

The Influence of Gender and Age on the Survival of Patients With Cirrhosis of the Liver

*Gafforov Xudoyor Xudoyberdiyevich*¹

Abstract: According to the literature, the male sex is associated in some studies with greater mortality in CL, and in another with less. In other studies, the relationship of gender with prognosis has not been established, therefore it is not taken into account in the prognostic models of the CLU. According to the literature, the male sex is associated in some studies with greater mortality in CL, and in another with less. However, in the more widely used universal models – Child-Pugh and MELD – age is not taken into account, and this does not make them less valuable for prediction.

Objective: to study the effect of gender and age on the survival of patients with cirrhosis of the liver of viral and alcoholic etiology.

Material and methods of research: To achieve this goal, we conducted an observational, prospective (cohort) study involving 249 patients with CL of viral (B, C, B +C), alcoholic and mixed (alcohol-viral) etiology with an assessment of the final solid point – the onset of death from CL or its complications. The age of patients is from 17 to 75 years (Me=50 years), 114 men (group 1) and 135 women (group 2). The diagnosis of CL was confirmed morphologically (laparoscopy with biopsy) in 45 patients, in the rest – based on the presence of signs of diffuse liver damage, the presence of hepatic cell insufficiency syndrome and portal hypertension syndrome (varicose veins of the stomach and esophagus, ascites).

Research results and discussion: When analyzing the survival rate of CL patients in groups of men and women who were comparable in age and Child-Pugh classes, no statistically significant differences were revealed. However, when comparing the survival rates of men and women within the Child-Pugh CL classes, statistically significant differences were revealed (Kaplan–Mayer method, Gehan–Wilcoxon test, $p=0.014$) in patients with Child-Pugh class C CL, which began to be determined from 3 months of follow-up. **Conclusions:** With decompensated cirrhosis of the liver (Child-Pugh class C), the chances of death in men are 2.2 times higher than in women. Age, as an independent value from other data, did not show itself as a prognostic factor of survival during 47 months of follow-up for cirrhosis of the liver of viral and alcoholic etiology.

Keywords: gender, factors in cirrhosis of the liver, to discover new links.

INTRODUCTION

The study of survival factors in cirrhosis of the liver (CL) is a fundamental problem of internal diseases, since it allows us to discover new links in the pathogenesis of the disease, improve diagnosis and develop more advanced treatment methods taking into account the individual characteristics of patients.

Various researchers attribute the gender and age of patients to the factors determining the prognosis for CL. According to the literature, the male sex is associated in some studies with greater mortality in CL, and in another with less. In other studies, the relationship of gender with prognosis has not been established; therefore it is not taken into account in the prognostic models of the CLU.

¹ Samarkand State Medical University



According to the majority of studies presented in the literature, older age refers to prognostically unfavorable factors for the development of a fatal outcome in CL, which is reflected in prognostic models and identified prognostic factors. However, in the more widely used universal models – Child-Pugh and MELD – age is not taken into account, and this does not make them less valuable for prediction.

Thus, the lack of unambiguous data on the influence of gender and age on the survival of patients with CL determines the relevance of this study.

Objective: to study the effect of gender and age on the survival of patients with cirrhosis of the liver of viral and alcoholic etiology.

MATERIAL AND METHODS OF RESEARCH

To achieve this goal, we conducted an observational, prospective (cohort) study involving 249 patients with CL of viral (B, C, B +C), alcoholic and mixed (alcohol-viral) etiology with an assessment of the final solid point – the onset of death from CL or its complications. The age of patients is from 17 to 75 years (Me=50 years), 114 men (group 1) and 135 women (group 2). The diagnosis of CL was confirmed morphologically (laparoscopy with biopsy) in 45 patients, in the rest – based on the presence of signs of diffuse liver damage, the presence of hepatic cell insufficiency syndrome and portal hypertension syndrome (varicose veins of the stomach and esophagus, ascites). The etiology of CL is determined by an indication in the anamnesis of long-term alcohol abuse and data from a virological examination of blood serum for markers of hepatitis B viruses (HBsAg, a/t classes M and G to HBcorAg, HBV DNA), C (a/t classes M and G to HCV, HCV RNA) and D (a/t to HDV). Patients with severe concomitant pathology were excluded from the study: right ventricular chronic heart failure, severe diabetes mellitus, oncopathology, tuberculosis, kidney diseases with renal insufficiency, lung diseases with respiratory insufficiency.

All patients lived in the Tomsk region. All patients included in the study received voluntary informed consent to participate in the study, and all patients were given an information sheet of the subject. No studies were conducted if there was a possibility of serious complications and the intended benefit from the study was less than the possible harm caused to the health of patients.

The follow-up period was 47 months. During the entire follow-up, 119 patients died.

Statistical data processing was carried out using the Statistica v6.0 program (StatSoft, USA). The frequency analysis of the distribution of etiological variants of CL, men and women among deceased and surviving patients of the same class (A, B or C) according to Child-Pugh for the studied periods was carried out according to tables 2×2 using the exact two-sided Fisher criterion. The study of survival was carried out by the Kaplan–Mayer method. The correlation between the variables was estimated by Spearman's method. The results for all the methods used were considered statistically significant at $p < 0.05$.

At the first stage, the association of the etiological variant of CL with the survival of patients at the same stage of the disease (one class of CL according to Child-Pugh) was analyzed. Since there were no statistically significant differences in the frequency of distribution of various etiological variants of CL in the groups of deceased and surviving patients for all periods, the groups were subsequently compared with each other for these periods without taking into account the etiological variants of the disease.

RESEARCH RESULTS AND DISCUSSION

When analyzing the survival rate of CL patients in groups of men and women who were comparable in age and Child-Pugh classes, no statistically significant differences were revealed. However, when comparing the survival rates of men and women within the Child-Pugh CL classes, statistically significant differences were revealed (Kaplan–Mayer method, Gehan–Wilcoxon test, $p = 0.014$) in patients with Child-Pugh class C CL, which began to be determined from 3 months of follow-up.



The median survival time of sick men with CL class C according to Child-Pugh was 4 months. Of the 34 men, 26 died. The median survival time of sick women with CL class C according to Child-Pugh was 19.3 months. Out of 50 women, 30 died. Percentage of male survivors (R_{mw})=0.235; 95 % CI [0.166; 0.304]. Percentage of female survivors (R_j)=0.40; 95 % CI [0.314; 0.486]. The chances of a fatal outcome in men are 3.25, and in women – 1.5. The odds ratio (OR) is $3.25/1.5 = 2.2$, i.e. the chances of dying in men with CL of various etiologies of class C according to Child-Pugh are 2.2 times higher than in women during the follow-up period of 47 months.

The implementation of the sex factor in the prognosis of survival with decompensated CL occurs from 3 months of follow-up, i.e. from the moment of the appearance of statistically significant differences in survival between men and women.

Thus, the female sex is associated with better survival with decompensated CL.

The best survival rate of women obtained in the course of this study can be explained from the point of view that the female body has better compensatory capabilities than the male one. These facts are reflected in the longer life expectancy of women compared to men. As for patients with CL, during decompensation of the disease, the compensatory reserves of the body become key to the survival of patients. As the results obtained by us show, the influence of the male sex on the unfavorable prognosis is realized just with a decrease in the compensatory reserves of the body – with a CL of class C according to Child-Pugh. From which it follows that these reserves are most likely more in women compared to men. It can be assumed that estrogens play a certain role in this. The vasodilating effect of estrogens is known, realized through stimulation of the synthesis of nitric oxide (NO) by the endothelium and through exposure to ion channels by the type of calcium antagonists. Estrogens reduce the synthesis of endogenous vasoconstrictors – endothelin-1, thromboxane, catecholamines. The latter increase vascular resistance and enhance sodium reabsorption in the kidneys, which contributes to an increase in blood pressure. It is likely that the inhibition of these mechanisms by estrogens leads to a slower increase in pressure in the portal vein and, consequently, a slow progression of portal hypertension with CL in women, which may explain their better survival. However, information confirming this assumption has not been found in the literature.

There is evidence that estrogens reduce the degree of exposure of damaging agents to the liver. The mechanism of protection is associated with a decrease in the transcription of the proinflammatory cytokine IL-6 gene and its secretion by Kupfer cells under the action of estrogens, as a result of which the activity of the inflammatory process in the liver decreases. In this regard, studies on the effect of sex hormones in CL on the expression of other genes, various polymorphic variants of which are associated with better survival of patients, in particular, on the expression of genes of glutathione-S-transferase enzymes of xenobiotic biotransformation processes, are promising.

Estrogen receptors are found on the membranes of different types of body cells: bone, muscle, secretory, nerve and blood cells, as well as in connective tissue. Perhaps the systemic effect of estrogens associated with this leads to an increase in the body's adaptation to extreme influences, as a result of which there is a better survival rate for women.

The study of more subtle mechanisms responsible for the better survival of women with CL requires separate studies to determine the effect of hormonal background and other sexual characteristics of the body on the survival of patients with CL.

The influence of the age of patients with CL on survival was studied by determining the correlation between age and time to death. Since the patients were at different stages of the disease, in order to correctly assess the impact of age on survival, stratification of patients by classes of Child-Pugh CL was carried out, and the correlation was studied within each class of CL.

Thus, the age of patients did not manifest itself as a factor affecting the survival of patients with CL. This can be explained by the fact that the known decrease in the compensatory capabilities of the body with age is not so pronounced as to statistically significantly worsen survival with CL.



CONCLUSIONS

1. With decompensated cirrhosis of the liver (Child-Pugh class C), the chances of death in men are 2.2 times higher than in women.
2. Age, as an independent value from other data, did not show itself as a prognostic factor of survival during 47 months of follow-up for cirrhosis of the liver of viral and alcoholic etiology.

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