ATTENTION: MEMBERS OF THE SCIENTIFIC JURY OF ACIBADEM CITY CLINIC UMBAL TOKUDA", EAD, ISSUED ORDER N 15-05-93/26.09.2023

REVIEW

WRITTEM BY PROF. DR.SCI. RADKA MLADENOVA ARGIROVA, VIROLOGIST, CLINICAL LAB. TOKUDA MEDCAL CENTRE , SOFIA

RE: Thesis titled "Place and role of an emergency department of a general hospital for active treatment in the application of a diagnostic-therapeutic algorithm in patients over 18 years , infected with SARS-CoV-2 virus" for awarding the scientific and educational degree "DOCTOR" in the field of higher education 7. Health care and sports, professional training 7.1. Medicine, doctoral program «Internal Diseases»

Author: **Dr. Parvoleta Krasteva Yakova - Krasteva - candidate on independent training, "Acibadem City Clinic UMBAL Tokuda" , Clinic of Internal Medicine,**

Research supervisor: Prof. Dr. Milena Staneva, Ph.D.

RESPECTED MEMBERS OF THE SCIENTIFIC JURY,

Dr. Parvoleta Krasteva was born in 1972. In 1996, she graduated from the Sofia Medical University, thereafter successively and permanently specialized in the field of emergency care and health management in Bulgaria and Turkey. The

COVID-19 pandemic found her as a Head of the Emergency Department at the Tokuda Medical Center, headed by her since March 2017. From June 2022, she was enrolled as a doctoral student in self-study in the "Internal Diseases" doctoral program.

Dr. Krasteva's dissertation is written on 171 standard pages, contains 4 appendices and is illustrated with 31 tables and 23 figures. It is structured in the standard way: Introduction – 3 pages; Literature review – 30 pages; Purpose and tasks – 1 page; Materials and methods – 9 pages; Own results – 52 pages; Discussion – 35 pages; Conclusions – 3 pages; Appendices – 9 pages; Bibliography - 273 authors.

RELEVANCE OF THE DISSERTATION

It is not necessary to convince you in the relevance of this work! We found ourselves suddenly under the conditions of a pandemic, without prior knowledge and training in clinical and laboratory diagnostics, without special knowledge of the causative virus, without any simple recommendation from the Ministry of Health or a specialized professional guild, nor a protocol for working with infectious patients in the conditions of a general hospital, without specific antiviral agents, etc. Under these conditions, each hospital adapts according to its specific structure and available resources. It turned out that many doctors and health managers do not know in detail the essence of triage, which is the basis of effective management of patient flow, especially under pandemic conditions.

There were no developed general protocols for patient triage, and there was no uniform form for triage in emergency departments in Bulgaria. Therefore, the excess mortality registered in Bulgaria is not surprising. As the virus spread and new viral variants emerged, predicting severe infection and death, our strategies for diagnosis, treatment and prevention had to be constantly adapted. There were

no developed protocols for patient triage, and no uniform form for triage in emergency departments in Bulgaria. Therefore, the excess mortality registered in Bulgaria is not surprising. As the virus spread and new viral variants emerged, predicting severe infection and death, our strategies for diagnosis, treatment and prevention had to be constantly adapted. Under these conditions, during the three pandemic years, the ER of Tokuda UMBAL handled not only the patients with COVID, but also the emergency patients without COVID, without abandoning them /except when severe lockdowns/. The head of the ER, Dr. Krasteva, presents here the results of the examination and follow-up of over 6,000 patients who visited ER and were referred for subsequent treatment, recovery and care.

THE LITERATURE REVIEW describes the main morphological, biochemical, antigenic and genetic composition of SARS-CoV-2, its replication, distribution and epidemiology. The main factors - constitutive, risk and social - in relation to infection and progressive development of the infection are discussed. Even here one can see where our knowledge is mainly incomplete - influence of gender, age, ethnicity, acquired health habits, incl. for the prevention and treatment of chronic diseases. The importance of socioeconomic status, access to health care, and especially the most common comorbidities—cardiovascular, arterial hypertension, and diabetes mellitus—as well as the various coagulation abnormalities are discussed in detail. The complications of kidney diseases, obesity, oncological diseases and a serious examination of the laboratory indicators were not omitted. The indicated factors and statuses are not only examined in great detail, but controversial or insufficient data are also highlighted, so that at the end of the overview, the goal and tasks of the current work are clearly outlined. Of course, contemporary literature is used. I have no objections to the

review, I recommend it to all my colleagues as an example for explaining the importance of a number of medical and social factors for the development of infectious diseases and their future studies.

THE GOAL AND TASKS – They are clearly and precisely formulated, the prognostic focus is underlined, as well as the wider view of the diagnostic-therapeutic algorithm in view of the possibilities of its use in other epidemics/pandemics. An extremely good impression is made by the emphasized care for the health personnel employed in the triage.

MATERIALS AND METHODS

Here is a summary of the volume of the dissertation work: The total number of examined patients with COVID in the COVID - zone of the ER for the period 11.03.2020. - 30.11.2021, is 6,280 over the age of 18, of which 3,355 (53.42%) are referred for home-ambulatory treatment and 2,925 (46.58%) are hospitalized. Of all examined infected patients (n=6280), the risk factors for progression, severe course of the infectious disease and death cutcome were followed in detail in 1256 patients. The outcome from ER after primary evaluation was 52.3% (657) treated as outpatients and 47.7% (599) hospitalized. Of those admitted for hospital treatment, 122 died (20.4% of those hospitalized and 9.7% of all who went through ER). The virus variants covered in the study are from the original /Wuhan/ virus to the delta variant, officially announced by the WHO on 11.05.2021. Appropriate descriptive, laboratory, epidemiological methods and approaches were used, skillfully interpreted after modern statistical processing by 6 different methods.

RESULTS. Algorithms for diagnosis and behavior in all kinds of patients are presented, these algorithms are not only presented, but also practically confirmed,

which makes them extremely valuable. Explicitly emphasized fact is that this work enriches not only scientific-practical, but also organizational ER to multi-specialty hospitals, facilitating the work of the few infectious disease departments in the country. It is in this section that the screening role of the ER is clearly differentiated and its organization is emphasized, paying special attention to the safety of patients and staff, combined with maximum opportunities to prevent nosocomial infection. The three triage categories according to the current standard of Emergency Medicine (EM) in Bulgaria are defined and described. Several of the prognostic factors discussed in the literature for complicated course and progression of COVID-19 have been tracked. The results of imaging diagnostics at the primary examination in X-ray and computed tomography (CT), a number of laboratory indicators - divided as categorical and quantitative variables, and each of these categories separately represented by risk factors for a complicated course, were analyzed and compared , progression and death, as well as from a minimal or extended suite of laboratory tests. In general, the values of all laboratory indicators included in the study show a statistically significant difference in the two groups of patients - hospitalized and referred for outpatient - home treatment ($p<0.001$). Multivariate analysis was used to determine the significant risk factors for hospitalization, progression of COVID-19, and hospitalization in outpatients compared with data from primary and follow-up examinations in ER, and death.

In the multiple binary logistic regression analysis model used, CPD/ARD, number of comorbidities, O_2 saturation, heart rate, X-ray result, and the inflammatory marker LDH remained significant predictors of death from COVID-19. No association between gender and disease outcome was demonstrated either in the

group with at least one comorbidity or in the group without any comorbidity. The used models of multivariate analysis make it possible to obtain specific numerical dependencies between individual factors, many of which are newly discovered/newly calculated, which is definitely a contribution of the work. I shall not stop your attention on the results of the application of therapy with monoclonal antibodies in ER for the period 01.11.2021-21.01.2022 - that would be better done by an infectious disease clinician.

Generally speaking, the present scientific work proposes dynamic algorithms based on the analysis of easily and quickly measurable parameters in ER for primary clinical and prognostic risk assessment and making effective decisions about therapeutic behavior in the conditions of the COVID-pandemic, according to the personnel resource and material hospital base and following the course of the pandemic and global strategies for diagnosis and therapy. These algorithms - they are 8 - are not only offered, but have also proven their importance in practice. Separately, Fig. 22 clearly shows the place and importance of ER in the general hospital, and Fig. 23 can be used as a ready-made scheme in case of suspected infectious disease. I particularly liked Chapter 4 of the dissertation, where the research results and algorithms are grouped and discussed.

CONCLUSIONS, CONTRIBUTIONS

I completely agree with the conclusions and contributions of the dissertation. I support the algorithms and forms created as I have witnessed their use in practice.

CRITICAL NOTES

The disseratation is written in a scientific and accessible language, a rich literature from international and national sources is skillfully used, the pros and cons of some "fashionable" diagnostic approaches and treatments are highlighted, to

which the candidate and her team have taken a critical view and accepted/rejected after serious consideration. There are also some purely medical disadvantages: for example, a one-time measurement and taking into account strongly and frequently changing indicators - e.g. heart rate, etc. In places there are repetitions and stylistic ambiguities in some titles of tables/figures or the quantities used are not clearly described everywhere, marked on the abscissa and especially the coordinate / e.g. Length of stay in hours of patients in the CU before hospitalization - fig. 17, the text under Table 23 is wider than the data in the table itself, etc. Such small remarks in no way diminish the value of the work.

PUBLICATION ACTIVITY

During the entire pandemic, the candidate was interested and participated in 3 publications on the topic, of course, the most - in national periodicals - "Emergency Medicine", "Medical Review", "Health Policy and Management" and 1 publication in print in the Medical Journal of the UMBAL "St. Anna". She also was the first author of 3 oral presentations on the topic at national scientific conferences.

THE ABSTRACT reflects the main results, conclusions, contributions and publications on the topic of the dissertation.

CONCLUSION The dissertation of Dr. Parvoleta Krasteva-Yakova reflects the enormous personal work, knowledge and contribution in the difficult conditions of a viral pandemic in a general hospital without an infectious disease department and with an insufficiently known causative agent - SARS-CoV-2. It is not only up-to-date, but also a good basis for analysis so that mistakes and delays that can cost lives are not repeated. With this work, the candidate proves her enormous potential for dynamism, adaptability and compliance with the number and

qualifications of the available composition of the medical center and the unconditional team interaction with the other units of the MBAL for solving diagnostic and therapeutic problems that arose during the pandemic in the daily care of the medical and all service personnel and prevention of nosocomial infections.

The work meets the requirements of the Regulations for the development of the academic staff of "Acibadem City Clinic UMBAL Tokuda" for the acquisition of the ONS "Doctor". All this makes me declare that Dr. Krasteva's dissertation work is a personal matter, practically and organizationally useful, and my proposal to the respected members of the Scientific Jury is to vote "for" awarding Dr. Parvoleta Krasteva-Yakova the educational and scientific degree "Doctor" in the field of higher education 7. Health care and sports, professional training 7.1. Medicine, Internal Medicine Doctoral Program..

Sofia, Oct.31st,2023

REVIEWER:

/Prof. Dr med. R.Argirova, virologiste, Clinical Lab., Tokuda Medical Diagnostic Center/