PhD THESIS

Prognostic factors in invalidity retirees with chronic liver disease

ABSTRACT

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Introduction

Chronic liver disease is one of the main health problems of the contemporary world, with significant variations depending on the particular social and economic context of each region, one of four causes of death in the world being represented in end-stage liver disease.

Romania holds first place in the European Community regarding the prevalence of hepatitis B and C. The latest study, conducted in 2009 by the Romanian Association for the Study of Liver in the general population found a prevalence of 5.59% of virus B and C virus of 4.56% with prevalence much different from high-risk population. The same study has examined the prevalence in the city / village populations and geographical areas, identifying "islands" of very high population ratio of hepatitis C (Craiova and Constanta).

Romania ranks fourth as a mortality rate of liver disease - 44.5 deaths per hundred thousand inhabitants, while the European average is 15 deaths per hundred thousand inhabitants. Worse is that in Romania are predominant genotypes B and C viruses. Both responds reluctantly to current treatments.

A WHO report released in early 2011 places Romania on the 4th place with heavy drinkers in Europe and 8th place worldwide with 15.3 liters of alcohol /capita annually. Chronic liver diseases lead in most cases to limitation or temporary loss of working capacity, with significant economic consequences, for both society and the individual.

In Romania, chronic liver disease is the leading cause of invalidity, with a prevalence of 7.80% of all disability retirements (INEMRCM Annual Report, 2011).

Patients studied in this work include cases that have lost their working capacity due to chronic liver disease, who were registered with The Medical and Work Capacity Recovery County Department. The invalidity of chronic liver disease of various etiologies is relatively common, but far less valued form of scientific research.

The work is structured as follow: knowledge level and personal contributions.
1. Knowledge level

First, the general theoretical data summarizes current literature on chronic liver disease.

**Chapter 1.** - The Nosology—definition, terminology, and classifications
**Chapter 2.** - Epidemiological data of chronic liver disease etiologic classes.
**Chapter 3.** - Histopathological changes in chronic liver disease, presenting the scoring systems of hepatitis activity and fibrosis, and histological characteristics of etiology.
**Chapter 4.** - The main etiopathogenic aspects of chronic viral liver disease, alcoholic and autoimmune.
**Chapter 5.** - Clinical features, biochemical, immunological and imaging to characterize positive diagnosis.
**Chapter 6** - Predictive role of prognostic factors in work capacity evaluation in patients with debilitating chronic liver disease.
**Chapter 7.** - Basics of medico-legal assessment of work ability and health professional education and social action underlying rehabilitation program in chronic liver disease.

2. Study Objectives

The second section contains research to clinical, laboratory, imaging, histology and response to therapy to identify prognostic factors of chronic liver disease.

I proposed the following objectives:
- Analysis of clinical and laboratory characteristics of specific disabling chronic liver disease;
- Study and elucidate the impact of co morbidities on the prognosis of chronic liver disease;
- Analysis of the effect of therapy on prognosis of chronic liver disease and the recovery of work capacity
- Analysis of individual variables that influence outcome in chronic liver disease and to establish correlations among all variables studied;
- Identifying variables that may influence prognosis and contribute to recovery of work capacity.

This creates the premises to identify patients I expect to obtain positive treatment response as a result of compliance of the rehabilitation program.
3. Materials and methods

The group of subjects concerning this research is composed of patients diagnosed with chronic liver diseases (chronic hepatitis and liver cirrhosis) who were registered with Department of Medical and Work Capacity Recovery Dolj in 2006-2010. At enrollment, all patients had lost the ability to work; at least half are diagnosed in grades I, II or III disability. During the study, disability was observed in its dynamics. At patients ranked with a degree of disability, the social worker made inquiries at the patient's home. Also, throughout the study, patients attended rehabilitation programs designed by the attending physician with the help of social insurance expert.

A total of 135 subjects were studied: 44 women and 91 men.

The family history-side: I noticed the presence of viral hepatitis, autoimmune diseases or liver carcinoma. Pathological personal histories that I recorded were surgical interventions, blood transfusions, dental interventions.

I noticed the presence of symptoms and fatigue, jaundice, bleeding events and neurological phenomena. Complete physical examination was performed on the appliances and systems.

**Immonochemical Exploration.**
- serum markers of cytolysis: ALT, AST initiation and development annually;
- serum markers of cholestasis: BT and fractions; γGT, FA - at baseline and evolving each year;
- serum markers of liver failure: protein electrophoresis (for albumin), prothrombin time;
- serum markers of mesenchymal activity: protein electrophoresis (for gamma-globulin);
- complete blood count;
- serum markers of metabolic syndrome: glucose, lipidogram;
- viral infection markers: HBsAg, anti HDV, HCV antibody;

**Imaging**
Evaluated ultrasound liver, spleen and spleno-portal axle.
Upper gastrointestinal endoscopy revealed esophageal varices and GPH; Histopathological examination. The material studied in this work was obtained from human liver through liver puncture.

**Study protocol for each patient to assess work capacity in accordance with the rules of admission to degree of disability in force, published in Official Gazette Nr.400/2000.**
4. Results and discussion

Study of socio-demographic data revealed a number of particular aspects of disability pensioners with chronic liver disease. Applicants for a disability pension are women under the age of 58 years and men younger than 63 years, but we included in the study subjects with 5 years less than those ages, could be traced to their development until the conditions for old age.

Gender distribution of study group revealed predominantly affecting men. Fewer women in the study is not necessarily due to greater frequency of disease among men, that as men age ranges included in the study were older than women, due to old age retirement age higher men. These results are consistent with published results indicating that men are more frequently affected by chronic liver disease. (Bialek SR, Redd JT, Lynch A, et al. 2008;).

Differences were significant in the average age in cases with ethanol etiology compared with those with viral etiology. The average age of disability pensioners with viral liver disease was 3 years and 10 months less than for cases of ethanol etiology.

The distribution by sex and age groups criteria shows a maximum frequency of liver damage at females aged 45.

55.5% of women surveyed who have viral liver infection with a previous history of blood transfusion, the latter with a median of 16.6 years.

Percentage distribution of the batch according to the degree of instruction indicates the educational school environment as being predominantly (62%), followed by at least about one third of cases, 31% (N = 42).

The average age of cases according to educational level showed an approximately 4 years older than those with minimal education to those with secondary or higher. This might suggest a lower addressability educational level of subjects with minimal production of which occurs late as a doctor in the natural history of disease. Seniority is directly related to the age that when subjects were asked for disability retirement.

Statistically significant differences (p <0.001) were observed between seniority and type of liver disease causative. Patients with alcoholic liver disease have on average worked more than six years of disability pensioners with viral liver disease and this could be explained by the fact that the liver disease of viral etiology appears at younger ages than alcoholic liver disease, between age and seniority is a linear correlation in individuals unaffected by any pathology.

Patients were categorized according to alcohol consumption in four categories: consumed alcohol, occasional alcohol consumption, moderate alcohol consumption and alcohol abuse.

We found that the age distribution of alcohol consumers is clearly in favor of the more than 50 years, 69.84% of subjects in the age group 50-59 years the consumption of alcohol.
Persons consuming alcohol, whether or not superimposed viral infection presents most commonly cirrhosis at baseline were 75.51% of the cases were already consuming alcoholic cirrhosis.

Gender distribution of cases according to BMI showed no significant differences, but remember that obesity high degree (II and III) was much more common in women.

Unlike cases with alcoholic etiology in cases with viral etiology were observed more cases with high degrees of obesity.

No significant differences were found between the incidence of obesity in cases with viral liver cirrhosis (25.93%) than those with chronic viral hepatitis (24.56%).

The analysis revealed the presence of symptoms of fatigue as a very common phenomenon in all liver diseases, regardless of etiology or form of liver injury. The presence of cholestatic forms was more common in cases with alcoholic liver disease (43.75%) compared with those with chronic viral liver disease (29.8%).

The incidence of diabetes was 20%, 27 cases associated with diabetes, chronic liver disease. A higher incidence was observed in cases with alcoholic fatty liver disease (26.92%) than cases with alcoholic cirrhosis. Also, the incidence was two times higher than in cases with viral liver cirrhosis from those with chronic viral hepatitis (13.33%).

Cytolysis liver enzyme values did not exceed 2.5 times normal values. Mean GPT were within the same values have remained the same downward trend over the study period.

Alcoholic chronic liver disease expressed GGT values of almost 2.5 times higher (284.88 U / l) compared with those observed in cases with viral etiology (119.2 U / l), find the differences between the two highest average statistically significant (p <0.001).

Damage prothrombin index as a negative factor in the development of liver disease was expressed by subtracting the mean values of 80.3% in its first year of the study to 71.8% last year. Statistically significant (p <0.001) was the difference between mean values of prothrombin index in cases with liver cirrhosis (67.5%) compared with those with chronic hepatitis (79.6%).

Evaluation of serum gamma electrophoretic surprised trend to growth from 24.9% to 27.2%, with values close to where etiology was alcoholic (26.4%) and those with viral etiology (26%). The only statistically significant difference was noted between the average in cases with liver cirrhosis and chronic hepatitis (p= 0.001) where gamma-globulins have recorded values of 26.7% and 25.8%.

Hepatomegaly was observed in a number of 56 cases (41.86%) during follow-up study with a higher frequency in cases with alcoholic liver disease (56.25%) than those of viral liver disease (33.33%).

The incidence of splenomegaly among patients with chronic liver disease was 83.46%, without significant differences according to etiology. 91.45% of cases with liver cirrhosis had splenomegaly.
Ascites was identified in more than half of the cases on which type of liver disease was cirrhotic (57.83%). Although, the differences were not statistically significant, there was a higher frequency of ascites in cases with chronic alcoholic liver disease (41.67%).

Antiviral treatment was carried out for nearly one third (32%) of cases with chronic liver disease with viral etiology, similar to HBV and HCV infection (approx. 33%) and lower for the cases with co-infection (25%). Profile approval for antiviral treatment showed a higher rate of acceptance for women, 50% of them benefit of this therapeutic alternative.

The evolution of chronic liver disease as a solution required the use of therapeutic transplantation in 6 cases, three of those enjoying the liver transplant during the period analyzed, the other three cases being on the waiting list. In all trials, the waiting list was found MELD score, which is to contain values between 11.5 and 21.

Employment in degrees of disability at baseline showed a predominance of grade 3 disability (56.3%). After analyzing the distribution of degrees of disability classification in the age groups was observed trend employment growth whereas a lower degree of disability cases with increasing age. If the study group, where age group 30-39 years were classified in grades 2 and 1 in 70% of cases (N = 8).

Possible explanation for a lower incidence of grade 3 is related to disability in young people refusing to retire to a young person, who prefers to work full time at the expense of accepting a degree of disability which would allow the 50% limit working hours, alternately hard and accepted by employers who would receive a reduced remuneration. Therefore reach a young staff to seek disability retirement when his ability to work is totally lost.

In our study, we assessed the evolution of liver disease based on its effects on work capacity. For this, we considered a positive development to preserve at least half the working capacities (employment in the third degree of disability), shapes that go into a lower grade of disability from the initial assessment or the forms fully regains the capacity to work. As liver disease and poor outcome in terms of ability to work, have found shapes that have completely lost the ability to work throughout the tracking (degree of disability), those who have moved to a higher degree of disability or those died of liver disease during the study.

We studied several factors that influence the prognosis suspect in order to identify those modifiable factors over which we can intervene to improve the development of liver disease.
5. Conclusions

1. Gender distribution of study group revealed a predominantly affecting of men (N= 90) than women (N = 45), sex ratio being 2.04. For women, average age (46.5 years) was almost three years less than for men (49 years), statistically significant difference (p = 0.011).

2. We observed a substantial impairment of urban cases (representing 58% of all cases) than in rural areas (representing 42% of study group). This is explained by socio-economic differences between the two habitats and lower reach of the rural population to medical services.

3. Profile grade school instruction reveals that nearly two thirds (62%) of patients with chronic liver disease have secondary education, the second rank is occupied by those with secondary education. (31%). Minimum educational level was associated with the highest percentage of drinkers (82.93%).

4. Seniority was correlated with gender (being higher in males by about five years), the environment of origin (an employment higher in urban subjects) and etiologic type of liver disease (higher average 6 years for subjects with alcoholic liver disease). These differences can be explained by the particular socio-cultural and economic factors in Romania.

5. Alcohol consumption has been recognized 61.5% of subjects in the study, with rates much higher among men (82, 41%). Also, alcohol consumption was associated with age, 69.84% of subjects in the age group 50-59 years the consumption of alcohol. A percentage of 40.23 of the cases with viral infection were admitted to alcohol consumption. Distribution of cases according to alcohol consumption and liver form shows that 75.51% of the cases had liver cirrhosis at enrollment were consuming alcohol.

6. Employment in degrees of disability at baseline show a predominance of employment in grade II and I of disability for age groups 30-39 years (young people seeking disability pension have more severe forms of liver disease).

7. Distribution of degrees of disability classification according to the etiology indicated 64.58% of cases with alcoholic liver disease disability in grades 3, compared to only 51.72% cases assigned to the same degree of viral liver disease.

8. The risk of chronic liver disease case is classified as grade 2 or a disability was 1.5 times higher than in cases with viral etiology compared to those with ethanolic etiology.

9. The risk of losing entirely the ability to work (disability grade 2 and 1) was nearly 3.5 times higher in cases with liver cirrhosis than in other cases. (p <0.001).

10. Findings of work capacity every year is justified by a disability in the studied group dynamics: almost half of patients with chronic hepatitis at enrollment had progressed to cirrhosis. This explains the small number of cases that have
recovered their ability to work and the relatively high number of cases were classified in grade I disability or died during the study.

11. Female gender was a prognostic factor associated with favorable trends, favorable development opportunity being 1.57 times higher in women compared with men.

12. Was found a higher risk of favorable or unfavorable development related to the age group of cases, which means that this potential risk factor, age was not associated with the group studied the evolutionary model.

13. Evaluation of body mass index as a modifiable risk factor, surprised its link with evolutionary model. The risk of unfavorable evolution was over four times higher in cases with higher than normal BMI compared with those whose BMI has framed the stage pre- or obesity. (P <0.001).

14. For drinkers, the risk of adverse movements was 1.74 times higher than those non-drinkers, the differences being statistically significant (p = 0.0019). The risk of unfavorable in cases with viral etiology was 1.62 times higher compared to drinkers consumed (p = 0.0074), with values of adverse developments with 38% higher in HCV infection compared to infection HBV. Quitting drinking was an increase of more than two times the chance of favorable evolution (p = 0.047).

15. Diabetes mellitus was identified as a prognostic factor. The incidence of adverse development was higher in cases with diabetes, 81.48% (N = 22) compared with those without diabetes, 57.41% (N = 62).

16. Immunochemical tests proved to have a role in prognosis were GOT and GGT (normal range were associated with 50-55% chance of favorable development). For hematological hypersplenism cases presented during the prosecution, adverse developments in risk was 2 times higher compared to other cases.

17. The presence of splenomegalia, ascites, esophageal varices, hepatic encephalopathy episodes - they were all statistically significantly correlated with the chances of recovery of work capacity.

18. The incidence of positive evolutionary model of working capacity in cases with chronic liver disease of viral etiology was almost two times higher in cases who received antiviral treatment, the differences between frequency and negative developments favorable being validated statistically (p = 0.022).

19. Liver transplant has not improved work capacity, but increased the odds of survival.

20. Modifiable prognostic factors were identified: obesity, alcohol consumption, comorbidities (related to diabetes), and the optimal therapeutic management.

21. Profile of patients who have regained the work capacity:
   young patient, female, viral chronic hepatitis, normal weight, with minimal fibrosis and minimal or moderate inflammation, and antiviral treatment.
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Published papers in doctoral thesis area
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**Knowledge of foreign languages:**
- English;
- French.