R E V I E W

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Subject: Dissertation on the topic: COVID -19 in patients with end-stage renal failure - complications, risk factors and mortality" with author Dr. Kiril Zhivkov Zhelyazkov, full-time doctoral student at the Second Department of Internal Medicine, doctoral program "Nephrology", professional field 7.1, Medicine, for the acquisition of the scientific degree "Doctor".

On the basis of Order of the Rector of MU-Varna No. R-109-516 of 16.12.2025, in view of a report with entry No. 102-3040/27.11.2025 by Prof. Dr. Mira Siderova, MD - Head of the Second Department of Internal Medicine, with a decision under protocol No. 51/15.12.2025 of the Faculty Council and a report with entry No. 103-8667/16.12.2025. by Prof. Dr. Yoto Yotov, MD - Dean of the Faculty of Medicine at MU-Varna, I have been appointed as a reviewer of a dissertation on the topic: "COVID -19 in patients with end-stage renal failure - complications, risk factors and mortality" for the acquisition of the scientific and educational degree "doctor" of Dr. Kiril Zhivkov Zhelyazkov, in the Field of Higher Education: 7.0 Health and Sports; professional field 7.1. Medicine, specialty "Nephrology".

The review was prepared in accordance with the requirements of the Act on the Development of Academic Staff in the Republic of Bulgaria and the Regulations for Application at the Medical University - Varna.

A. Brief biographical data

Dr. Zhelyazkov was born in 1990 in Varna, where he completed his secondary education in 2009 at the Third High School "Acad. Metodiy Popov". He studied medicine at MU-Varna, where he graduated in 2016. In December of the same year, he started working as a resident at the Clinic of Nephrology and Dialysis at the University Hospital "St. Marina", Varna. In the period 2018-2022, he was a resident in the same clinic, and in 2022, he acquired a specialty in nephrology. Since 2019, he has been a full-time assistant at the Clinic of Nephrology and Dialysis at the Second Department of Internal Medicine, and since 2024 - a lecturer. He was enrolled as a full-time doctoral student with Order No. R-109-473/04.11.2020.

Member of the Bulgarian Medical Association and the Bulgarian Society of Nephrology. Fluent in English.

B. Significance and relevance of the topic being developed

Dr. Kiril Zhelyazkov's dissertation is dedicated to an extremely important and contemporary problem not only in nephrology, but also in medicine – the impact of COVID-19 infection in patients with end-stage chronic kidney disease (CKD) treated with hemodialysis (HD). The topic remains relevant, as the infection quickly turned into a pandemic, which by the end of 2022 affected over 732 million people with over 6.73 million deaths. On the other hand, different variants emerged such as "Alpha", "Delta", Omicron ", etc., which quickly spread around the world and in our country. The introduced antiviral treatment and vaccine reduced the mortality rate, but it remained high for Bulgaria (over 1% of the population by 2021). In addition, a large part of our population remained unvaccinated for various reasons. Additionally, the pandemic has particularly severely affected patients with chronic diseases and impaired immune defense, such as patients on dialysis. They are at particularly high risk not only because of their comorbidities, but also because of the need to visit a dialysis center three times a week, where they come into contact with other patients and service personnel. The infection affects the adequacy of dialysis by disrupting the two main indicators: urea reduction ratio (URR) and Kt /v , which includes dialysis parameters clearance , duration of the HD procedure and volume of distribution.

In this way, Dr. Zhelyazkov's study acquires particular importance both for the present and in the future. In Bulgaria, CKD affects about 13% of the population, and about 2,500 patients are on HD treatment, and their number will increase over time. In this sense, the work has scientific-theoretical and scientific-practical significance. Currently, this is the first systematic work in our country, concerning the problem and examined in depth.

C. Evaluation of the dissertation work

The dissertation covers 110 standard pages, illustrated with 15 tables and 16 figures (color), which help to better understand the material. The literature review includes 206 sources, all in Latin and most of them from the last 5-6 years. The literature review is spread over 45 pages; aim, tasks, material and methods – 2 pages. The own results cover 29 pages, and the discussion – 10 pages.

D. Evaluation of the literature review

The literature review summarizes the current knowledge about CKD and COVID -19 infection. The dissertation is very well informed about both diseases. The current definition and staging of CKD are presented, as well as the epidemiology of the disease. The leading etiological factors are indicated - diabetes mellitus and arterial hypertension, as well as the steady increase in CKD on a global and national scale. It is emphasized that CKD is not only an independent risk factor for death, but also a

significant "catalyst" for cardiovascular complications. On the other hand, COVID -19 additionally burdens HD patients, as their comorbidities are added by the severe infection, which worsens the adequacy of dialysis treatment. A wide place in the review is given to COVID -19, both in the sacred and in the native aspect. The high mortality rate is noted and the importance of newly emerged variants with higher transmissibility is indicated.

A special place is given to the introduced vaccine against COVID -19 and its role in reducing morbidity and mortality. It is indicated that in Bulgaria by the end of 2021. only 30% of the population had been vaccinated, compared to over 70% of residents in the European Union; thus, the mortality rate in our country exceeds 1% of the population.

The review examines in detail and in-depth the pathophysiological mechanisms of COVID -19, which affect the body, especially micro- and macrovascular damage. It is noted that patients with CKD are among the most at-risk groups, due to a negative combination of immune dysfunction , persistent systemic inflammation and accumulation of uremic substances. HD itself per se is an additional risk, because patients are forced to visit HD centers, which violates the necessary social distance and further increases their exposure in the treatment sectors. As a negative psychological factor, there is resistance to the vaccine created for various reasons. All this, taken together, worsens the adequacy of dialysis treatment and worsens the clinical manifestation. Additionally and correctly, some limitations in the review are also noted, such as inaccurate timing of blood sampling, etc. Several hypotheses have also been formulated that should be tested in the course of the study – about a decrease in Kt /V , about a higher mortality rate in the COVID -19 group, about the role of vaccination. In this way, the comprehensive review provides a natural and logical bridge to the own results in the dissertation.

E. Evaluation of purpose, objectives and methodology

The goal that the dissertation candidate sets is to determine the impact of COVID -19 on the population of patients undergoing HD treatment at the University Hospital "St. Marina", Varna. For its implementation, five tasks have been formulated, directly related to the goal set.

Material and methods. A retrospective observational study was performed . cohort study, which was conducted at the Nephrology and Dialysis Clinic of St. Marina University Hospital, Varna for the period 2020-2022. A total of 190 patients were included, divided into two groups: **A.** those with proven COVID -19 infection (101 people) and **B.** patients without data on such (89 people). The data were extracted from the electronic information system and medical records. Clear criteria for inclusion and exclusion from the study were formulated. The two groups of patients are comparable in average age and gender. Demographic and clinical characteristics are presented for

them - concomitant diseases, indicators of dialysis adequacy, 6-month survival after infection, as well as vaccination status.
Statistical processing was performed using Jamovi version 2.2.2. KENY 19/18.09.2025

F. Evaluation of results

1. Mortality . A total of 98 fatal cases were registered – 55 of them in the group with COVID -19 and 43 – in the group without infection. The statistical analysis does not show a significant difference between the two groups, i.e. belonging to one of them cannot be an independent predictor of a fatal outcome. In other words, COVID -19 represents only one of the various risk factors in HD patients and cannot explain the high mortality a priori . Of the mortality factors with the greatest burden are age and the presence of cardiovascular diseases (CVD). In principle, age is an independent risk factor in all chronic diseases and the study once again shows this fact in HD patients, especially in conditions of severe infection. The presence of CVD is a clearly significant risk factor for death, with the study indicating a five-fold higher probability of a fatal outcome. A new, so far unspecified factor is the immunization status of the patients. It turns out that vaccinated patients have an approximately 53% lower risk of death compared to unvaccinated patients . This is particularly important from a practical point of view, because it highlights the effect of immunization in these patients and is one of the main conclusions of the work. On the other hand, diabetes mellitus as a comorbidity and gender do not play a significant role in survival . Summa summarum Age, CVD, and vaccination status appear to be the most important predictors of fatal outcome in the context of COVID infection.
Regarding HD treatment, increased mortality was found in patients with Kt /v<1.3 . Patients with Kt /v<1.3 had an approximately 59% higher risk of death compared to those with Kt /v>1.3 . These findings were not statistically significant, but have practical significance as a prognostic factor for survival . The finding that women in the study had higher dialysis adequacy indicators compared to men, which can be explained by the physiological difference between the sexes, is of confirmatory nature. From a practical point of view, the finding that the type of vascular access (permanent catheter or AV fistula) had no significant impact on dialysis adequacy indicators during the course of COVID -19, is interesting.

Discussion

This chapter covers 10 pages. It comments on the obtained own results with those of other authors. The available literature is abundant and modern, which makes the discussion relevant. The importance of vaccination and the adequacy of dialysis treatment are confirmed. All this enriches the knowledge on this important problem and could be used in nephrological practice.

Conclusions

8 conclusions have been formulated that correlate well with the results obtained during the study.

Evaluation of contributions

The dissertation contains contributions of a scientific-theoretical (4) and a practical-applied (5) nature. Of particular importance is the contribution of the dissertation itself, which is the first of its kind in Bulgaria. On the other hand, the contribution that immunization has a pronounced protective effect in HD patients, reducing overall mortality and the risk of CV fatal outcomes, is relevant. Another important conclusion is that the type of vascular access does not have a reliable significance in terms of dialysis adequacy, while the indicator Kt /v<1.3 is associated with an approximately 59% higher risk of death (without statistical significance, but with a clear trend).

G. Scientific production. Recommendations to the author

1. In connection with the dissertation work, 4 scientific publications have been published in Bulgarian medical periodicals. In them, Dr. Zhelyazkov is the lead author in two and the second author in two. They reflect the main stages of the preparation of the dissertation, as well as the final results related to it.
2. It would be good to expand the study, at least on the territory of the country, in order to obtain even greater clarity on this important problem in Bulgaria. It is desirable to publish the most important data in international medical journals with an impact factor, which could be cited by foreign authors as well.

H. Conclusion

The problems with risk factors related to the survival of HD patients remain relevant to this day, and studies are numerous, including in our country. This already global disease is a severe somatic suffering with different dimensions. The emergence of the COVID -19 pandemic brought the entire medical system to its knees, and among the most severely affected were HD patients. In this regard, Dr. Zhelyazkov's dissertation is relevant and contributes to domestic practice and literature.

In summary, all of the above gives me full reason to give my positive opinion and to propose to the members of the esteemed scientific jury to vote for awarding the educational and scientific degree "Doctor" to Dr. Kiril Zhivkov Zhelyazkov.

16.02.2026 Assoc. Prof. Dr. Dobrin Paskalev, MD

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