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# Analysis of causes of death in patients with alcoholic liver cirrhosis associated with non-alcoholic fatty liver disease

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**Today, it has been proven that about 10% of deaths among young and middle-aged people relate to the consumption of alcoholic beverages. Alcohol is ranked third among the causes of mortality in young people after tobacco and arterial hypertension, and second place – among the causes of liver transplantation in Europe. In Ukraine, mortality due to alcoholic liver disease (ALD) has taken second place in the structure of causes of death from diseases of the digestive system.**
***The objective:*** **to study the peculiarities of the causes of death in patients with ALD at the stage of liver cirrhosis (LC) associated with non-alcoholic fatty liver disease (NAFLD) on the basis of the analysis of pathoanatomical research protocols.**
***Materials and methods*****. 216 protocols of the pathoanatomical study of the patients who died from LC have been analyzed.**
***Results*****. It was found that people who abused alcohol died at the stage of subcompensation and compensation from pancreatic necrosis, and at the stage of decompensation – from the gastrointestinal bleeding (GIB) (more than half patients), hepatic, hepatic-renal insufficiency (HRI) and sepsis. The causes of death of people with NAFLD at the stages of compensation and subcompensation were myocardial infarction, cardiogenic shock, pulmonary embolism, mesenteric thrombosis and brain stroke; and in the stage of decompensation in most cases the hepatic and HRI were detected. In patients with a combination of ALD disease and NAFLD at the stage of LC, the causes of death were the following disorders at the stage of compensating: myocardial infarction, cardiogenic shock, pulmonary embolism, mesenteric thrombosis, brain stroke and pancreatic necrosis; at the stage of subcompensation, apart from the mentioned disorders, were: GIB and sepsis, and at the stage of decompensation there were myocardial infarction, cardiogenic shock, pulmonary embolism, mesenteric thrombosis, brain stroke, hepatic and HRI, GIB, sepsis, and hepatocellular carcinoma (5.7% of patients).**
***Conclusions*****. Patients with NAFLD at the stages of compensation and subcompensation of LC are more likely to have acute cardiovascular mortality than patients with ALD. Patients with a combination of ALD and NAFLD, in addition to acute cardiovascular mortality, have more often septicemia and HRI, and hepatocellular carcinoma is diagnosed.**
***Key words:*** *liver cirrhosis, alcoholic, non-alcoholic fatty liver disease, cause of death.*

## Аналіз причин смертності хворих на алкогольний цироз печінки у поєднанні з неалкогольною жировою хворобою печінки

***Н.Р. Матковська***

На сьогодні доведено, що близько 10% смертей серед осіб молодого і середнього віку пов'язані саме із вживанням спиртних напоїв. Алкоголь посідає третє місце серед причин смертності у молодих осіб після тютюнопаління та артеріальної гіпертензії та друге місце серед причин трансплантації печінки в Європі. В Україні смертність внаслідок алкогольної хвороби печінки (АХП) посіла друге місце у структурі причин смерті від хвороб органів травлення.
***Мета дослідження:*** вивчення особливості причин смерті осіб з АХП на стадії цирозу при поєднанні з неалкогольною хворобою печінки (НАЖХП) на підставі аналізу протоколів патологоанатомічного дослідження.
***Матеріали та методи.*** Проаналізовано 216 протоколів патологоанатомічного дослідження померлих внаслідок цирозу печінки (ЦП).
***Результати.*** Виявлено, що особи, які зловживали алкоголем, померли на стадії субкомпенсації та компенсації ЦП від панкреонекрозу, а на стадії декомпенсації – від шлунково-кишкової кровотечі (ШКК) (більше половини хворих), печінкової і печінково-ниркової недостатності та сепсису. Причинами смерті осіб з НАЖХП на стадіях компенсації та субкомпенсації стали інфаркт міокарда, кардіогенний шок, тромбоемболія легеневої артерії, мезентеріальний тромбоз та інсульт головного мозку, а на стадії декомпенсації у більшості – печінкова та печінково-ниркова недостатність. В осіб із поєднанням АХП та НАЖХП на стадії цирозу причинами смерті стали на стадії компенсації інфаркт міокарда, кардіогенний шок, тромбоемболія легеневої артерії, мезентеріальний тромбоз, інсульт головного мозку та панкреонекроз, на стадії субкомпенсації до таких причин приєдналися ШКК та сепсис, а на стадії декомпенсації – інфаркт міокарда, кардіогенний шок, тромбоемболія легеневої артерії, мезентеріальний тромбоз, інсульт головного мозку, печінкова та печінково-ниркова недостатність, ШКК, сепсис та гепатоцелюлярна карцинома (5,7% осіб).
***Заключення.*** У хворих на неалкогольну хворобу печінки (НАЖХП) на стадіях компенсації та субкомпенсації цирозу печінки частіше виникають гострі серцево-судинні летальні наслідки порівняно з пацієнтами з алкогольною хворобою печінки (АХП). В осіб у разі поєднання АХП та НАЖХП, окрім гострих серцево-судинних летальних наслідків, частіше виникає септичний стан та печінково-ниркова недостатність, а також у них виявлено гепатоцелюлярну карциному.
***Ключові слова:*** *алкогольна хвороба печінки, неалкогольна жирова хвороба печінки, причини смерті.*

## Анализ причин смертности у больных алкогольным циррозом печени при сочетании с неалкогольной жировой болезнью печени

***Н.Р. Матковская***

На сегодня доказано, что около 10% смертей среди лиц молодого и среднего возраста связаны именно с употреблением спиртных напитков. Алкоголь занимает третье место среди причин смертности молодых людей после курения и артериальной гипертензии и второе место среди причин трансплантации печени в Европе. В Украине смертность вследствие алкогольной болезни печени (АБП) заняла второе место в структуре причин смерти от болезней органов пищеварения.
***Цель исследования:*** изучение особенностей причин смерти лиц с АБП на стадии цирроза при сочетании с неалкогольной болезнью печени (НАЖБП) на основе анализа протоколов патологоанатомического исследования.

***Материалы и методы.*** Проанализировано 216 протоколов патологоанатомического исследования умерших от цирроза печени (ЦП).
***Результаты.*** Выявлено, что лица, которые злоупотребляли алкоголем, умерли на стадии субкомпенсации и компенсации ЦП от панкреонекроза, а на стадии декомпенсации – от желудочно-кишечного кровотечения (ЖКК) (более половины больных), печеночной и печеночно-почечной недостаточности и сепсиса. Причинами смерти лиц с НАЖБП на стадиях компенсации и субкомпенсации были инфаркт миокарда, кардиогенный шок, тромбоэмболия легочной артерии, мезентериальный тромбоз и инсульт головного мозга, а на стадии декомпенсации в большинстве – печеночная и печеночно-почечная недостаточность. У лиц с сочетанием АБП и НАЖБП на стадии цирроза причинами смерти стали на стадии компенсации инфаркт миокарда, кардиогенный шок, тромбоэмболия легочной артерии, мезентериальный тромбоз, инсульт головного мозга и панкреонекроз, на стадии субкомпенсации к таким причинам присоединились ЖКК и сепсис, а на стадии декомпенсации были инфаркт миокарда, кардиогенный шок, тромбоэмболия легочной артерии, мезентериальный тромбоз, инсульт головного мозга, печеночная и печеночно-почечная недостаточность, ЖКК, сепсис и гепатоцеллюлярная карцинома (5,7% умерших).
***Заключение.*** У больных с неалкогольной болезнью печени (НАЖБП) на стадиях компенсации и субкомпенсации цирроза печени чаще возникают острые сердечно-сосудистые летальные исходы по сравнению с пациентами с алкогольной болезнью печени (АБП). У лиц при сочетании АБП и НАЖБП, кроме острых сердечно-сосудистых летальных исходов, чаще возникает септическое состояние и печеночно-почечная недостаточность, а также у них выявлена гепатоцеллюлярная карцинома.
***Ключевые слова:*** *алкогольная болезнь печени, неалкогольная жировая болезнь печени, причины смерти.*

The mortality rate of the Ukrainian population is among the highest in Europe and in the world. Not only the maintenance of unsatisfactory indicators of the general coefficient and the intensity of mortality, but also their increase are observed. The average life expectancy is low, and according to European standards, it is very low and drops behind most developed countries. An average Ukrainian lives 10years less, and men even 15 years less, compared to people of developed countries [15, 18, 3]. Among the reasons that affect such indicators is the increase in the incidence of non-infectious diseases. According to WHO, 41 million people (71%) die annually from these disorders all over the world; 15 million of them die between 30 and 69 years old. The leading place in prevalence and mortality among non-infectious diseases belongs to cardiovascular diseases (stroke, heart attack) and malignant neoplasms [22]. Non-infectious diseases are the result of the combination of genetic, physiological, environmental and behavioural factors. Use of tobacco, lack of physical activity, malnutrition and alcohol abuse belong to them. Today, it has been proven that about 10% of deaths among young and middle-aged people relate to the consumption of alcoholic beverages. Alcohol is ranked third among the causes of mortality in young people after tobacco and arterial hypertension, and second place – among the causes of liver transplantation in Europe [1, 2, 19]. In Ukraine, mortality due to alcoholic liver disease (ALD) has taken second place in the structure of causes of death from diseases of the digestive system [7, 12].

Recently, attention has been attracted to the increase in the prevalence of another liver disorder – non-alcoholic fatty liver disease (NAFLD). It is registered in 20-35% of the adult population, both in industrialized and developing countries [17, 10, 14]. This prevalence is because of the asymptomatic course in the form of fatty hepatose, which, under adverse conditions, progresses to steatohepatitis and, subsequently, transforms into the liver cirrhosis (LC) [6, 11, 4, 13]. Patients with NAFLD, according to literature data, have an increased risk of hepatocellular carcinoma (HCC) [5, 16, 9]. The combination of NAFLD with other pathologies is prognostically unfavourable [20, 21, 8]. We couldn't find any publications on the mortality analysis of patients with ALD in combination with NAFLD.

***The objective:*** to study the peculiarities of the causes of death in patients with alcoholic liver disease at the stage of cirrhosis associated with non-alcoholic liver disease on the basis of the analysis of pathoanatomical research protocols.

## MATERIALS AND METHODS

216 protocols of the pathoanatomical study of the patients who died from LC have been analyzed on the basis of the pathoanatomical department of the Ivano-Frankivsk Regional Clinical Hospital for the period of 2005–2018. The average age of the patients was 54±13.4 years: women – 46.3±8.1 years old, men – 58.9±12.3 years old, the average duration of the disease – 6.3±1.7 years. By age, the patients were distributed as follows: 79 young people (53 of them were men, 26 – women), 103 middle-aged (76 men, 27 women), 34 elderly (23 men, 11 women). Among the deceased, 69 (31.9%) patients with ALD (Group I), 42 (19.4%) patients with NAFLD (Group II) and 105 (48.6%) persons with a combination of ALD and NAFLD (Group III).

Basing on the Child-Pugh score, the data are as follow: 6 (8.7%) deceased in Group I with stage A (IA Group), 9 deceased (13.0%) with stage B (IB Group), 54 (78.3%) persons with stage C (IC Group); Group II – 14 (42.9%) persons with stage A (IIA Group), 19 (45.2%)with stage B (IIB Group), 9 (11.9%) with stage C (IIC Group); Group III – 18 (17.1%) persons with stage A (IIIA Group), 34 (32.4%) with stage B (IIIB Group), 53 (50.5%) patients with stage C (III C Group).

The following formula was used to determine the body mass index (BMI): BMI=weight (kg)/height ($м^2$). To assess the fat depot, the thickness of the skin-fat fold over the triceps (TSFF) was determined using the Bass caliper.

The exclusion criteria were dead patients with detected liver cirrhosis of the viral, toxic (except alcohol) and autoimmune genesis, metabolic diseases of the liver. Statistical processing of the obtained results was carried out using the software package Statistica v. 12.0, StatSoft, USA and Microsoft Exel. The arithmetic average (M) and the standard deviation (SD) were used as the parameters of parametric statistics. To determine the significance of the differences between groups during the distribution, close to normal, the t-criterion Student was used. Statistically significant differences were considered at $p<0.05$.

## RESULTS

According to the results of the study, it was revealed that BMI in patients of IA+B, IIA+B, IIIA+B Groups significantly differed (21.43±1.62), (33.54±2.93), (29.57±2.41) kg/$м^2$, respectively ($p<0.05$). For patients of IC, II, III Groups, these indicators were (18.23±1.46), (26.72±2.65), (19.14±1.57) kg/$м^2$, respectively. A significant difference was found between the indicators of the BMI of the Group IIC and IC, IIIC Groups ($p<0.05$). TSFF in the patients of all groups decreased from stage A to stage C. The TSFF parameters were significantly different between IA+B, IIA+B, IIIA+B Groups and were (13.47±0.92) mm (22.97±1,49) mm, (18.54±1.31) mm ($p<0.05$). The TSFF of the deceased of Group IIC was (12.26±0.87) mm and significantly differed from such parameters in IC (6.79±0.43 mm) and IIIC (7.04±0.38 mm) Groups ($p<0.05$).

Pancreonecrosis was the cause of death of all patients with alcoholic LC with stages A and B, and in 16.7% (3 out of 18) and 2.9% (1 out of 34) persons with a combination of ALD and NAFLD at the stages of compensation A and B by Child-Pugh (Table). Gastrointestinal bleeding (GIB) caused death in 26.3% (5 out of 19), 26.5% (9 out of 34), 72.2% (39 out of 54), 22.2% (2 out of 9), and 7.6% (4 out of 53) persons of IIB, IIIB, IC, IIC and

**Causes of death of patients with alcoholic liver cirrhosis associated with non-alcoholic fatty liver disease**

| Causes of death | Class of LC by Child-Pugh score | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | A, abs/% | | | B, abs/% | | | C, abs/% | | |
| | Gr.I, n=6 | Gr.II, n=14 | Gr.III, n=18 | Gr.I, n=9 | Gr.II, n=19 | Gr.III, n=34 | Gr.I, n=54 | Gr.II, n=9 | Gr.III, n=53 |
| Pancreatic necrosis | 6/100 | - | 3/16.7 | 9/100 | - | 1/2.9 | - | - | - |
| Gastrointestinal bleeding | - | - | - | - | 5/26.3 | 9/26.5 | 39/72.2 | 2/22.2 | 4/7.6 |
| Hepatic insufficiency | - | - | - | - | - | 3/8.9 | 9/16.7 | 2/22.2 | 5/9.4 |
| Hepatic-renal failure | - | - | - | - | 2/10.5 | 3/8.9 | 4/7.4 | 1/11.1 | 8/15.1 |
| Sepsis | - | - | - | - | - | 1/2.9 | 2/3.7 | 1/11.1 | 7/13.2 |
| Myocardial infarction | - | 4/28.6 | 4/22.2 | - | 4/21.1 | 5/14.7 | - | 2/22.2 | 6/11.3 |
| Thromboembolism of the pulmonary artery | - | - | 2/11.1 | | - | 2/5.8 | | | 5/9.4 |
| Cardiogenic shock | - | 2/14.3 | 2/11.1 | | 1/5.3 | 2/5.8 | | | 2/3.8 |
| Mesenteric thrombosis | - | 2/14.3 | 3/16.7 | - | 1/5.3 | 3/8.9 | - | - | 4/7.6 |
| Stroke of the brain | | 6/42.8 | 4/22.2 | - | 6/31.5 | 5/14.7 | - | 1/11.1 | 6/11.3 |
| HCC | - | - | - | - | - | - | - | - | 6/11.3 |

IIIC Groups, respectively. Hepatic insufficiency was detected in 8.9% (3 out of 34), 16.7% (9 out of 54), 22.2% (2 out of 9) and 9.4% (5 out of 53) persons of IIIB, IC, IIC and IIIC Groups respectively. The hepatic-renal failure was revealed in 10.5% (2 out of 19), 8.9% (3 out of 34), 7.4% (4 out of 54), 11.1% (1 out of 9) and 15.1% (8 out of 53) persons of IIB, IIIB, IC, IIC and IIIC Groups, respectively. A septic state at the stages of subcompensation and decompensation was revealed in 2.9% (1 out of 34), 3.7% (2 out of 54), 11.1% (1 out of 9) and 13.2% (7 out of 53) persons of IIIB, IC, IIC and IIIC Groups, respectively.

Acute heart failure caused the death of 30.9% (13 out of 42) people with NAFLD and 28.6% (30 out of 105) persons with ALC in combination with NAFLD. In particular, myocardial infarction was detected in 28.6% (4 out of 14), 22.2% (4 out of 18), 21.1% (4 out of 19), 14.7% (5 out of 34), 22.2% (2 out of 9) and 11.3% (6 out of 53) cases in IIA, IIIA, IIB, IIIB, IIC and IIIC Groups respectively; thromboembolia of the pulmonary artery (TEPA) was in 11.1% (2 out of 18), 5, 8% (2 out of 34) and 9.4% (5 out of 53) persons of IIIA, IIIB and IIIC Groups respectively; cardiogenic shock caused the death in 14.3% (2 out of 14), 11.1% (2 out of 18) , 5.3% (1 out of 19), 5.8% (2 out of 34) and 3.8% (2 out of 53) persons of IIA, IIIA, IIB, IIIB, IIC and IIIC Groups, respectively. Among acute vascular disorders, the mesenteric thrombosis was detected in 14.3% (2 out of 14), 16.7% (3 out of 18), 5.3% (1 out of 19), 8.9% (3 out of 34) and 7, 6% (4 out of 53) patients of IIA, IIIA, IIB, IIIB and IIIC Groups, respectively; and a brain stroke – in 42.8% (6 out of 14), 22.2% (4 of 18), 31.5% (6 out of 19), 14.7% (5 out of 34), 11.1% (1 out of 9) and 11.3% (6 out of 53) persons of IIA, IIIA, IIB, IIIB and IIIC Groups, respectively. In 11.3% (6 out of 53) persons of Group IIIC the cause of death was the hepatocellular carcinoma (HCC).

Pancreatic necrosis was the cause of death in patients with ALD in 21.7% (15 out of 69) cases with stage A and B; 56.5% (39 out of 69) patients with stage C died from GIB; 13.1% (9 out of 69) and 5.8% (4 out of 69) patients with stage C had hepatic and hepatic-renal insufficiency respectively; 2.9% (2 out of 69) patients with stage C had sepsis.

The cause of death of patients with NAFLD at the stage of LC were: GIB in 11.8% (5 out of 42) and 2.4% (1 out of 42) persons with subcompensation and decompensation stages, respectively; hepatic insufficiency in 7.1% (3 out of 42) persons with stage C; hepatic-renal insufficiency in 4.8% (2 out of 42) and in 9.5% (4 of 42) patients with stages B and C, respectively; sepsis in 2.4% (1 out of 42) persons with stage C. In the deceased of Group II, among the cardiovascular diseases with lethal outcomes were: myocardial infarction in 9.5% (4 out of 42) and 9.5% (4 out of 42); cardiogenic shock in 4.8% (2 out of 42 42) and 2.4% (1 out of 42); mesenteric thrombosis in 4.8% (2 out of 42) and 2.4% (1 out of 42); brain stroke in 14.3% (6 out of 42) and 14.3% (6 out of 42) of patients with stages A and B respectively, and with stage C, myocardial infarction and stroke of the brain were in 22.2% (2 from 9) and 11.1% (1 out of 9) persons, respectively.

Among the causes of death in patients with ALD associated with NAFLD were pancreatic necrosis in 2.8% (3 out of 105) and 1% (1 out of 105) patients with stages A and B, respectively; GIB in 8.6% (9 out of 105 ) and 3.8% (4 out of 105) patients with Stages B and C, respectively; hepatic insufficiency in 2.8% (3 out of 105) and 4.8% (5 out of 105); liver and kidney insufficiency in 2,8% (3 out of 105) and 7.6% (8 out of 105) persons with stages B and C respectively and sepsis in 1% (1 out of 105) and 6.6% (7 out of 105) patients with stages B and C respectively.

With regard to cardiovascular mortality in such patients, the myocardial infarction was registered in 3.8% (4 out of 105), 4.8% (5 out of 105) and 5.7% (6 out of 105) patients with stages A, B and C, respectively; cardiogenic shock was found in 1.9% (2 out of 105), 1.9% (2 out of 105) and 1.9% (2 out of 105) persons with stages A, B and C, respectively; mesenteric thrombosis was in 2.8% (3 out of 105), 2.8% (3 out of 105) and 3.8% (4 out of 105) cases at the stages A, B and C, respectively; the brain stroke was in 3, 8% (4 out of 105), 4.8% (5 out of 105) and 5.7% (6 out of 105) persons with stages A, B and C, respectively. HCC was detected in 5.7% (6 out of 105) patients suffering from ALD associated with NAFLD with stage C.

Thus, when comparing the analysis of the pathoanatomical study protocols of patients with ALD, NAFLD and a combination of ALD with NAFLD at the stage of the LC, it was found that people who abused alcohol died at the stage of subcompensation and compensation from pancreatic necrosis, and at the stage of decompensation – from the GIB (more than half patients), hepatic, hepatic-renal insufficiency and sepsis. The causes of death of people with NAFLD at the stages of compensation and subcompensation were myocardial infarction, cardiogenic shock, pulmonary embolism, mesenteric thrombosis and brain stroke; and in the stage of decompensation in most cases the hepatic and hepatic-renal insufficiency were detected. In patients with a combination of ALD and NAFLD at the stage of LC, the causes of

death were the following disorders at the stage of compensating: myocardial infarction, cardiogenic shock, pulmonary embolism, mesenteric thrombosis, brain stroke and pancreatic necrosis; at the stage of subcompensation, apart from the mentioned disorders, were: GIB and sepsis, and at the stage of decompensation there were myocardial infarction, cardiogenic shock, pulmonary embolism, mesenteric thrombosis, brain stroke, hepatic and hepatic-renal insufficiency, GIB, sepsis, and HCC.

## CONCLUSIONS

Patients with NAFLD at the stages of compensation and subcompensation of LC are more likely to have acute cardiovascular mortality than patients with ALD. Patients with a combination of ALD and NAFLD, in addition to acute cardiovascular mortality, have more often septicemia and hepatic-renal insufficiency, and in 5.7% of patients HCC is diagnosed.

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