PhD Thesis Evaluation Report

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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 Stoynov, MD, PhD

I. Qualification and professional career

Radin Tsonev, MD, is an established physician with over 25 years of experience in leading gastroenterology clinics in Bulgaria and abroad, a hepatologist with 20 years of experience and a manager with extensive management experience as head of the Gastroenterology Department since 2013. Radin Tsonev holds certified Level 3 ultrasound skills and has over 20 years of experience. He is skilled in many conventional and invasive procedures under ultrasound control. He participated in the creation of the so called clinical pathways in gastroenterology in 2000. He has authored numerous publications in national and international journals with high impact factor.

II. Assessment of the work presented

1. Structure, layout and abstract

Structure: The dissertation is written on 105 pages, including 47 tables and 21 figures. The chapters are structured in the following way: Introduction and literary review - 43 pages; Materials, methods and results - 45 pages; and Discussion and conclusions - 6 pages The bibliographic reference contains 125 literary sources, 6 of which are from Bulgarian and 119 from foreign authors.

The **abstract** gives the exact results and ideas of the scientific work.

The **introduction** outlines the enormous health and social significance of the problem of chronic hepatitis C and cirrhosis. It is indicated that 3% of the world's population are carriers of HCV. According to WHO data, the total number of people infected with HCV alone in Europe is over 8.9 million, and in Bulgaria the incidence is 1.2% - about 80,000

people, a mathematical estimate. Based on the natural history of HCV infection, it is estimated that 10-20% of patients develop liver cirrhosis and 1-5% will develop HCC within 20-30 years. This puts these diseases among the group of one of the most dangerous types of pandemics even before HIV. That is, the prevalence rate, the high rate of disability and their oncogenic potential, as well as the considerable financial resources allocated for their treatment, make them a socially significant factor influencing the development of society. The second direction in the research of the PhD candidate is to evaluate the quality of life of patients with HCV infection due to the fact that patients' self-assessment of their quality of life and their health status is more important for the results of medical care than that of medical specialists.

The **literature review** is well-structured, comprehensive and demonstrates the in-depth knowledge of the doctoral candidate on the topic, as well as his analytical reading of the medical data available so far. It is structured in 4 sub-topics. The literature review neatly delineates the gaps in our current medical knowledge and argues for the need for scientific development.

2. Purpose and objectives

The **purpose** of the dissertation is clearly formulated and logically and substantiated by it, 6 tasks have been derived that meet the stated goal. The tasks are focused mainly on outlining the role of the non-invasive TE-FibroScan study in the diagnosis, monitoring of fibrotic activity and the treatment of patients with HCV and cirrhosis, and its effectiveness is compared with the gold standard in diagnosis - liver biopsy and laboratory activity processes. A second guideline in the goals of the dissertation is to study the quality of life of patients with chronic HCV and cirrhosis, which logically determines the need for a psychological evaluation of the patient and a multidisciplinary team including a clinician, clinical psychologist or psychotherapist to achieve a better physical health and the pursuit of a better quality of life.

3. Material and methods

The study cohort of 366 patients with chronic viral hepatitis and cirrhosis (males - 193, females - 173) is a representative sample, enough to perform the set tasks. This chapter describes in detail and in a logical sequence the studies performed in the patients studied. All patients underwent fasting TE-FibroScan with assessment of fibrotic activity in kPa, with assessment of fibrosis from 1 to 4, liver enzyme activity studies - AST and ALT were performed and liver biopsy was performed according to Menghini or targeted - true- cut biopsy to evaluate the severity of histological changes on the Metavir system. All patients completed a quality of life questionnaire. The statistical methods used in the data processing are impressive. The statistical nature of the variables, the arguments for choosing a specific statistical method and the interpretation of the results from a statistical point of view are described in detail.

4. Results and discussion

Comparisons between liver biopsy data and laboratory activity show that there is no relationship between necroinflammatory activity from morphological changes and fibrotic activity, since 92.3% of patients with low inflammatory activity A from liver biopsy do not correspond to the degree of liver disease from liver biopsy - 45.1%. The author gives a positive answer to the question set beforehand whether there is a statistically significant difference in the arithmetic mean between the FibroScan data in kPa before treatment and the FibroScan data in kPa after treatment. Fibrosis regression is detected during antiviral treatment, and the author recommends that the test be performed every 12 months for reliable control. The presence of less correlation and greater dispersion of results in patients with low fibrosis by the FibroScan examination requires that several sequential series of studies be performed in each patient - at least 3 series of 10 standardized studies maintaining an IQR factor below 30% to avoid scattering results. These 3 series need to be polypositional in different intercostal spaces along the mid axillary line.

Quality of life and fibrosis As a final result, the author summarizes that there is no correlation between the variables studied and the patient's self-assessment.

Discussion of results

In this section, the author emphasizes the need for FibroScan testing to be performed by specialists with good clinical experience and expertise, and to conduct a series of 3 consecutive 10 fold studies in different intercostal spaces of the mid axillary line in order to avoid errors and scatter the results.

5. Main conclusions

The analysis of the results of the conducted research leads to the formation of 6 main conclusions. The author concludes that the use of non-invasive methods for assessing hepatic elasticity and, respectively, for evaluation of fibrosis and steatosis are readily reproducible, safe, not disrupting the quality of life of patients with chronic viral C-hepatitis and cirrhosis, and financially viable. But, on the other hand, the author rightly notes that the initial enthusiasm on a national scale has led to an overestimation of the methodology's capabilities. He notes that the use of FibroScan as an only diagnostic mean in clinical practice would lead to incorrect assessment of fibrosis even in cases of successful eradication of HCV. Therefore, the author recommends that in the clinical practice, fibrotest, such as serum biomarker or FIB-4, should be used in addition to the FibroScan.

6. Contributions

The main contributions of the dissertation are formulated in 6 main points, namely:

1. An up-to-date comparison has been made between the use of TE- FibroScan versus liver biopsy.

2. A new scenario is proposed for performing the FibroScan test and applying several consecutive series of 10 studies in different intercostals along the mid axillary line,

with no more than 30% IQR coefficient and scattering the results and adding an additional Fibrotest or FIB marker -4.

3. A model of behavior in the monitoring of patients with chronic hepatitis-C-viral infection in Bulgaria has been developed with the help of TE- FibroScan for dynamic assessment of fibrosis every 12 months.

4. Creating a new cut-off for hepatitis-C fibrosis from the previously accepted F0/1 to 7.1 kPa to 8 KPa, F2 from 8 to 10kPa, F3-10 to 14 kPa, F4 and cirrhosis above 16 kPa.

5. In order to improve the quality of life in patients with chronic viral C-hepatitis and cirrhosis, create a multidisciplinary team of hepatologists, nurses, psychologists, psychiatrists and coordinators.

6. Creating a simplified diagnostic model containing positive serology, viral load and genotyping, fibrosis assessment with FibroScan.

Related publications – The author presents a list of publications and participation in scientific forums, which contains 13 titles in Bulgarian and 9 in English. This scientific activity is sufficient to assume that the scientific interests of the thesis are sustainable and there is consistency in his scientific pursuits.

CONCLUSION: I am convinced that the doctoral dissertation of Radin Tsonev Tsonev *Assessment of liver fibrosis and quality of life in patients with chronic viral C-hepatitis and cirrhosis* fully covers the scientific criteria for awarding the scientific and educational degree "DOCTOR" and I submit my POSITIVE evaluation of the dissertation and urge the honorable chairman of the jury and the other members of the jury to vote affirmatively.

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