

To the chairman
of the Scientific Jury
appointed with order
of the Rector of
Medical University, Varna
N R -109-242/26.07.2019

REVIEW

By prof. Borislav Georgiev Georgiev, Ph.D.,
Head of the Cardiology Clinics, MHAT “National Heart Hospital” Sofia,
Member of the Scientific Jury of the call for the academic position
“Associate Professor” in the higher education sphere 7. Health care and sport; professional
field 7.1 “Medicine” and “Internal Diseases” scientific specialty, promulgated in the State
Gazette, issue 43/31.05.2019

Documents for the above mentioned call have been submitted by one applicant – Dr. Yavor Kostadinov Kashlov, Ph.D., resident medical officer of Cardiology at the Internal Medical Department. The submitted documents by the applicant are in conjunction with the requirements of the regulation for the academic position “Associate Professor” and the rules of Medical University – Varna. I do not find any gaps in the submitted documentation and I declare that I have no common scientific work with the doctoral student.

Biographical data

Yavor Kostadinov Kashlov graduated medicine in MU – Varna in 2009. Dr. Kashlov was awarded the scientific PhD degree in the scientific field “Internal diseases” in 2017 after defending his thesis on “*Biological markers of necrosis and necroptosis in cardiovascular diseases*”. Since 2011 he has been Adjunct Assistant and since 2013 he has been regular Assistant Professor. From October 2017 he has been Chief Assistant Professor in “Propedeutics of Internal Diseases” department, Faculty of Medicine in Medical University – Varna.

Scientific research

1.1. Publications

Dr. Yavor Kostadinov Kashlov has presented the following for the call:

- His own monograph in Bulgarian with the title “*Cell death in myocardial infarction and heart failure*”, 2019, Medical University - Varna publishers
- 5 real full text publications in scientific journals with an impact factor
- 5 real full text publications in scientific journals, indexed/abstracted in WOS/Scopus
- 20 real full text publications in non-abstracted journals with scientific abstracting
- 2 summaries from scientific researches

1.2 Scientific forums

Dr Yavor Kostadinov Kashlov has presented 2 summaries – an oral presentation on the original results on “*HMGB1 and RIPK3 as Markers for Necrosis and Necroptosis in Myocardial Infarction with ST Elevation*” at BIT’s 10th Annual International congress of Cardiology – Rome, 2018, and a summary at the European Congress of Heart Failure 2016, Florence, on the topic “*Changing trends in heart failure hospitalizations 2010-2015 for patients with HFpEF*”

and HfrEF“.

He has a published summary в *the European Society for Medical Oncology* on the topic “*Levels of miR-17, miR-21, miR-29a and miR-92 as recurrence markers after adjuvant chemotherapy in Nx lymph node status colon cancer patients*“.

1.3 Authorship and citations

Overall impact factor (original articles and summaries), indexes of citation:

- Overall impact factor of periodical editions – 26.32 (outgoing No 310/07.07.2019 of the Central Medical Library of Medical University – Varna)

Indexes of citations, a reference from the Central Medical Library (outgoing No 305/27.06.2019)

- 8 Bulgarian citations
- 18 citations in the databases Web of Knowledge and Scopus (without self-citations).

2. Profile of the scientific research, practical and applied activity

In conjunction with the profile of the scientific work at the Internal Medicine Department, where the call was posted for the position of Associate Professor, Dr. Kashlov works in different fields of the Internal Medicine.

3. Most significant scientific contributions

Basic scientific and scientifically applicable contributions

The contributions of the presented publications for this call have been grouped in topics, in connection with the author’s work in the fields: cell death, cardiovascular and cancer diseases, the diagnostic role of the biomarkers, biomarkers in cardiovascular diseases, and biomarkers in cancer patients.

1. Scientific contribution in the sphere of cell death

The author’s monograph reviews the cause and effect connection between the types of cell death and their influence on the development of socially significant diseases like heart failure and myocardial infarction. Special attention has also been paid to another significant phenomenon which takes place in the era of introducing more and more new drugs in Oncology as well as in Cardiology. This phenomenon is called cardiotoxicity and has side effects of a given medicine with the development of excessive myocardial cell death.

The author analyses the types of cell death. Special place is given to one of the most researched forms of cell death – apoptosis. Necroptosis and its unregulated form – necrosis - have been reviewed and reported in detail regarding cardiovascular diseases.

A separate chapter is dedicated to autophagy, its morphology, mechanisms and influence on cardiovascular diseases. The types of myocardial infarction have been reported as well as the cellular mechanisms in which occur the types of cell death involved in myocardial infarction.

A special place is given to a modern problem, connected with the introduction and distribution of new medication which causes cardiotoxicity. Ferroptosis is given special consideration, too.

In a very clever manner in his book the author introduces the main contributions of his thesis, namely: the role of the serum markers for necrosis and necroptosis in patients with cardiovascular diseases; the role of necroptosis as new mechanism of cell death in patients with acute myocardial infarction with ST elevation (STEMI) after successful reperfusion; the role of necroptosis in ischemic-reperfusion injury when testing STEMI patients; the predictive value of

the necroptosis marker – RIPK3 – for bad ejection fraction when dehospitalising STEMI patients and the data about the role of RIPK3 and HMGB1 in STEMI patients.

For the first time in Bulgarian medical literature in the publication “*Programmed necrosis and cardiovascular diseases*” the connection between a comparatively new type of cell death – necroptosis - is taken into consideration - and cardiovascular diseases. This is an opportunity for an in-depth analysis and the development of potentially new therapeutic and diagnostic methods in view of optimizing the treatment of patients with cardiovascular diseases.

The article “*Serum levels of RIPK3 and troponin I as potential biomarkers for predicting impaired left ventricular function in patients with myocardial infarction with ST segment elevation and normal troponin I levels prior percutaneous coronary intervention*” reviews a new kind of cell death – programmed necrosis or necroptosis in cardiovascular diseases.

This is the first clinical article in the accessible literature that treats the significance of necroptosis in terms of ischemic reperfusion heart injury in patients with acute myocardial infarction with ST segment elevation, who were treated successfully with percutaneous coronary intervention.

In the research “*The role of HMGB1 in the pathogenesis of myocardial infarction*” for the first time in Bulgaria the data from previous reports was confirmed that STEMI patients have higher levels of HMGB1 compared to healthy individuals. Besides, it was demonstrated that the high levels of HMGB1 upon admission of STEMI patients are connected with a higher risk of death in those patients. HMGB1 has the potential to be a new biomarker to improve the prognosis in STEMI patients.

For the first time in Bulgarian medical literature in the publication “*The role of autophagy for the development of myocardial infarction and heart failure*” the link between autophagy and cardiovascular diseases like myocardial infarction and heart failure is reported. The mechanisms and the role of cell death is described in physiological and in pathological conditions. The therapeutic modulation of autophagy is of interest in view of treating myocardial infarction and heart failure.

The article “*Myocardial infarction and long non-coding RNA*” reports for the first time in Bulgaria the potential role of four long non-coding RNAs as biomarkers in the diagnosis of myocardial infarction. Non-coding RNA (LncRNA) has a regulating role on the gene expression at the level of epigenetic control, transcription and translation of RNA. Some LncRNA is with impaired expression in the peripheral blood in patients with acute myocardial infarction and can be useful in diagnosis as well as in improving the prognosis in these patients.

In the original research “*Association between serum CK18 levels and the degree of liver damage in fructose induced metabolic syndrome*” for the first time in Bulgaria a new biomarker was reported for apoptosis which participates in the pathogenesis of liver damage in metabolic syndrome. The raised CK 18 serum levels correlate with the histological changes in liver, induced by a fructose rich diet. The research demonstrates the reliability of CK 18 as a biomarker for non-invasive evaluation of liver damage in terms of metabolic syndrome.

II. Scientific contributions in the sphere of diagnostic role of biomarkers in cardiovascular diseases.

The article “*Micro RNA 208a – biomarker for diagnosis in cardiovascular diseases*” reviews miRNA as possible markers of damage in cardiovascular disease. This is the first clinical article in Bulgarian medical literature which treats the significance of miRNA in cardiovascular diseases.

In the research “*Dynamic change of NT-PROBNP in patients with ST-elevation myocardial infarction treated with primary coronary intervention*” for the first time in Bulgaria is reported

the possibility NT – pro BNP to be used as a biomarker which evaluates the gravity of ischemic cardiac disease.

III. Scientific contributions in the sphere of the diagnostic role of the biomarkers

For the first time in Bulgaria in the publication “*Expression of liver HMGB1 levels in fructose – induced fatty liver*” the connection between HMGB1 in rats with fructose induced fatty liver is proven. The research of the processes which lead to hepatocellular cell death, is important for clinical practice in evaluating the gravity of liver damage, as well as the application of effective interventions in preventing it.

For the first time in the Bulgarian medical literature in the article “*Ferroptosis and its potential role in cardiovascular diseases*” the potential role of ferroptosis is reported in the pathogenesis of different cardiovascular diseases. Ferroptosis is a new, relatively unexplored form of cell death with potential therapeutic and diagnostic future in many diseases.

For the first time at an international forum the Bulgarian research “*HMGB1 and RIPK3 as Markers for Necrosis and Necroptosis in Myocardial Infarction with ST Elevation*” is reported for necrosis and necroptosis in myocardial infarction. Two new potential biomarkers are reviewed and presented – HMGB1 and RIPK3.

IV. Scientific contribution in the sphere of the diagnostic role of the biomarkers in cancer patients

For the first time in Bulgaria in the article “*First line 5-FU-based chemotherapy with/without bevacizumab for metastatic colorectal cancer: one center experience results*” the serum levels of some isoforms of the VEGF family are reported as well as the research on their predictive value in response to anti-angiogenesis therapy.

For the first time in Bulgaria in the publication “*RIPK3 expression as a potential predictive and prognostic marker in metastatic colon*” the potential role of the expression levels of RIPK3 is reported in primary tumors in patients with metastatic cancer of the colon as a potential and promising prognostic marker.

For the first time in accessible literature in B “*Serum expression levels of miR-17, miR-21, and miR-92 as potential biomarkers for recurrence after adjuvant chemotherapy in colon cancer patients*” new small molecules (microRNA) are reported. Their concentration in the serum after the completion of adjuvant chemotherapy has the ability to differentiate between early patients (Nx nodal status) with relapse and those without relapse in the disease. This is one of the few articles in accessible literature which also treats the same problem for the patients in the IInd and IIIrd stage and demonstrates the superiority of these molecules over the standard marker, used up to now – CEA.

For the first time in accessible medical literature in “*Role of the pretreatment 18F-fluorodeoxyglucose positron emission tomography maximal standardized uptake value in predicting outcomes of colon liver metastases and that value's association with Beclin-1 expression*” the potential connection between the SUV max and the autophagy marker– Beclin-1 – in the primary tumor is reported. The prognostic value of SUV max is shown in liver metastases.

In the review article “*BECLIN-1 as a potential predicative marker for 5-FU based chemotherapy in patients with metastatic colon carcinoma*” the authors pay attention to some main pathways and regulators, connected with cell death and survival, which provide the metabolic resistance in tumors, leading to resistance to chemotherapy and unsuccessful cancer treatment.

For the first time in Bulgaria a review is made on the topic “*Autophagy in solid tumors*” of the process autophagy in Oncology. Autophagy is important for all cells in the removal of damaged or “old” proteins and organelles. The damages in autophagy are connected with sensitivity to metabolic stress, genomic damage and tumorigenesis. Although autophagy participates in tumour suppression, it also provides tolerance in cell stress, allowing the tumour cells to survive in adverse conditions. Stress-induced autophagy in tumour cells can lead to treatment resistance and tumour latency, with a possible tumour growth recurrence and progression. The clarification of the role of autophagy in cancer treatment is of significance, because many anti-cancer therapies are connected with its activation.

For the first time in the world data is reported in “*Levels of miR-17, miR-21, miR-29a and miR-92 as recurrence markers after adjuvant chemotherapy in Nx lymph node status colon cancer patients*” that the expression levels of miR-17, miR-21 and miR-92 in the Nx patient group are of statistical importance and can be viewed as non-invasive diagnostic biomarker for relapse after adjuvant chemotherapy with patients with carcinoma in the colon.

V. Scientific contributions in the sphere of Oncology

Screening distress in cancer patients is recommended by many organisations, including The National Comprehensive Cancer Network (NCCN). The aim of the research “*Analysis of the connection between the distress levels and the problem list*” is to measure the distress level before the commence of treatment of patients in the Clinic of Medical Oncology in “Sveta Marina” University multiprofile hospital for active treatment – Varna and its connection with some parameters of the problem list, pointed out by the patients. 225 cancer patients took part in the research within one year. We demonstrated the need of introducing a concept for combating and treating the psychosocial distress on national level in view of improving the prognosis of cancer patients in Bulgaria.

The interest towards “*Distress screening of cancer patients*” is increasing significantly, but here come up the relevant proofs of problems in understanding and applying identification programmes. A nurse who works in Oncology, is just as important in distress screening. Nowadays screening mechanisms and the role of the separate participants (health specialists) still undergoes development and is subject for discussion. The screening of a certain disease or a health issue depends on some main factors: the health issue itself (the cancer disease in this case), the type of screening test and the national health care system.

In the article “*Neuro toxicity of anticancer medicine*” it is reported that these effects from chemotherapy occur relatively often and are the reason of modification of the dosage of medicine – dose limiting toxicity. The risk of developing neurotoxicity is increased with upping the applied dose and, unlike myelotoxicity (the main limiting factor in most chemotherapy regimens), which can be overcome with growth factors or bone marrow transplantation; has no standard behaviour to limit it.

In the article “*Distress screening in cancer patients and factors that have impact on its level*” 225 cancer patients, who took part in the research, were described within one year. 123 of them have metastatic disease. NCCN distress thermometer was used at the beginning of the treatment of every patient to determine the distress level. The research showed that female patients and those with bad performance status experience higher distress levels. Diagnosing a cancer disease leads to the same distress levels in patients with metastatic and non-metastatic disease.

In the article “*Radiation treatment and cell death. Significance of the types of cell death in radiation treatment in cancer diseases*” for the first time in Bulgarian medical literature current forms of cell death are reviewed that have been induced by the radiation treatment. Revealing the exact mechanisms of cell death, induced by ionizing radiation, will provide opportunities

for developing new target therapies. Combining them with radiation treatment will help customize and approve the complex treatment of cancer diseases.

The article *“Cardiotoxicity”* reports a current problem, connected with the introduction of effective but toxic medicine for the heart. This phenomenon is called cardiotoxicity. The article familiarizes us with new biomarker diagnosis and new therapeutic strategies (introduced for the first time in Bulgarian medical literature).

VI. Scientific contributions in the sphere of cardiovascular treatment.

The article *“Heart failure treatment in patients with thalassemia major”* familiarizes us with the modern understanding of patho-physiological mechanisms, in which cardiac injury occurs in patients with thalassemia major. An undeniable advantage is the review in detail of therapeutic options for limiting this injury. This can serve to improve the prognosis and medical care in this specific patient population.

In the article *“Diastolic dysfunction and cardiomyopathy in sickle cell anemia”* deep and selective differentiation of cardio myopathy types is performed in patients with sickle cell anemia. Impaired diastolic left ventricular function is much more common than systolic dysfunction in patients with sickle cell anemia and it is evaluated as an independent risk factor for death in these patients.

In the review article *“Frequency, diagnosis and treatment of pulmonary hypertension in sickle cell anemia”* are presented the problems linked with the diagnosis, the treatment and the prognosis of pulmonary hypertension in patients with sickle cell anemia. The comprehensive and in-depth description of the problem is striking. The article sheds new light on the significance of pulmonary arterial hypertension in determining the prognosis of patients with sickle cell anemia.

For the first time at a European congress are reported *“Changing trends in heart failure hospitalizations 2010-2015 for patients with HFpEF and HFrEF”*, which introduce the trends in hospitalization regarding heart failure in Bulgaria for the period 2010 – 2015.

In a sequel of 3 articles the transaortic catheter implantation of the aortic valve is introduced. At the dawn of the new century an alternative came up of operative change of aortic valves, namely – trans-catheter aortic implantation. The article *“Durability of biological prostheses used for management of degenerative aortic stenosis – TAVR vs. SAVR”* introduces us with the advantages, the risks and the prognosis in this type of procedure.

In the publication *„Transcatheter aortic valve implantation in a patient with prosthetic mitral valve – clinical case“* is presented a case of transaortic catheter implantation of aortic valve in a patient with a prosthetic mitral valve. The procedure in this co-morbidity is difficult due to a possible confrontation of both valves. Our experience shows that the transcatheter implantation of aortic valve in the presence of the prosthetic mitral valve can be a reliable and safe method for smooth post-implantation period. In the clinical case *“Snare maneuver for management of low TAVI implantation - clinical case”* the successful application of a new kind of technique was presented for closure of para-valvular regurgitation after transcatheter implantation of aortic valve. Due to lack of official guidelines in solving this problem our experience gives a reliable and effective alternative in the implantation of an additional valve.

4. Teaching activity

Dr. Yavor Kostadinov Kashlov has been assistant in Internal Diseases/ Chief Assistant Professor since 2013. He teaches university students (information courtesy of the Administration office of MU – Varna).

The teaching workload of Dr. Yavor Kashlov meets the requirements for academic workload for holding the academic position of “Associate Professor”.

Pursuant to the requirements of the National centre for information and documentation for the academic position of “Associate professor”, Dr. Kashlov meets most of the minimum requirements, as follows:

Indicator group	Minimum number of points	Indicator	Applicant
A	50	1. Thesis for the educational and scientific degree “Doctor”.	50
B	100	3. PhD thesis - monograph	100
C	60/n	7. Publications and reports, published in scientific editions, abstracted and indexed in worldwide databases with scientific information.	131.91
	30/n	8. Publication and reports, published in non-abstracted magazines with scientific review or published in edited collective volumes	100.78
D	15	10. Citations or reviews in scientific editions, abstracted and indexed in worldwide databases with scientific information or in monographs and collective volumes	270
	5	12. Citations or reviews in non-abstracted magazines with scientific review.	40
E	40	15. Acquired medical specialty	40
	30	22. Training of interns, graduates students and doctoral students (seminars and practicums)	30
	200	TOTAL	762.69

On the basis of the above data for Dr. Yavor Kashlov, he can be characterized as:

- an explorer, who is capable of independent creative scientific work in the sphere of vascular pathology
- an erudite doctor of broad medical perimeter

In conclusion, I consider that Dr. Yavor Kostadinov Kashlov PhD meets the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria and the Rules of its application of Medical University – Varna. I suggest to the esteemed Scientific Jury that he should be awarded the academic position “Associate Professor” in the higher education sphere 7. Health care and sport; professional field 7.1 Medicine, “Internal diseases” scientific specialty.

14.09.2019

Prepared by:



(Prof. Borislav Georgiev, Ph.D)