Review

by

Prof. Dimitar Bogdanov Maslarov, MD, DSc

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of a dissertation thesis entitled:

"Predictive Factors for Mortality in Patients with Ischemic Stroke at Young and Middle Age"

submitted for the award of the educational and scientific degree "Doctor" (PhD)

in Higher Education Area 7. Health and Sports,

Professional Field 7.1. Medicine,

Scientific Specialty Neurology,

by Dr. Paola Nikolay Kulicheva,

full-time PhD candidate in the doctoral program Neurology,

enrolled by Order No. R-109-479 / 04.11.2020

at Medical University "Prof. Dr. Paraskev Stoyanov" – Varna,

with scientific supervisor: Assoc. Prof. Darina Kirilova Georgieva-Hristova, MD, PhD.

By decision of the Chair of the Scientific Jury and in accordance with Order of the Rector of Medical University – Varna No. R-109-476 / 20.11.2025, I have been appointed as an external member of the Scientific Jury. In this capacity, I hereby present the present review.

Dr. Paola Nikolay Kulicheva was deregistered by Order No. R-109-476 / 20.11.2025 of the Rector of Medical University "Prof. Dr. Paraskev Stoyanov" – Varna, on the basis of a report with incoming No. 102-2857 / 07.11.2025 submitted by Prof.

Silva Peteva Andonova-Atanasova, MD, PhD, Head of the Department of Neurological Diseases and Neurosciences, a decision adopted under Protocol No. 49 / 10.11.2025 of the Faculty Council, and a report with incoming No. 103-8040 / 19.11.2025 submitted by Prof. Yoto Trifonov Yotov, MD, DSc, Dean of the Faculty of Medicine at Medical University – Varna.

The present review has been prepared in accordance with the Academic Staff Development Act, the Regulations for its Implementation, and the Regulations governing the conditions and procedures for the acquisition of scientific degrees and the holding of academic positions at Medical University "Prof. Dr. Paraskev Stoyanov" – Varna.

Education and Professional Development

Dr. Paola Nikolay Kulicheva obtained the educational and qualification degree Master of Medicine in 2017 at Medical University "Prof. Dr. Paraskev Stoyanov" – Varna.

In September 2018, she commenced her specialty training in Neurology at the Second Clinic of Neurological Diseases, including the Stroke Unit for Acute Cerebrovascular Diseases and the Intensive Care Unit for Neurological Diseases at University Hospital "St. Marina" – Varna.

Since 4 November 2020, she has been enrolled as a full-time PhD candidate at the Department of Neurological Diseases and Neurosciences, Medical University – Varna. In 2023, she acquired the medical specialty Neurology.

She has completed certified training in Doppler Sonography (2023). Dr. Paola Nikolay is fluent in English and French.

She is a member of the Bulgarian Medical Association and the Bulgarian Society of Neurology.

Structure of the Dissertation

The dissertation of Dr. Paola Nikolay is developed in a total volume of 174 pages and includes 46 figures and 41 tables.

It comprises the following sections: Introduction – 1 page; Literature Review – 42 pages; Aim and Objectives – 1 page; Materials and Methods – 2 pages; Original Results – 57 pages; Discussion – 24 pages; Conclusion – 2 pages; Conclusions – 1 page; Contributions – 2 pages; Limitations of the Study – 1 page; References – 22 pages; Publications Related to the Dissertation – 1 page. The work is illustrated with a total of 46 figures and 41 tables.

The bibliography includes 253 references, of which 6 are in Cyrillic and 247 in Latin script, with approximately 30% of the cited sources published within the last 10 years.

The dissertation was reviewed and approved for public defense by the Department of Neurology and Neurosciences at the Medical University of Varna, as documented in Protocol No. 9/04.11.2025 of the Departmental Council.

Literature Review

The literature review encompasses a total of eight main sections, covering all modifiable and non-modifiable risk factors for cerebral infarction, analyzed and presented within the framework of contemporary concepts and current scientific understanding.

The Aim of the study

The aim of the present study is to conduct a retrospective, observational, single-center cohort study in patients aged up to 59 years with acute ischemic stroke, with the objective of identifying independent predictors of mortality by assessing the impact of risk factors, demographic characteristics, clinical status at admission, laboratory and neuroimaging findings, length of hospitalization, and the treatment administered.

Objectives

1. To perform a retrospective cohort analysis of patients with acute ischemic stroke aged 18–59 years who were hospitalized at the Second Department of Neurology of St. Marina University Hospital, Varna, during the period 2017–2022.

2. To describe the clinical, demographic, and neuroimaging characteristics of patients with ischemic stroke aged up to 59 years.
3. To analyze the association between comorbid conditions and the risk of mortality during the acute phase of ischemic stroke in the target patient population.
4. To assess the impact of clinical status at admission, including NIHSS score, vital signs, and the presence of disturbances of consciousness, on the risk of mortality.
5. To investigate the prognostic value of neuroimaging findings, including lesion localization, hemispheric involvement, presence of a hyperdense cerebral artery sign, and ASPECTS score, for predicting mortality.
6. To evaluate the significance of laboratory parameters, including inflammatory and metabolic markers, as well as length of hospital stay, as potential prognostic factors.
7. To analyze the relationship between etiological subtypes of ischemic stroke according to the TOAST classification and mortality in patients aged 18–59 years.
8. To apply multivariable logistic regression analysis to identify independent risk factors associated with in-hospital mortality in the studied patient cohort.

Materials and Methods

The clinical material of the present study includes a total of 168 patients aged 18–59 years, stratified into two groups: a target group consisting of 67 patients who experienced in-hospital mortality, and a control group comprising 101 patients who survived the stroke. Group allocation was based on the following inclusion and exclusion criteria.

Inclusion criteria: Patients with acute ischemic stroke hospitalized at the Second Department of Neurology, including the Neurological Intensive Care Unit and the Acute Stroke Unit, at St. Marina University Hospital, Varna, during the period 2017–2022;

patients aged 18–59 years at the time of hospitalization; and the presence of a clinically and neuroimaging-confirmed acute ischemic stroke.

Exclusion criteria: Patients younger than 18 years or older than 59 years; patients diagnosed with intracerebral (intraparenchymal) hemorrhage or subarachnoid hemorrhage.

The study was approved by the Research Ethics Committee of the Medical University of Varna (Decision No. 133, dated 22 June 2023).

A retrospective analysis of the available medical records of patients with ischemic stroke was performed.

Clinical Methods

The clinical methods applied in the study included the following:

1. Clinical assessment of vital signs at admission, including systolic blood pressure and heart rate.
2. Determination of the patients' risk profile. Risk factors were systematized as follows: Non-modifiable risk factors: sex, age, previous ischemic stroke or transient ischemic attack, and previous myocardial infarction. Modifiable risk factors: arterial hypertension, atrial fibrillation, ischemic heart disease, chronic left-sided heart failure, diabetes mellitus, dyslipidemia, obesity, smoking, alcohol abuse, and use of psychoactive substances. Less frequently documented modifiable risk factors: right-to-left shunt, acute inflammatory process, obstructive sleep apnea syndrome, deep vein thrombosis, and malignant diseases.
3. Laboratory investigations, including leukocyte count, serum C-reactive protein, serum sodium, and serum glucose levels.
4. Neuroimaging studies, comprising non-contrast computed tomography of the brain and magnetic resonance imaging of the brain.

5. Clinical assessment scales, including the National Institutes of Health Stroke Scale (NIHSS), the Glasgow Coma Scale (GCS), and the Alberta Stroke Program Early CT Score (ASPECTS).

Statistical Methods

The statistical analysis included assessment of distribution characteristics using measures of skewness and kurtosis, the Mann–Whitney U test, the χ^2 test, Fisher's t-test, calculation of odds ratios (OR) with 95% confidence intervals (CI), and multivariable logistic regression analysis.

Original Results

The results are structured into twelve sections. The first section presents the demographic characteristics of the study population, as well as non-modifiable risk factors. The second through fourth sections report the findings related to modifiable and less frequently documented risk factors. The fifth section presents the results of the analysis of etiological subtypes according to the TOAST classification. The sixth and seventh sections include results related to the assessment of neurological deficit using the NIHSS and the evaluation of level of consciousness using the Glasgow Coma Scale. The eighth section describes the results of the analysis of vital parameters. The ninth section presents the findings from the neuroimaging studies. The tenth section reports the results of laboratory investigations. The eleventh section describes the results related to additional factors, including the type of treatment administered and the duration of hospitalization. The twelfth section presents the results of the multivariable logistic regression analysis, which includes predictors of mortality that demonstrated statistical significance in the preceding analyses and are grouped into four main regression models.

Conclusions

The main conclusions of the dissertation are as follows:

1. Low systolic blood pressure (≤120 mmHg), severity of neurological deficit (NIHSS >15 points), and chronic left-sided heart failure are the strongest and independent predictors of mortality.
2. Several factors, including elevated C-reactive protein levels, increased leukocyte counts, and heart rate >100 beats/min, demonstrate prognostic significance in the initial stages of the analysis; however, their independent effect is mediated or displaced by stronger clinical predictors included in the final multivariable model.
3. Certain factors show prognostic value in individual models but lose their statistical significance after the inclusion of more powerful predictors. These include age, acute inflammatory processes, elevated heart rate, increased CRP levels, leukocyte count, and the number of comorbid conditions.
4. Factors such as prior vascular events, selected comorbidities (ischemic heart disease, diabetes mellitus, dyslipidemia, deep vein thrombosis, and malignant disease), low level of consciousness, and length of hospital stay lose their statistical significance in multivariable analysis, indicating that their effects are mediated by other variables.
5. Variables including sex, arterial hypertension, atrial fibrillation, obesity, obstructive sleep apnea, behavioral risk factors, neuroimaging parameters (ASPECTS score, hyperdense middle cerebral artery sign, vascular localization), as well as serum sodium levels, do not demonstrate a statistically significant association with in-hospital mortality in the studied population.
6. A comprehensive risk assessment at admission, incorporating both acute and background clinical parameters, is crucial for the early identification of high-risk patients and for optimizing therapeutic strategies.

Contributions

Original contributions:

1. Focused analysis of a young and middle-aged cohort. This dissertation provides a detailed descriptive and comparative analysis of the demographic, clinical, and

neuroimaging characteristics of patients aged 18–59 years. The applied approach enables more precise identification of factors specific to this age group, with potential relevance for improving prognostic assessment.

2. Identification of independent prognostic factors. Through the use of multivariable logistic regression analysis, independent risk factors associated with in-hospital mortality were identified. This statistical approach allows differentiation between variables with a direct and independent impact on mortality and provides a foundation for further clinical and research-oriented investigations.

3. Comprehensive analysis of prognostic markers. The study integrates and evaluates the impact of a broad spectrum of potential prognostic factors, including clinical parameters (such as NIHSS and vital signs), neuroimaging findings (lesion localization and ASPECTS score), laboratory markers (inflammatory and metabolic parameters), and etiological subtypes according to the TOAST classification. This integrated analysis facilitates a deeper understanding of the interactions among different mechanisms associated with mortality.

Confirmatory Contributions:

1. Confirmation of chronic left-sided heart failure as an independent predictor of mortality following ischemic stroke. The analysis demonstrates that chronic left-sided heart failure is one of the most significant independent prognostic factors for mortality, underscoring the critical role of cardiac status in determining outcomes after acute ischemic stroke.

2. Validation of the NIHSS as a principal predictor of mortality after ischemic stroke. A significant association was identified between the severity of neurological deficit at admission, as assessed by the NIHSS, and mortality. This finding confirms the prognostic value of the NIHSS also in young and middle-aged patient populations.

3. Prognostic significance of hemodynamic parameters. Reduced systolic blood pressure (≤120 mmHg) and tachycardia (≥100 beats/min) were identified as independent predictors of mortality.

4. Prognostic value of laboratory markers. Elevated levels of C-reactive protein and leukocyte count were associated with an increased risk of mortality. These readily available parameters have practical relevance for early risk assessment and patient stratification.

Limitations of the Study

1. Small sample size. The limited size of the study cohort, particularly within subgroups characterized by less frequent risk factors such as use of psychoactive substances, alcohol abuse, obstructive sleep apnea, right-to-left shunt, and malignant diseases, may have reduced the statistical power of the analysis. This limitation likely contributed to the lack of statistically significant associations between these factors and mortality, despite their established prognostic relevance in larger studies.

2. Retrospective design. As a retrospective study, the analysis relied on available medical records. Incomplete documentation or missing data for certain variables may have influenced the results or restricted more detailed analyses of specific factors.

3. Limited geographic scope. Data were collected from a single medical center, which limits the generalizability of the findings to broader populations at the national or international level.

4. Focus on in-hospital mortality. The study evaluated only mortality occurring during hospitalization, which does not provide a comprehensive picture of long-term outcomes. Factors that are not significant for early mortality may have a substantial impact on long-term survival and functional recovery.

Publications

Two full-text scientific publications directly related to the dissertation, published in peer-reviewed scientific journals during the period 2021–2025.

Summary of the Doctoral Dissertation

The summary of the doctoral dissertation comprises 63 pages, includes 31 figures and 26 tables, and provides an accurate and comprehensive representation of the dissertation.

Remarks

A very limited number of citations of Bulgarian studies and publications on the topic are included, which, however, is not unprecedented among doctoral candidates at the Medical University of Varna.

Absence of participation in Bulgarian congresses and scientific conferences.

The certificate of specialty training is not signed by Dr. Paola Nikolay, which renders it formally invalid.

Conclusion

The candidate in the present competition 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, and scientific specialty Neurology, is Dr. Paola Nikolay Kulicheva, a full-time doctoral candidate in the doctoral program Neurology, enrolled by Order No. R-109-479/04.11.2020 at the Medical University "Prof. Dr. Paraskev Stoyanov" – Varna, under the supervision of Assoc. Prof. Darina Kirilova Georgieva-Hristova, MD, PhD.

The thesis submitted for review represents a retrospective study conducted by the author and is characterized by originality and thoroughness. The results obtained have a clear contributory value for practical neurology.

Based on the above, I am firmly convinced that the overall clinical and research activity of Dr. Paola Nikolay Kulicheva meets the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria and the Regulations for the Development of the Academic Staff at the Medical University "Prof. Dr. Paraskev Stoyanov" – Varna. Therefore, I recommend that the honorable members of the Scientific Jury award her the educational and scientific degree "Doctor".

03 January 2026
Sofia

Prof. Dimitar Bogdanov Maslarov, MD, DSc

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