

PhD Thesis Evaluation Report

By Prof. Milena Staneva Staneva, MD, PhD

Head of Angiology Clinic,

Acibadem City Clinic MHAT Tokuda EAD

of the dissertation for obtaining the educational and scientific degree "Doctor" in the field of higher education 7. Health and sport, professional field 7.1. Medicine, Doctoral Program in Internal Medicine.

Author: Radin Tsonev Tsonev, MD

PhD form: Self-study

Scientific Unit: Clinic of Gastroenterology, Acibadem City Clinic MHAT Tokuda EAD

Subject: Assessment of Liver Fibrosis and Quality of Life in Patients with Chronic Viral Hepatitis C and Cirrhosis

Scientific adviser: Prof. Simeon Georgiev Stoyanov, MD, PhD

1. General presentation of the procedure and the doctoral student

At a meeting of the Scientific Council of Acibadem City Clinic MHAT Tokuda EAD (Record of proceedings 27 / 18.06.2019) and by order No 315 / 16.08.2019 of the Executive Director and the Procurator of the Hospital, I have been appointed an internal member of the Scientific Jury in connection with the thesis of Radin Tsonev, MD. I am assigned to deliver a thesis evaluation report.

No gaps were found in the documentation provided by Radin Tsonev, the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria (LDASRB), the Regulations for the implementation of the LDASRB (RILDASRB) and the Rules for the conditions and procedure for acquiring academic degrees and occupying academic positions at Acibadem City Clinic MHAT Tokuda EAD were met.

I declare that I have no conflict of interest with the author of the thesis.

Radin Tsonev graduated from the Medical University of Sofia in 1988 and completed his mandatory military service by serving as an aviation physician in Graf Ignatievo (Bulgaria) for 2 years. From 1990 to 1994 he was a resident physician in the Internal Medicine ward of the MHAT - Lom. From 1994 to 2007 he worked as a gastroenterologist at the V MHAT Sofia, and since 2007 - in MHAT Tokuda Sofia. Since 2013 he has been the Head of the Gastroenterology Department. Radin Tsonev acquired a specialty in Internal Medicine (1995), Gastroenterology (1997), Certificate of Professional Qualification in Level 1 and Level 2 Ultrasound (1993) and in Invasive Ultrasound (1994, with an update in 2010). He attended a number of training programs in gastroenterology and ultrasound abroad.

He is a member of the Bulgarian Medical Association (BMA), Bulgarian Society of Gastroenterology, Hepatology, Endoscopy and Ultrasound in Medicine (BSGHEUM), Bulgarian Association of Ultrasound in Medicine (BAUM), European Society of Gastrointestinal Endoscopy (ESGE), European Association for the Study of the Liver (EASL), Bulgarian Association for the Study of the Liver (BASL).

2. Relevance of the topic

Chronic hepatitis C infection is a socially significant disease because it affects a large population, has a prolonged asymptomatic period, and leads to serious complications, the most common of which are liver fibrosis and cirrhosis and neoplasms. With the development of hepatology, the diagnosis, as well as the treatment and prognosis of patients with adult hepatitis C are improved. The study of the quality of life in these patients reflects their subjective opinion on the impact of the disease on the daily life of the patients. Radin Tsonev's dissertation is devoted to the study of the importance of non-invasive measurement of hepatic fibrosis by transient elastography (TE) - FibroScan and liver biopsy in patients with chronic hepatitis C and cirrhosis and evaluation of the effect of treatment on the quality of life of patients with chronic liver disease. The topic is relevant from a practical point of view.

3. Acquaintance with the issue at hand

The doctoral student knows the status of the problem and appreciates the literary material creatively.

4. Research methodology

The chosen research methodology enables the achievement of the set goals and provides adequate answers to the questions discussed in the dissertation.

5. Characterization and evaluation of the dissertation work and its contributions

Radin Tsonev's PhD thesis is written in a volume of 105 pages, contains 47 tables and 21 figures. It is structured correctly and includes the following sections: Abbreviations and symbols used - 1 page; Introduction - 4 pages; Literature Review - 38 pages; Purpose and tasks - 1 page; Materials and Methods - 11 pages; Own results - 33 pages; Discussion and Conclusion - 5 pages; Bibliography - 5 pages; Annexes - 4 pages. The bibliographic reference contains 125 literary sources, 6 of which are in Cyrillic and 119 in Latin. Of these, 18 (14.6%) have been published in the last 5 years.

The **Introduction** clearly defines the problem and substantiates the purpose of research in the dissertation work.

The **Literature Review** is well structured and in line with the topics being discussed. It is written competently and demonstrates profound knowledge of the issue in its various aspects. The social significance of chronic hepatitis C infection, the role of liver biopsy in diagnosis, non-invasive methods for assessing liver fibrosis, quality of life and health care in HCV patients are examined.

The **Purpose** of the dissertation is well formulated in accordance with the topic of the dissertation and the presented literature review. The assigned tasks, 6 in total, are completely sufficient and have been fully accomplished in the dissertation.

The **Materials and Methods** section describes in detail 366 patients with chronic viral hepatitis and cirrhosis, of which 193 men and 173 women, aged 18 to 75 years, who were enrolled in the study between 2016 and 2018. Of these, 241 patients had hepatitis C, 37 had hepatic C cirrhosis, and 88 had hepatitis B. All patients underwent Menghini liver biopsy or targeted liver biopsy, as well as TE-FibroScan while fasting with fibrotic activity assessment in kPa and received a fibrosis score from 1 to 4. Comparable liver density testing was performed in 149 patients with hepatitis C using TE before and after a 12-month treatment period with direct-acting antivirals (DAAs). All patients completed a quality of life questionnaire. It was evaluated using the SF-8 Health Survey, scientifically validated and reliable for physical and mental health status. For statistical data processing appropriate methods and an up-to-date statistical program (IBM Statistics SPSS Statistics Base 23) were used, which guarantee the reliability of the results obtained.

Results and Discussion: The results presented are convincing and clear. The more notable ones are the following.

- There was no correlation between the degree of fibrosis and cytolytic activity - AST and ALT.
- Comparability of liver biopsy and TE-FibroScan results has been established in patients with liver fibrosis, especially in F3 and F4. For F1 and F2 this correlation is lower. These results lead to the conclusion that an additional method, fibrotest or APRI, is needed to improve the comparability of liver biopsy and TE-FibroScan results.

- Significant difference is shown by the results of TE-FibroScan in patients with liver fibrosis before and after 12 months of treatment with DAAs.
- The factors that shape patients' opinions about their quality of life are the mental state and the emotional experience of the disease, treatment and recovery.
- It is recommended that the care for the quality of life of patients during and after their illness remains a holistic approach. For this purpose, it is necessary to build a multidisciplinary team involving hepatologists, nurses, psychologists, psychiatrists and coordinators.

Conclusions and Contributions: Based on the results obtained, the PhD candidate logically arrives at 7 conclusions. The contributions are 6. The conclusions correspond to the tasks set. I accept the above conclusions and contributions. It is of great importance to identify the factors affecting the quality of life of HCV patients as well as the need to create a multidisciplinary team in their treatment.

6. The Abstract

The abstract is presented in 63 pages and reflects what is written in the dissertation.

7. Evaluation of publications and personal contribution of the doctoral student

The PhD candidate has submitted 4 publications (2 of them in international journals, one with IF) and 18 scientific reports, 12 of them in national and 6 in international scientific forums. Two of the Bulgarian publications and 7 of the reports are single-author papers. This scientific activity is sufficient to show that the doctoral candidate is consistent in his scientific activity.

8. Critical remarks and recommendations

The following technical remarks could be made without reducing the scientific value of the thesis:

- The small number of literary sources (14.6%), both Bulgarian and international, from the last 5 years, is surprising, despite the numerous publications on the subject in specialized scientific journals.
- The literature used is not written on standard typing pages.
- The publications related to the dissertation are not sorted by type (publication or scientific report) and are not written according to BSS.

CONCLUSION

The dissertation contains scientific and applied results that make an original contribution to medical science, broadening our knowledge in the field of diagnosis and monitoring of patients

with HCV. It complies with all the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria (LDASRB), the Regulations for the implementation of the LDASRB (RILDASRB) and the Rules of Acibadem City Clinic MHAT Tokuda EAD. The submitted materials and dissertation results fully comply with the specific requirements adopted in connection with the Regulations of Acibadem City Clinic MBAL Tokuda EAD for the application of LDASRB.

Radin Tzonev Tzonev is a clinical physician, a specialist in gastroenterology and internal medicine with over 25 years of experience. The dissertation shows that the doctoral degree candidate possesses in-depth theoretical knowledge and professional skills in the scientific specialty Internal Medicine, demonstrating qualities and skills for conducting independent research.

In consideration of the foregoing, I give my positive review and strongly recommend to the members of the Scientific Jury to favorably evaluate the thesis *Assessment of Liver Fibrosis and Quality of Life in Patients with Chronic Viral Hepatitis C and Cirrhosis* and award Radin Tsonev Tsonev Doctorate Degree in Internal Medicine.

Sept. 20th, 2019

PhD Thesis Evaluation Report by:

Sofia, Bulgaria

Prof. Dr. Milena Staneva, MD