

PhD Thesis Evaluation Report

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of dissertation thesis 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 Stoynov, MD, PhD

Chronic hepatitis C infection is a socially significant disease due to the large number of the population it affects, has a prolonged asymptomatic period and leads to severe complications, including high oncogenic potential. Introducing a number of modern technologies into routine clinical practice has led to a dramatic change in the perception and diagnosis of HCV, including the possibilities for diagnostics, improvement in treatment, prognosis and quality of life of patients with chronic liver disease. No less importance has the financial resource needed for early detection and treatment of patients with chronic hepatitis C infection (HCV). In the past years the tendency is to improve the therapeutic results, eradicate the virus almost to a 100% and to reduce the prices of the medicines used. Chronic HCV infection leads to development of histological changes in the form of liver fibrosis (CFP) and cirrhosis, as well as neoangiogenesis and regeneration. The need to track these changes poses the question of looking for new medically non-invasive technologies, which is also preferred for diagnostics in all areas of medicine. Recently, there have been numerous and controversial studies comparing diagnostic options between liver biopsy (LB) and non-invasive methods for assessing fibrosis (F) - a major morphological substrate in HCV. Quality of life in patients with chronic liver disease (CLD) and HCV are defined as the patient's assessment of the overall diagnostic and therapeutic period and its reflection on daily life. The answers from the patients surveys show some subjectivity, based on the patient's psychological characteristics,

the environment in which the patient lives, the social group and last but not least the degree of awareness of his or her illness. Especially HCV and cirrhosis have continuous evolution of pathological changes, potential oncogenicity, the progression of the disease, the need for invasive diagnostic methodologies, the result of long-lasting treatment, fears of infecting others, etc.

Radin Tsonev's PhD thesis is written in a volume of 105 pages, contains 47 tables and 21 figures. The bibliographic reference contains 125 literary sources, 6 of which in Cyrillic and 119 in Latin.

The literature review is presented on 33 pages - about 31% of the dissertation work. It presents the nature of HCV, early screening programs to determine the target groups, the natural course of infection and the results of the specific treatment. It is emphasized that the progression of the disease determines the social importance, and the pursuit of early detection of infection leads to earlier specific treatment interrupting the natural course of the disease, which prevents fibrogenesis. The author has thoroughly described the screening programs available for early detection of HCV with a primary target for the world to deal with this infection by 2030. The pathogenesis of liver fibrosis is discussed and its consequences, as well as the role of liver biopsy for taking material for histological examination with its advantages and disadvantages. Contradictory publications are presented for comparison with non-invasive methods of assessment of liver fibrosis. Particular attention is paid to reports of non-invasive assessment methods for fibrosis - instrumental test and direct biomarkers. It is recommended that an instrumental method be combined with a biomarker, which increases the diagnostic value in various degrees of fibrosis, especially in moderate degree of fibrosis. Separate and combined algorithms for non-invasive evaluation of liver fibrosis, the essence of disease monitoring, antiviral treatment and prognostic value for risk groups for early development of liver fibrosis with HCV etiology are described.

In recent decades, the concept of "quality of life" has become popular in all areas of medicine and healthcare. It is defined as reflection of the patient's subjective opinion on the impact of his illness on daily life and the ability to satisfy its specific physical and mental health needs. In this part of the literature review a critical assessment of the proposed methodologies and scales for reporting quality of life in patients with CLD is made in detail.

The purpose and tasks of the dissertation are clearly formulated, focusing on comparative assessment between non-invasive measurement of liver fibrosis by TE-FibroScan and liver biopsy in patients with chronic hepatitis "C" and cirrhosis and evaluation of the effect of treatment as well as assessment of the quality of life of chronic liver disease patients.

The study included 366 patients with chronic viral hepatitis and cirrhosis, divided into 3 groups - 241 patients had hepatitis C, 37 had hepatic C cirrhosis and 88 had hepatitis B. All patients underwent standard laboratory, virological, immunological, morphological and instrumental methods of diagnosis, including TE- Fibro-Scan under basal conditions. In 149 patients with hepatitis C, a comparable study was performed of liver density by TE before treatment with direct-acting antiviral agents (DAAs) with 12 months of follow-up. After

filling out the questionnaire, the quality of life is rated on a point scale (SF - Health Survey) - SF 8, considered reliable for the physical and mental health status.

The selected set of statistical methods includes correlation, regression, dispersion and discriminant analysis and methodologies of the descriptive statistics. The statistical methods listed allow the values of the variables to be converted to quantitative scales while maintaining rank equivalent, which guarantees credibility, actual analysis and conclusions.

After statistical processing and analysis of the obtained the results, it is shown that when comparing between transient elastography (FibroScan) and liver biopsy there is dependency and concurrence of results more pronounced in patients with moderate and severe fibrosis (F3-F4) with maximum values up to 79.2%. In this sense, the proposal to add the study of a second non-invasive fibrosis marker - fibrotest or APRI – is appropriate, given that it further increases the diagnostic value of FibroScan.

There is no correlation between the presence of liver fibrosis and histological data for activity of inflammation. There is also no correlation observed between the degree of fibrosis and increased values of ASAT and ALAT probably due to the inclusion in the study of patients with advanced chronic liver disease without ascites, as well as patients without biochemical data of inflammatory activity of liver cells.

From the results provided, it is established with statistical certainty that fibrosis decreases after 12 months of antiviral treatment with DAAs, which makes elastography the recommended method for follow-up in chronic liver disease with HCV etiology. Fibrosis scores assessed by FibroScan and with biopsies show more pronounced reliability in comparison of the same values in patients with HBV.

No statistical difference in self-assessed quality of life is found in patients with and without liver fibrosis assessed by the Levin test and T- test. Regardless of the research and treatment done, patients report improvements in quality of life most likely due to the information obtained about the nature of the disease and the prospects for the future treatment and follow-up. The eventual replacement of liver biopsy with non-invasive assessment methods of fibrosis, the quality of life will improve significantly. In the monitoring of patients with CLD it is also important to actively involve a psychologist who has a direct attitude to justify the enhancement of the quality of life to become a team approach from a hepatologist, nurse, psychologist (psychiatrist) and coordinator.

The author has formulated seven main conclusions that are a concentrated expression of the results obtained. Valuable at the conclusions are their scientific and practical direction and precisely meet the goals and objectives set.

I agree with the contributions made by the author, which have confirmatory and scientific and practical character and after discussing the recommendations in the Bulgarian Group for Study of Chronic Viral Liver Diseases they can be evaluated for eventual inclusion into routine gastroenterological clinical practice, more precisely in the diagnostic algorithm, treatment and monitoring of patients with CLD.

Radin Tsonev, MD, has submitted a list of 22 publications related to the dissertation, consisting of articles and abstracts in Bulgarian and foreign journals and participation in congresses, symposiums, conferences and workshops programs.

In conclusion, sufficient data is provided to show that non-invasive assessment methods for advanced liver fibrosis are accurate, cost-effective and easy to implement and reproduce. Combined algorithms can help increase their diagnostic value. Besides the initial assessment of the liver fibrosis, the proposed algorithms can also be used to track patients at risk for developing complications, giving priority to antiviral treatment and to liver transplant as well as follow-up of hepatic fibrosis regression in response to antiviral treatment. Liver biopsy in diagnostic algorithms and tracking could be replaced by non-invasive ones, especially combined methods for liver fibrosis evaluation. Limited biopsy application can be implemented only in patients who have inconclusive non-invasive tests which have produced unreliable and inaccurate results. Assessment of quality of life in patients with proven liver fibrosis at different stages should continue beyond clinical observation and treatment by a multidisciplinary team composed of a hepatologist, nurse, psychologist (psychiatrist) and coordinator.

Considering that what is presented is a large-scale study with sufficient number of patients with CLD in Bulgaria with HCV etiology which is first of its kind in our country, as well as the set of modern research methods used directly related to the purpose and tasks of the dissertation work, well chosen and precisely applied statistical processing, the doctoral student's ability to select and process real medical information, as well as the scientific and practical conclusions drawn, I suggest the honorable jury to vote affirmatively on the acquisition of the scientific degree "Doctor" by Radin Tsonev Tsonev, MD.

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Sofia, Bulgaria

Prof. K. Katsarov, MD, PhD