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ПОЛОВЫЕ РАЗЛИЧИЯ В РАЗВИТИИ АЛКОГОЛЬНОЙ БОЛЕЗНИ ПЕЧЕНИ

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SEX SPECIFIC DIFFERENCES IN THE DEVELOPMENT OF ALCOHOLIC LIVER DISEASE

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Резюме. Алкогольная болезнь печени (АБП) - это спектр заболеваний печени, возникающих вследствие чрезмерного употребления алкоголя. Она представляет собой глобальную угрозу здоровью, где цирроз печени, вызванный употреблением алкоголя, занимает 8-е место среди наиболее распространенных неинфекционных причин смерти. Чрезмерное употребление алкоголя оказалось наиболее распространенным фактором риска развития и прогрессирования цирроза печени. Цирроз печени остается важной глобальной проблемой здравоохранения, на долю которого ежегодно приходится около 1,2 миллиона смертей, при этом распространенность заболевания заметно варьируется по регионам. В странах Восточного Средиземноморья и Юго-Восточной Азии высокие показатели обусловлены гепатитами С и В соответственно, в то время как в западных странах распространены заболевания печени, связанные с употреблением алкоголя. В 2010 году Беларусь занимала первое место в мире по потреблению 17,5 л чистого алкоголя на душу населения в год. Однако, по данным Всемирной организации здравоохранения (ВОЗ), к 2016 году потребление алкоголя на душу населения в Беларуси снизилось до 11,2 л. Несмотря на эту тенденцию, Беларусь остается в числе стран с наибольшим количеством лет жизни, потерянных из-за алкоголя.

Ключевые слова: алкогольная болезнь печени (АБП), липополисахаридсвязывающий белок (LBP), оценка по шкале Чайлд-Пью, биохимические маркеры, эстроген.

Resume. Alcohol liver disease (ALD) is a spectrum of liver conditions that arises due to excessive alcohol consumption. It poses a global health threat where liver cirrhosis due to alcohol consumption takes the lead as the 8th most common non-communicable cause of death. Excessive alcohol consumption has proven to be the most prevalent risk factor in the development and progression of liver cirrhosis. Liver cirrhosis remains a significant global health issue, accounting for approximately 1.2 million deaths annually, with notable regional variations in prevalence. The Eastern Mediterranean and Southeast Asia experience high rates due to hepatitis C and B, respectively, while alcohol-related liver disease is prominent in Western countries. In 2010, Belarus was rated #1 in the world with 17.5 L of pure alcohol consumption per capita per year. However, according to the World Health Organization (WHO), by 2016, per capita alcohol consumption in Belarus has dropped to 11.2 L. Despite this improved trend, Belarus remains among the countries with the most estimated years of life lost due to alcohol.

Keywords: alcoholic Liver Disease (ALD), Lipopolysaccharide binding protein (LBP), Child-Pugh’s score, biochemical markers, estrogen.

Relevance. Globally, we can see an increasing trend of liver cirrhosis in females compared to males, whereas in the European region, an increasing trend of liver cirrhosis in

males can be seen. However, several studies have continued to prove that females are more prone to developing ALD compared to men at the same level of alcohol consumption. According to a research study conducted by Nobuhiro et al., it is proposed that excessive alcohol consumption makes the gut permeable, thereby releasing endotoxins (lipopolysaccharides), and the sex difference in alcoholic liver injury may be due to the difference in the induction of CD14 and LBP (lipopolysaccharide binding protein) levels in the liver, which can be influenced by oestrogen. This was determined by an investigation about the effect of oestrogen on the response of Kupffer cells to endotoxins in rats. Serum TNF-a levels were measured, and the levels were almost twice as high in oestrogen-pretreated rats as compared with the controls. Further observations showed that oestrogen sensitises Kupffer cells to endotoxins in vivo and increases both CD14 and LBP in the liver, which leads to the sensitisation of the liver to endotoxin and thereby augments ethanol-induced liver injury in females. Females may also have different alcohol pharmacokinetics and pharmacodynamics compared to males. Females tend to have lower overall water content and smaller stature than males, leading to higher blood alcohol concentrations for the same amount of alcohol consumed. According to Frezza et al., females have less alcohol dehydrogenase activity in the gastric mucosa, which leads to increased alcohol bioavailability.

Aim: our present research aims to confirm the distinct sex differences in alcohol-consuming patients who develop liver cirrhosis through a case study, presenting the acquired data and subsequent conclusions.

Objectives:

1. Investigate why women are more susceptible to alcohol-related liver disease (ALD) than men at comparable levels of alcohol consumption.
2. Discuss the role of estrogen in increasing liver sensitivity to endotoxins and ethanol-induced injury.
3. To analyze collected clinical data (e.g., biochemical markers, disease severity, alcohol consumption patterns) stratified by gender.

Material and methods. A total of 300 case reports were reviewed from the Gastrointestinal Department of the EV Klumov 3rd City Clinical, Minsk. Cases were reviewed to identify patients diagnosed with liver disease of purely alcoholic etiology. Twenty-six cases meeting the inclusion criteria were identified. These cases were categorized into two groups based on gender and a comparative analysis between the groups was performed. The computer program “Statistica 10.0” was used for the analysis of data.

Results and their discussion. 12 female patients (mean age: 49.91 ± 7.61 years) were compared with 14 male patients (mean age: 53.07 ± 14.5 years). This showed that Females who develop ALD are slightly younger, but no significant age difference was found between genders. A larger sample size may reveal a statistically significant difference. The drinking habits, regularity and the type of prefered alcohol were recorded and a comparison between Males and Females was made. This revealed that Males were more likely to be regular drinkers compared to females. They generally preferred alcoholic beverages with higher alcohol content, such as vodka and whiskey. In contrast, females tended to favour drinks with lower alcohol percentages, such as wine and beer.

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All female patients (100%) developed liver cirrhosis, while 71.42% (n=10) males developed the same ($\chi2$ = 4.052, p=0.045). Ascites was found in 83.33% (n=10) females and 28.57% (n=4) males ($\chi2$ = 7.797, p = 0.006). 10 out of 12 (83.33%) Female patients developed Encephalopathy of varying degree while only 8 out of 14 (57.14%) Male patients developed the same ($\chi2$ = 2.081, p = 0.150). Although Anemia was more prevalent amongst females (91.67%) compared to males (64.28%) it was not statistically significant ($\chi2$ = 2.729, p = 0.099). Thrombocytopenia was observed in five female and male patients which accounts to 41.67% and 35.71% respectively ($\chi2$ = 0.097, p = 0.756) (fig 1.).

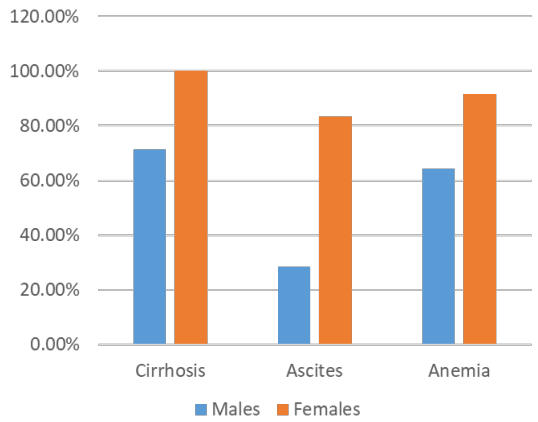

Fig. 1 – Graph illustrating the gender-based difference in complications

Males showed considerably greater GGT levels 257.64 (117.9; 702.44) U/L than females 69.31 (51.18; 387.96) U/L (p = 0.04), according to an analysis of serum biochemical parameters. In a similar vein, males had considerably higher CRP levels 35.46 (15.20–56.10) mg/L than females 8.8 (7.40–40.50) mg/L (p = 0.04). Males had higher ALT 69.47 (18.24; 52.93) than Females 27.15 (15.28; 31.68) (p=0.15). Similarly, AST was higher in Males 101.31 (61.65; 180.36) in comparison to Females 49.87 (28.60; 89.52) (p=0.08). The ratio between AST/ALT was found to be higher in males 3.45 (2.54; 4.33) than females 2.51 (1.07; 3.14) (p=-.15). Albumin – on the other hand – was higher in Females 32.7 (26.23; 39.59) than Males 27.81 (24.95; 33.91) (p=0.38). Total Bilirubin was higher in Males 74.97 (37.70; 108.41) than Females 36.68 (9.21; 120.11) (p=0.38). (fig 2.).

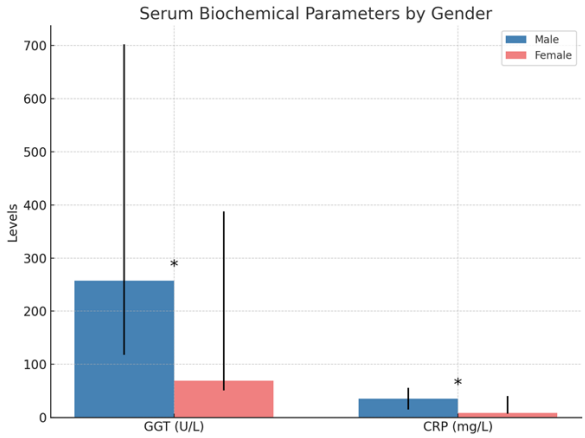

Fig. 2 – Graph illustrating serum biochemical parameters by gender

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Parameter	Male (Median, IQR)	Female (Median, IQR)	p-value
ALT (U/L)	69.47 (18.24–52.93)	27.15 (15.28–31.68)	0.15
AST (U/L)	101.31 (61.65–180.36)	49.87 (28.60–89.52)	0.08
AST/ALT Ratio	3.45 (2.54–4.33)	2.51 (1.07–3.14)	0.15
GGT (U/L)	257.64 (117.90–702.44)	69.31 (51.18–387.96)	**0.04**
CRP (mg/L)	35.46 (15.20–56.10)	8.8 (7.40–40.50)	**0.04**
Albumin (g/L)	27.81 (24.95–33.91)	32.7 (26.23–39.59)	0.38
Total Bilirubin (µmol/L)	74.97 (37.70–108.41)	36.68 (9.21–120.11)	0.38

Fig. 3 – Table illustrating statistical results of the study

In this study, several moderate correlations were observed between clinical and biochemical parameters. Alcoholic liver cirrhosis showed a moderate positive correlation with hepatomegaly (r = 0.51), suggesting that liver enlargement in these patients is likely due to chronic inflammation, steatosis, and progressive fibrosis. A similar association was noted between alcoholic liver cirrhosis and anemia (r = 0.52), which may be attributed to factors such as nutritional deficiencies, gastrointestinal bleeding, or bone marrow suppression commonly seen in advanced liver disease. Additionally, a moderate correlation was found between ALT levels and alcohol intake (r = 0.53), indicating that higher alcohol consumption is associated with increased hepatocellular injury, as reflected by elevated ALT levels. These correlations highlight the multifaceted impact of chronic alcohol use on liver structure and function. Furthermore, the Child-Pugh classification was used to group the patients into 3 severity groups (A, B and C). Majority of the Females were classified as class C (58%) while rest of the females were class B (42%). Whereas in Males all 3 classes were seen, with Class A, B and C having 14%, 50% and 36% respectively.

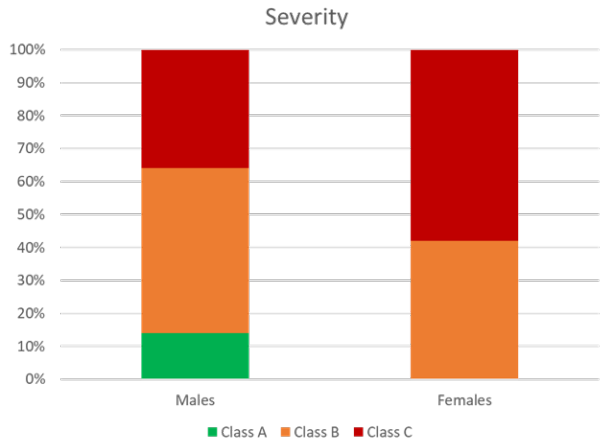

Fig. 4 – Child-pugh classifications (males and females)

Conclusion:

1. The study found that while women with Alcoholic Liver Disease (ALD) were often younger and showed more advanced disease severity (higher Child-Pugh classes, more cirrhosis/ascites) than men despite similar or lower alcohol consumption, the age difference between sexes was not statistically significant, though a larger sample might clarify this trend.

2. Women with ALD exhibited more advanced disease progression (e.g., cirrhosis, fibrosis) despite lower CRP and GGT levels, suggesting structural liver damage rather than active inflammation, while men's higher biochemical markers likely reflected greater alcohol-induced hepatocellular injury.

3. The findings emphasize the need for early screening and intervention in women, as they may develop more severe ALD despite lower alcohol consumption, while also benefiting more from abstinence due to better liver outcomes and reduced disease progression–highlighting the critical role of timely diagnosis and alcohol dependence counseling to improve prognosis in both sexes.

Literature

1. Sex Difference in Alcohol-Related Organ Injury by Nobuhiro Sato, Kai O. Lindros, Enrique Baraona, Kenichi Ikejima, Esteban Mezey, Harri A. Järveläinen, Vijay A. Ramchandani https://doi.org/10.1111/j.1530-0277.2001.tb02371.x.

2. Y. Lamboeuf, G. de Saint Blanquat, R. Derache, Mucosal alcohol dehydrogenase- and aldehyde dehydrogenase-mediated ethanol oxidation in the digestive tract of the rat, Biochemical Pharmacology, Volume 30, Issue 5, 1981, Pages 542-545, ISSN 0006-2952, https://doi.org/10.1016/0006-2952(81)90643-2. (https://www.sciencedirect.com/science/article/pii/0006295281906432).

3. World Health Organization – Alcohol Use https://www.who.int/news-room/fact-sheets/detail/alcohol.

4. Bizzaro, D., Becchetti, C., Trapani, S., Lavezzo, B., Zanetto, A., D'Arcangelo, F., Merli, M., Lapenna, L., Invernizzi, F., Taliani, G., Burra, P., AISF Special Interest Group on Gender in Hepatology, 2023. Influence of sex in alcohol-related liver disease: Pre-clinical and clinical settings. United Eur. Gastroenterol. J. 11, 218–227. https://doi.org/10.1002/ueg2.12370.

5 .Carlini, L.E., Fernandez, A.C., Mellinger, J.L., 2024. Sex and gender in alcohol use disorder and alcohol-associated liver disease in the United States: A narrative review. Hepatology. https://doi.org/10.1097/HEP.0000000000000905.

6. Gavaler, J.S., 1982. Sex-Related Differences in Ethanol-Induced Liver Disease: Artifactual or Real? Alcohol. Clin. Exp. Res. 6, 186–196. https://doi.org/10.1111/j.1530-0277.1982.tb04961.x.

7. Kezer, C.A., Simonetto, D.A., Shah, V.H., 2021. Sex Differences in Alcohol Consumption and Alcohol-Associated Liver Disease. Mayo Clin. Proc. 96, 1006–1016. https://doi.org/10.1016/j.mayocp.2020.08.020.

8. Listabarth, S., König, D., Berlakovich, G., Munda, P., Ferenci, P., Kollmann, D., Gyöeri, G., Waldhoer, T., Groemer, M., Van Enckevort, A., Vyssoki, B., 2022. Sex Disparities in Outcome of Patients with Alcohol-Related Liver Cirrhosis within the Eurotransplant Network–A Competing Risk Analysis. J. Clin. Med. 11, 3646. https://doi.org/10.3390/jcm11133646.

9. Llamosas-Falcón, L., Probst, C., Buckley, C., Jiang, H., Lasserre, A.M., Puka, K., Tran, A., Rehm, J., 2022. Sex-specific association between alcohol consumption and liver cirrhosis: An updated systematic review and meta-analysis. Front. Gastroenterol. 1, 1005729. https://doi.org/10.3389/fgstr.2022.1005729.

10. Zhu, Y., Xu, X., Fan, Z., Ma, X., Rui, F., Ni, W., Hu, X., Gu, Q., Shi, J., Wu, C., Yeo, Y.H., Li, J., 2024. Different minimal alcohol consumption in male and female individuals with metabolic dysfunction-associated fatty liver disease. Liver Int. 44, 865–875. https://doi.org/10.1111/liv.15849.