Age"

The present review has been prepared on the basis of Order of the Rector of Medical University „Prof. Dr. Paraskev Stoyanov" - Varna, Bulgaria № R-109-476/20.11.2025, in accordance with the requirements of the Act on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for the Implementation of the Act (Articles 53 and 57) and the Regulations for the Development of the Academic Staff of the Medical University „Prof. Dr. Paraskev Stoyanov" - Varna, Bulgaria.

Within the defense procedure, Dr. Kulicheva has submitted all required materials in compliance with the Regulations for the Academic Staff of Medical University „Prof. Dr. Paraskev Stoyanov" - Varna, Bulgaria.

Brief biographical data of the PhD candidate:

Dr. Paola Nikolay Kulicheva was born in 1993. She graduated with a degree in „Medicine" in 2017 from the Medical University „Prof. Dr. Paraskev Stoyanov" - Varna, Bulgaria.

From October 2017 to April 2018, she was employed as a resident physician at the Center for Emergency Medical Care - Varna. From September 2018 to the present, she has been working at the Second Neurology Clinic with the Stroke Unit and Intensive Neurology Care Unit at UMHAT „Sveta Marina" EAD - Varna, Bulgaria. In 2023, she obtained her specialty in „Neurology". She is proficient in English and French.

In 2023, Dr. Kulicheva completed a certified training course in „Ultrasound Diagnostics of the Nervous System", acquiring professional qualification.

Dr. Kulicheva was enrolled as a full-time PhD student at the Department of „Neurology and Neurosciences" of Medical University „Prof. Dr. Paraskev Stoyanov" - Varna, Bulgaria, on 04th November 2020 and was deregistered with the right to defense on 20th November 2025.

The submitted dissertation is structured in accordance with accepted academic standards. It comprises 173 pages, including 46 figures and 41 tables and consists of the following sections literature review 41 pages, aim and objectives 1 page, materials and methods 3 pages, results 57 pages, discussion 24 pages, conclusion 4 pages, conclusions 1 page, contributions 1 page, references 23 pages, publications, related to the dissertation 1 page, and appendices 2 pages.

The bibliographic list includes 253 sources, of which 6 are in Cyrillic and 247 in Latin script.

The chosen topic, focusing on predictive factors for fatal outcome in young stroke patients, is of particular importance due to the fact that younger patients often have different etiologies, risk profiles, and fewer comorbidities compared to older individuals. This makes prognostic assessment in this population both challenging and clinically significant. Ischemic stroke remains a leading cause of mortality and disability worldwide, despite advances in prevention and treatment. According to the World Health Organization, it is the second most common cause of death among individuals over 60 years of age and the fifth among those aged 15-59 years. This highlights the substantial burden of the disease in young and middle-aged patients and necessitates a focus on the specific factors determining unfavorable outcomes. A more precise prognostic approach in this population has the potential to improve survival and reduce long-term social

and economic consequences through more targeted and effective treatment and better healthcare resource management.

The literature review represents a comprehensive and in-depth analysis of the available scientific literature, with most cited sources published within the last decade. The thorough analysis logically leads to a clearly defined and scientifically grounded research aim.

The aim of the dissertation is clearly formulated - to conduct a retrospective, observational, single-center cohort study of patients up to 59 years of age with acute ischemic stroke, aimed at identifying independent predictors of fatal outcome by assessing the impact of risk factors, demographic characteristics, clinical status at admission, laboratory and neuroimaging findings, length of hospital stay, and administered treatment.

The objectives related to the main aim are specific, well-defined, and comprehensive, namely: to perform a retrospective cohort analysis of patients aged 18-59 years with acute ischemic stroke; to describe the clinical, demographic, and imaging characteristics of the patients; to analyze the relationship between comorbidities and the risk of fatal outcome during the acute phase of ischemic stroke; to assess the impact of clinical status at admission (including NIHSS score, vital signs, and presence of impaired consciousness) on mortality risk; to examine the role of imaging findings, including infarct location and volume, hemispheric involvement, and ASPECTS score, in predicting fatal outcome; to evaluate the significance of laboratory parameters (including inflammatory and metabolic markers) and length of hospital stay as potential prognostic factors; to analyze the association between ischemic stroke etiological subtypes according to the TOAST classification and fatal outcome; and to apply multivariate logistic regression analysis to identify independent risk factors associated with early post-stroke mortality.

The clinical cohort included a sufficient number of patients (168) with ischemic stroke, hospitalized at the Second Neurology Clinic of UMHAT „Sveta Marina" EAD - Varna, Bulgaria during the period 2017-2022. The study population was divided into two groups - a target group, consisting of 67 patients who died during hospitalization and a control group of 101 patients with favorable outcomes, selected using age-matching principles.

The inclusion and exclusion criteria are clearly defined, ensuring accurate interpretation of the results.

Clinical methods involved a retrospective analysis of available medical documentation, including discharge summaries, medical histories,

laboratory results, imaging studies, and standard 12-lead electrocardiograms. All patients (target and control group) were assessed for the presence of major risk factors for ischemic stroke and associated mortality, including non-modifiable, modifiable, and less commonly documented modifiable risk factors. Laboratory tests included leukocyte count and biochemical analysis of serum CRP, sodium, and glucose levels. Neurological deficit at admission was assessed using the standardized NIHSS scale, and level of consciousness was evaluated using the Glasgow Coma Scale. Neuroimaging included head CT or MRI.

The statistical methods were appropriately selected in accordance with the study objectives and ensured reliable evaluation of the obtained results.

The dissertation by Dr. Paola Kulicheva is distinguished by detailed analysis of the results and clear presentation of the conclusions derived from them. A key conclusion is that comprehensive risk assessment at admission, incorporating both acute and background factors, is crucial for early identification of high-risk patients and optimization of therapeutic strategies. Low systolic blood pressure (≤120 mmHg), severity of neurological deficit (NIHSS >15), and chronic left-sided heart failure are identified as the strongest and independent predictors of fatal outcome in young patients. Some factors demonstrate prognostic value in individual models but lose significance when stronger predictors are included, such as age, acute inflammatory response, elevated heart rate, increased CRP levels, leukocytosis, and number of comorbidities. Factors, such as previous vascular events, certain comorbid conditions (ischemic heart disease, diabetes mellitus, dyslipidemia, deep vein thrombosis, malignancy), decreased level of consciousness, and length of hospital stay lose statistical significance in multivariate analysis, indicating mediated effects.

Contributions of original character

A specific analysis of demographic, clinical, and imaging characteristics of ischemic stroke patients up to 59 years of age is presented, enabling more accurate identification of factors specific to this group and contributing to improved prognosis.

Independent prognostic factors associated with early post-stroke mortality are identified.

The study integrates and analyzes the impact of a wide range of potential prognostic factors, including clinical indicators (NIHSS and vital parameters), imaging findings (localization, ASPECTS), laboratory markers (inflammatory and metabolic), and etiological subtypes (TOAST

classification), providing a comprehensive view of mechanisms leading to unfavorable outcomes.

Contributions of confirmatory character

The pivotal role of chronic left-sided heart failure (CLHF) as a powerful independent predictor of fatal outcome following ischemic stroke is emphasized.

The severity of neurological deficit at admission, measured by the NIHSS scale, is confirmed as the strongest independent predictor of mortality.

Low systolic blood pressure (≤120 mmHg) and tachycardia (≥100/min) are confirmed as independent predictors of fatal outcome.

Elevated CRP levels and leukocytosis are confirmed as independent predictors of mortality in ischemic stroke, offering practical value due to their accessibility for early risk assessment.

Conclusion

The presented dissertation by Dr. Paola Nikolay Kulicheva fully meets the regulatory requirements of the Act on the Development of the Academic Staff in the Republic of Bulgaria and the Regulations of the Medical University „Prof. Dr. Paraskev Stoyanov" - Varna, Bulgaria for awarding the educational and scientific degree „Doctor".

I propose that the esteemed members of the Scientific Jury vote in favor of awarding the educational and scientific degree „Doctor" in the scientific specialty „Neurology" to Dr. Paola Nikolay Kulicheva.

Varna, Bulgaria

10th January 2026

Member of the Scientific Jury: