ISSN: 2692-5400
DOI: 10.33552/AJGH.2021.03.000557
Academic Journal of Gastroenterology & Hepatology
Iris Publishers

Research Article

Comparative Analysis of Risk Factors for Liver Cirrhosis in the World

Ludmila Radkevich* and Dariya Radkevich

Center for Theoretical Problems of Physicochemical Pharmacology, Russian Academy of Sciences, Russia

***Corresponding author:** Ludmila Radkevich, Center for Theoretical Problems of Physicochemical Pharmacology, Russian Academy of Sciences, Moscow, Russia.

Received Date: November 23, 2021

Published Date: December 14, 2021

Introduction

Objective: To investigate risk factors for liver cirrhosis in two groups of countries of the world with the maximum and minimum burden of liver cirrhosis.

Materials and Methods: A comparative analysis of the risk factors and disease burden of several NCDs in 2004 (GBD 2004) was performed using the Mann-Whitney U test in two groups of countries of the world, 21 countries in each group.

Results: In accordance with the set goal, in our studies it was found that in group 1 of countries in comparison with group 2 of countries, the burden of Cirrhosis of the liver is 12 times higher (p≤0,001). The burden of comorbid liver cirrhosis diseases - alcoholism and cardiovascular disease was also 2 times higher in group 1 of countries in comparison with group 2 of countries (p≤0, 001). The burden of diabetes was not statistically significant between groups 1 and 2 countries. Major risk factors for liver cirrhosis - The burden of viral hepatitis B and C did not differ statistically between groups 1 and 2. Consumption levels of food, including animal fats, red meat, the energy of animal products and total energy was on average 1.5 - 2 times higher in group 2 countries with a low burden of liver cirrhosis and comorbid diseases (p≤0.003). Consumption of all types of alcoholic beverages: pure alcohol, spirits, wine and beer did not differ statistically between the two study groups of countries (p = 0.7).

Conclusion: The results obtained do not allow us to draw a conclusion about the risk factors for liver cirrhosis in this study. Further research on risk factors for liver cirrhosis is needed.

Keywords: Cirrhosis of eternity; Cardiovascular diseases; Diabetes mellitus; Alcoholism; Risk factors; Levels of alcohol, Food consumption

Abbreviations: AB: Alcoholic Beverage; AP: Animal Products; BMI: Body Mass Index; BP: Blood Pressure; CAB: Alcoholic Beverage Consumption; CD: Communicable Maternal, Perinatal Diseases; Cho: Blood Cholesterol; CL: Consumption Level of Selected Foods; CHD: Coronary Heart Disease; CV: Cereals and Vegetables; CVD: Cardiovascular Diseases; DALY: The Disability-Adjusted Life Year; DRD2 and DRD3: Genes Encode Type 2 and 3 Dopamine Receptors; EEI: Ecological Efficiency Index; FAO: Food and Agriculture Organization of the United Nations; FS: Fruits and Sweeteners; ICD-10: Codes - Is the 10th Revision of the International Statistical Classification of Diseases; GBD: Global Burden Diseases; GDP: Domestic Gross Product; Glu: Blood Glucose; HPI: Happiness Index; IHD: Index of Human Development; LE: Life Expectancy for Men and Women; LPA: Low Physical Activity, LMA: Linear Multiple Regression Analysis; M: Male; NS: Nutritional Structure; MSP: Metabolic Syndrome Predictors; NCD: Non-Communicable Diseases; P: Person; QOL: Quality of Life; QR: Quartile Range; RE: Rating Educations; SNP: SNP Market - Online Store of Electronics and Equipment; SLC6A4: Encodes a Sodium-Dependent Transmembrane Transporter a Neurotransmitter Serotonin Reuptake Protein; TDC: Total Daily Consumption; UN: United Nations; UV: Ultraviolet Level; WHO: World Health Organization

Introduction

Liver cirrhosis is the final pathological result of various chronic liver diseases. Many types of cells, cytokines and miRNAs are involved in the initiation and progression of liver cirrhosis. Defenestration and capillarization of liver sinusoidal endothelial

cells are major contributing factors to hepatic dysfunction in liver cirrhosis. Activated Kupffer cells destroy hepatocytes and stimulate the activation of hepatic stellate cells (HSCs). Recently, miRNAs as a post-transcriptional regulator have been found to play a key role in fibrosis and cirrhosis [1]. Cirrhosis is the 12th leading cause of death in the United States. Newer research has established that early cirrhosis may be reversible. When clinical signs, symptoms, or abnormal liver function tests are discovered, further evaluation should be pursued promptly. Only one in three people with cirrhosis knows they have it. Most patients with cirrhosis remain asymptomatic until the onset of decompensation. The most common causes of cirrhosis are viral hepatitis, alcoholic liver disease, and nonalcoholic steatohepatitis [2].

Alcohol is a major risk factor for liver cirrhosis with risk increasing exponentially. Women may be at higher risk compared to men even with little alcohol consumption. More high-quality research is necessary to elucidate the role of other risk factors, such as genetic vulnerability, body weight, metabolic risk factors, and drinking patterns over the life course [3]. Alcohol use disorders cause significant morbidity and early mortality but remain largely unexplored. Medicines are used much less. Excessive drinking is a significant cause of mortality, morbidity, and social problems in many countries. Mean baseline alcohol consumption was 244 g/week (30.5 standard UK units) among the studies that reported these data. Authors found moderate-quality evidence that brief interventions can reduce alcohol consumption in hazardous and harmful drinkers compared to minimal or no intervention [4,5].

Among men, conventional epidemiology showed that self-reported alcohol intake had U-shaped associations with the incidence of ischaemic stroke. men who reported drinking about 100 g of alcohol per week (one to two drinks per day) had lower risks of all three diseases than non-drinkers or heavier drinkers [6]. About 2 billion people consume alcohol worldwide and upwards of 75 million are diagnosed with alcohol-use disorders and are at risk of alcohol-associated liver disease [7]. Alcohol consumption had a significantly larger impact on mortality of liver cirrhosis compared with morbidity. Also, the same amount of average consumption was related to a higher risk of liver cirrhosis in women than in men [8]. In Western countries, non-alcoholic fatty liver disease is becoming the most common indication for liver transplantation [9].

Cirrhosis with portal hypertension and related complications are associated with a high mortality. Excess of circulating vasodilators and cardio depressive substances lead to a hyperdynamic circulation with changed myocardial structure and function. The entity cirrhotic cardiomyopathy seems to be involved in different aspects of hepatic decompensation, which focuses on new targets of treatment. Areas covered [10]. Patients suffering from liver cirrhosis (LC) frequently require non-hepatic abdominal surgery, even before liver transplantation. LC is an important risk factor itself for surgery, due to the higher than average associated morbidity and mortality [11]. Alcohol abuse has been estimated to be the third largest risk factor for disease and disability in the world [12]. Despite extensive research into understanding the pathophysiology of liver disease, there are still no targeted treatments available [13].

Patients who have undergone liver transplants for alcoholic liver disease have a higher risk of cardiovascular and cerebrovascular events, and malignant tumors [14]. Authors call for attention to defining safe limits for ethanol consumption in different demographic regions of the world [15]. The authors analyze the strengths of alcohol models and summarize the results of alcohol-induced liver and other organ damage [16]. The infraslow acetylator genotypes NAT2 will have the greatest impact on the increased risk of anti-TB drugs ATDILI [17]. A higher mortality rate from liver cirrhosis was found in countries with a high proportion of rapid NAT2 phenotypes [18,19]. Despite extensive experience and knowledge, the risk factors for liver cirrhosis remain not fully understood. Safe doses and timing of their use are a big problem.

Material and Method

Study design: statistical analysis of observations. For the purposes of the study, a database was created on the burden of NCDs, cardiovascular diseases, diabetes, alcoholism, cancer, and cirrhosis of the liver (ICD-10 codes). Two groups of countries were created:

Group 1 - countries with the highest burden of liver cirrhosis - 21 countries.

Group 2 - countries with the lowest burden of liver cirrhosis - 21 countries.

Table 1: Country Groups 1 & 2 – Lists.

Countries male age st 2004	IPC 2000	lat°	UV rad J/m2 2004	% NAT2	Cirrhosis of the liver	Beverages, Alcoholic 2005	Wine 2005	Beer 2005	AB amount 2005	Pure alcoholmale 2018
1 group of countries										
Kyrgyzstan	1 644	43,2	3094	74	1 321	12	2	19	33	10,8
R Moldova	1 840	46,8	1910		1 275	65	15	35	115	18,3
Guatemala	4 812	14,6	5141		1 103	4	0	21	25	4
Sri Lanka	4 423	6,6	5264		979	1	0	7	8	6,8

Ukraine	3 803	50,2	1843		972	23	12	110	145	14
Turkmenistan	4 227	37,6	3164	56	931	0	14	8	22	8,4
Nicaragua	2 739	12,1	5078	62	924	6	0	30	36	8,5
Bolivia	3 497	16,3	5344		880	5	2	59	66	6,8
Mexico	10 429	19,3	4974	70	869	2	0	147	149	8
Kazakhstan	7 888	43,2	2257	65	763	8	7	63	78	7,9
Haiti	1 379	18,1	5016		757	25	0	0	25	4,5
Russian F	6 825	55,5	1795	46	741	29	17	158	204	19,1
Romania	5 873	43,5	2071		741	9	58	170	237	18,6
Honduras	2 638	14,3	4924		699	7	1	42	50	6,1
Uzbekistan	1 984	41,2	3172	68	677	5	4	9	18	4,5
Sudan	1 812	19,3	5783		677	1	0	1	2	0,9
Guyana	3 577	6,5	5203		640	17	0	50	67	11
Mauritius	8 780	20,3	5055		573	2	4	81	87	7
Slovenia	18 036	46,1	2256		567	7	35	221	263	18,4
Peru	5 202	12,1	5906		560	11	5	65	81	9,8
Korea R	18 083	37,3	2535	90	557	14	1	99	114	14,7
2 group of countries										
Ireland	30 155	51,8	1509		97	22	39	432	493	19,6
Malta	19 411	35,9	3091		96	8	57	104	169	12,4
Australia	26 406	34	3206	43	95	5	60	240	305	16
Turkey	9 576	41,1	2924		95	2	1	30	33	3,6
Norway	36 928	59,6	1439	44	93	7	43	152	202	11,2
Saudi Arabia	34 140	21,3	5384		93	0	0	0	0	0,3
Algeria	8 093	36,4	3253		91	0	0	10	10	1,6
Greece	19 504	37,9	2753	34	86	12	68	89	169	16,2
Jordan	5 735	31,9	4026		85	0	0	5	5	1,2
The Netherlands	31 573	52,2	1662	42	80	11	53	227	291	14,8
Brunei	65 035	4,6	5148		80	0	0	3	3	0,7
Cape Verde	3 040	14,5	5372		77	1	21	70	92	8,8
Sweden	29 258	59,2	1587	32	72	10	40	143	193	13,7
Fiji	5 290	18,1	4431		68	2	3	63	68	5,5
Israel	24 942	32,5	3682	38	65	6	3	42	51	6,6
Cyprus	21 696	35,2	3439		58	9	51	119	179	16,9
Iran (Islamic Republic of)	9 436	35,7	4038		57	0	0	2	2	1,8
New Zealand	21 510	36,5	2487	42	48	10	24	213	247	16,4

Kuwait	55 421	29,2	4214		42	0	0	2	2	0
Iceland	29 498	65,2	957		14	7	26	177	210	13,9
Albania	4 027	41,2	2542		-	3	13	41	57	11,6

Legend	
IPC	Per capita income
lat°	Geographic latitude
UV rad J/m2 2004	in the capitals of the countries
% NAT2	% of fast NAT2 acetylipres in countries
Cirrhosis of the liver	Disease incidence (DALY) in countries
Pure alcohol l / person / year	
Alcoholic drinks	g / person / day
AB amount	Total consumption of cream alcohol, wine and beer

Disease burden (DALY) data for men in 21 countries,

Age-standardized were selected from the GBD 2004 database [20]. To characterize the "quality of life" (QOL) in the countries a number of indicators were used: income per capita or gross domestic product (GDP) in 2000 - 2016 (US dollars per person per year) [21]; the geographical position of the countries by latitude and the level of ultraviolet radiation in the capital (UV) (J/m2 2004) [22]; life expectancy for men and women (LE) [23]; access to good health care, clean water, and clean air [24]; Happiness Index (IH) in 2016 [25]. Body mass index (BMI) ≥ 25 kg/m2 and ≥ 30 kg/m2 have been studied as predictors of metabolic syndrome (MSP) - the percentage of men and women in the country who are overweight and obese; the % of population with blood cholesterol (Chol ≥ 5.0 mmol/L and ≥ 6.2 mmol/L); blood glucose level (Glu ≥ 7.0 mmol/L); blood pressure (BP ≥ 140/90 mm Hg); low physical activity (LPA) ≤ 60 min/day walking [26]. The daily level of food consumption (TDC) (g/person/day) (50 types of products) for each country was selected from the FAO database for 1992 - 2005 [27]. The nutritional structure (NS) of the countries is presented in the form of 4 blocks in absolute and percentage terms (TDC): 1 - products of animal origin (AP); 2 - cereals and vegetables (CV); 3 - fruits and sweeteners (FS); 4 - alcoholic beverages (AB) [27]. Statistical analysis of the study results was performed using Mann-Whitney-Wilcoxon U-criterion. U is the numerical value of the Mann-Whitney test. The central tendency in the sample data distribution was represented by the median with a quartile range and a mean with a standard deviation. The variance of the data in the samples was estimated using a quartile range (QR) between the first and third quartiles, that is, between the 25th and 75th percentiles. The level of statistical significance, reflecting the degree of confidence in the conclusion about the differences in the indicators of groups 1 and 2 countries: two levels of accuracy were estimated: (1) $p \leq 0.01$, 1% error probability; (2) $p \leq 0.05$, 5% error probability. The Bonferoni correction was also used to assess the significance of the study results, taking into account the two hypotheses $p \leq 0.025$ for multiple comparisons. Analysis of the Burden of Cardiovascular Diseases, Prostate and Breast Cancer and Alcoholism in Countries with High and Low Daily Alcohol Consumption 14 Citation: Ludmila Alexandrovna Radkevich and Daraya Andreyevna Radkevich. "Analysis of the Burden of Cardiovascular Diseases, Prostate and Breast Cancer and Alcoholism in Countries with High and Low Daily Alcohol Consumption". EC Pharmacology and Toxicology 9.10 (2021): 12-25. NCD burden and MSP dependence on TDC products, including CAB, were analyzed using Multiple Linear Regression Analysis for independent variables (LMA). Standardized NCD burden of disease indicators: cardiovascular, prostate cancer, breast cancer, and alcoholism from 2004 for 158 countries [20] and MSP predictors [26] were used as the dependent variable, LMA. Daily blocks of TDC: AP (animal products), CV (cereals and vegetables), FS (fruits and sweeteners) and AB (alcoholic beverages) for 158 countries (2003 - 2005) were used as predictors (independent variables) [27]. A stepwise procedure of inclusion of independent variables was applied to obtain the best regression equations containing the minimum number of predictors statistically significantly associated with the dependent variable. The quality of the regression model was assessed using multiple correlation coefficient (R1), coefficient of determination (R2), Fdistribution, t-criteria for regression coefficients, and residuals analysis. The residuals in all models had a normal distribution. Analysis of the values and signs of the coefficients of β* and β regression equations allowed us to estimate the contribution of UP of different products to the values of the specified types of NCD and MS predictors. All calculations were performed using the program STATISTICA (version 13).

Result

We performed an analysis of risk factors for liver cirrhosis based on a comparison of quality of life, incidence of liver cirrhosis and comorbid pathologies, metabolic syndrome, and levels of food consumption, including alcoholic beverages, in two groups of countries in the world with the highest and lowest burden of liver

cirrhosis.Group 1 includes 21 countries with the highest burden of liver cirrhosis in the world in 2004 [GBD] (Table 1).

Group 2 shows the minimum burden of liver cirrhosis in 21 countries of the world in 2004 [GBD, Geneva, 2009] (Table 1).

The burden (DALY) of liver cirrhosis in group 1 was 12 times higher than that of liver cirrhosis in group 2 (p≤0.001) (Table 2).

In Group 1, the burden of cirrhosis was 819 ± 222 (Mean 1 ± Std. Dev. 1) and 757 ± 254 (Median 1 ± Quartile 1) (Table 2).

In group 2 countries, the burden of liver cirrhosis was 71 ± 27 (Mean 2 ± Std.Dev.2) and 80 ± 34 (Median 2 ± Quartile 2) (Table 2).

In Group 1 countries, the highest burden of cirrhosis was in 3 countries: Kyrgyzstan (1321 DALYs),

R Moldova (1275 DALY) and Guatemala (1103 DALY). In group 2, the minimum burden (DALY)) of liver cirrhosis was in 3 countries: Kuwait (42 DALYs), Iceland (14 DALYs), Albania (0 DALYs) (Table 1).

Quality of life in 1 and 2 groups of countries

The countries of the 1st group were 4 times poorer than the countries of the 2nd group. The per capita income in the 1st group of countries was 4 times lower than the 2nd group of countries (p≤0.001) (Table 2). The geographic latitude and the level of ultraviolet radiation in the capitals of the countries of groups 1 and 2 did not differ statistically (p = 0.3). Wherein, The 1st group of countries was located 20 ° east of the Greenwich meridian compared to the 2nd group of countries (p≤0.010) (Table 2). In the 1st group of countries, social conditions were 1.5 - 2 times worse: prosperity, education, social capital, corruption, health care, clean water and air, environmental safety, Human Development Index and Happiness Index (p≤0.01) (Table 2). Life expectancy in group 1 of countries for women was 7 years, for men it was 10 years shorter than group 2 of countries (p≤0.001) (Table 2). In group 1, countries statistically significantly belonged to the NAT2 phenotype of rapid acetylation, in contrast to group 2 countries (p≤0.001) (Table 2).

Table 2: Comparative analysis of the quality of life, the burden of NCDs and the metabolic syndrome (Mann-Whitney U-test).

	U	Z	p-value	Mean 1	Median 1	Quartile 1	Mean 2	Median 2	Quartile
The quality of life									
IPC 2000	49,00	- 4,30	0,0000	5690	4227	4187	23365	21696	20719
G I Gini Index 2021	152,00	- 0,80	0,4214	1	1	0	1	1	0
lat°	176,00	- 1,11	0,2684	29	20	29	37	36	9
UV rad J/m2 2004	168,00	1,31	0,1908	3895	4924	2884	3197	3206	1551
lon°	118,00	2,57	0,0103	65	68	43	45	30	31
Prosperity Rating	114,00	2,49	0,0127	74	72	27	43	39	66
Rating Educations	88,00	3,17	0,0015	71	72	35	37	30	59
Rating of the Social capital	161,00	1,26	0,2059	69	72	47	54	44	92
Rank of corruption 2016	48,00	4,09	0,0000	114	124	51	46	42	56
HPI 2016	93,00	- 2,53	0,0114	5,486	5,756	0,880	6,369	6,434	1,924
IHD Index of human development	76,50	- 3,61	0,0003	0,756	0,739	0,096	0,881	0,916	0,157
EEI Ecological efficiency index	54,00	- 4,06	0,0000	48	50	8	66	67	21
Access to the street. medicine1990	37,50	- 3,91	0,0001	79	75	17	96	100	8
Access to clean water1990	78,50	- 2,96	0,0030	68	71	43	90	99	16
Air pollution for children under 5 years old 2004	113,00	2,33	0,0198	81	35	64	19	1	46
female life expectancy	51,50	- 4,24	0,0000	72	73	5	80	81	5
male life expectancy	46,50	- 4,36	0,0000	66	67	7	75	76	4
Gender 2008	166,50	1,35	0,1784	6	6	4	5	5	1
% NAT2 8/7	-	3,18	0,0015	66	67	13	39	42	9
Burden of disease DALY									
M Death	43,00	4,45	0,0000	2080	1331	575	774	657	442
All Causes	36,00	4,63	0,0000	25544	24450	9658	13988	11647	7117
Infectious and parasitic diseases	67,00	3,85	0,0001	2853	2260	2071	702	303	586

Tuberculosis	43,00	4,45	0,0000	648	472	519	142	12	92
Hepatitis B (g)	140,00	2,01	0,0442	41	17	45	14	8	10
Hepatitis C (g)	208,00	- 0,30	0,7628	7	2	7	6	5	9
NCD Noncommunicable diseases	39,00	4,55	0,0000	15054	14597	3974	10339	9536	3893
Liver cancer	115,00	2,64	0,0083	85	59	53	49	36	24
Diabetes mellitus	162,00	1,46	0,1446	446	412	281	346	308	205
Alcohol use disorders	98,00	3,07	0,0021	955	951	722	448	378	405
Cardiovascular diseases	107,00	2,84	0,0045	4363	4120	3365	2537	2028	2305
Hypertensive heart disease	112,00	2,72	0,0066	348	259	277	149	40	164
Ischaemic heart disease	152,00	1,71	0,0872	2147	1735	2330	1288	1047	1159
Cerebrovascular disease	90,00	3,27	0,0011	1124	1118	796	593	404	375
Cirrhosis of the liver	-	5,53	0,0000	819	757	254	71	80	34
Nephritis and nephrosis	90,00	3,27	0,0011	255	209	261	103	54	107
Self-inflicted injuries	108,00	2,82	0,0048	516	450	445	206	168	271
MS Metabolic syndrome predictors									
Male BMI>25 (kg / m2)	87,00	- 3,35	0,0008	44	45	12	59	62	10
Male BMI>30(kg / m2)	92,50	- 3,21	0,0013	13	13	6	22	23	6
Male ch > 5.0 (mmol / L)	62,00	- 3,97	0,0001	36	34	18	53	56	13
Male ch > 6.2(mmol / L)	69,00	- 3,80	0,0001	8	7	6	15	15	7
Male glu > 7.0 (mmol / L)	143,50	- 1,92	0,0543	10	10	3	11	11	3
Male BP >140/90(mm Hg	154,00	1,66	0,0969	33	31	10	29	29	8
Male LA <60 minutes / day walking	30,00	- 2,21	0,0274	27	28	11	41	46	24

Legend	
IPC 2000	Per capita income
G I	Gini Index 2021
lat°	Geographic latitude
UV rad J/m2 2004	in the capitals of the countries
lon°	Geographic
IHD	ndex of human development
EEI	Ecological efficiency index
HPI	Happiness index
% NAT2 8/7	% of fast NAT2 acetylipres in countries
MS	Metabolic syndrome predictors
DALY	Burden of disease per 100,000 population
BM	Body Mass Index
Ch	Blood cholesterol
Glu	Blood glucose
BP	Blood pressure kprvi
LA	Low physical activity

Disease burden in countries 1 and 2

In the 1st group of countries, the overall mortality was 3 times higher, and the overall morbidity was in 2 higher in comparison with the 2nd group of countries (p≤0.001) (Table 2).

Infectious morbidity in the 1st and 2nd groups of countries

In the first group of countries, in comparison with the second group of countries, the burden of Infectious and parasitic diseases

was 4 times higher (p≤0.001); including 3 times higher burden of Hepatitis B (g) (p≤0.044); there was no statistical difference in the burden of Hepatitis C (g) (p = 0.8) and was 4 times the burden of Tuberculosis (p≤0.001) (Table 2).

Non-communicable morbidity in groups 1 and 2

Group 1 compared to Group 2 has 1.5 times the NCD burden (p≤0.001); 1.7 times the burden of liver cancer (p≤0.008); no statistically significant difference in the burden of diabetes mellitus (p = 0.15); 2.1 times higher burden of Alcohol use disorders (p≤0.002); double the burden of Cardiovascular diseases, Hypertensive heart disease and Cerebrovascular disease (p≤0.003); 12 times the burden of Cirrhosis of the liver (p≤0.001); 2.5 times higher burden of Nephritis and nephrosis (p≤0.001) and 2.5 times higher burden of Self-inflicted injuries (p≤0.005) (Table 2), (Figures 1-4) Predictors of Metabolic Syndrome in Groups 1 and 2 In the 1st group of countries, in comparison with the 2nd group of countries, the number (%) of men with disorders of the predictors of Metabolic Syndrome (p≤0,001) was on average 1.5 - 2 times lower (Table 2). In the 1st group of countries, in comparison with the 2nd group of countries, there were 1.5 times less men with overweight, 2 times less men with obesity and hyperlipidemia, as well as 1, 5 times fewer men with low physical activity (p≤0.001). In the 1st group of countries there was no statistical difference from the 2nd group of countries in the number of men with hyperglycemia and hypertension in the countries (p = 0.1) (Table 2).

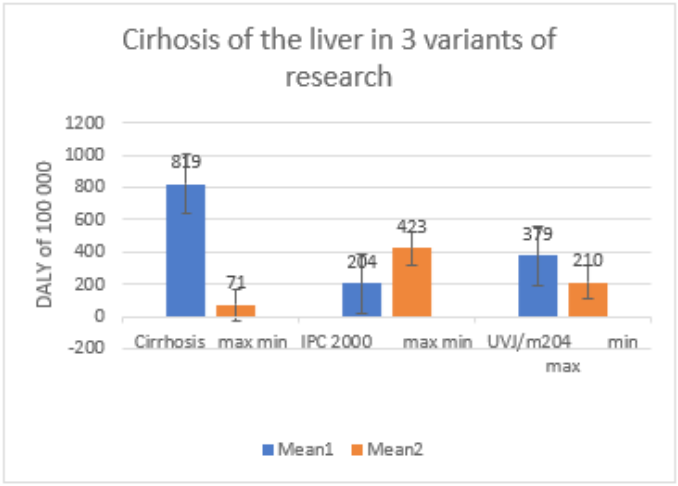

Figure 1: Burden of cirrhosis of the liver in Maxi and Mini countries: 2- Burden of cirrhosis of the liver in Maxi and Mini countries; 3. Burden of cirrhosis of the liver in countries with UV mini maxi.

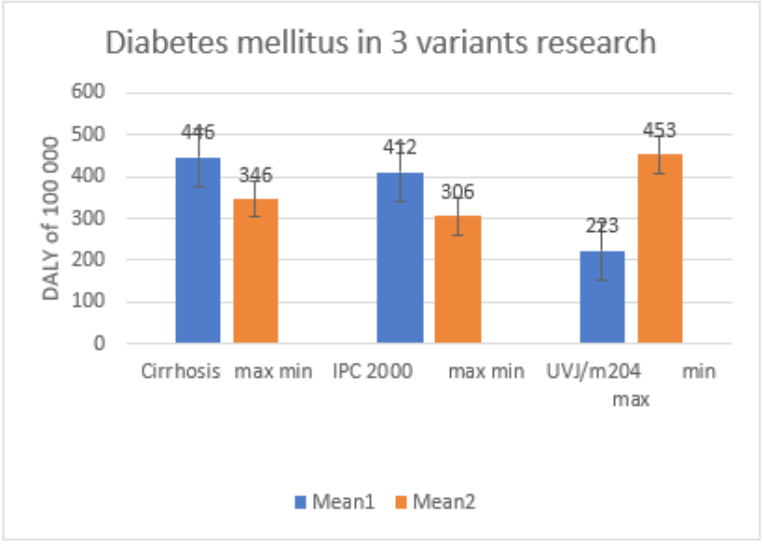

Figure 2: Burden of cardiovascular disease in countries with maxi and mini cirrhosis: 2- Burden of cardiovascular disease in countries with maxi and mini income; 3. Burden of Cardiovascular Disease in UV Mini Maxi Countries.

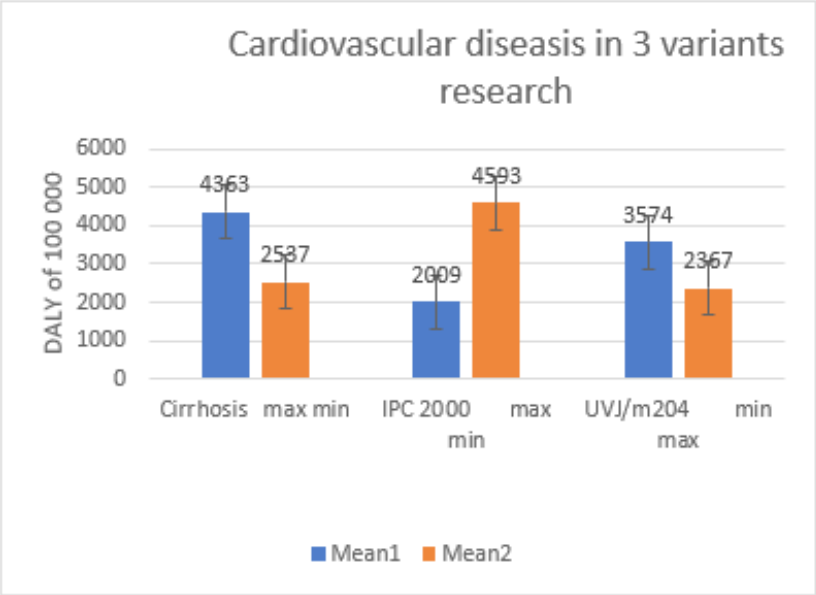

Figure 3: Burden of diabetes in countries with maxi and mini cirrhosis: 2 - diabetes burden in countries with maxi and mini income; 3. The burden of diabetes in countries with UV mini maxi.

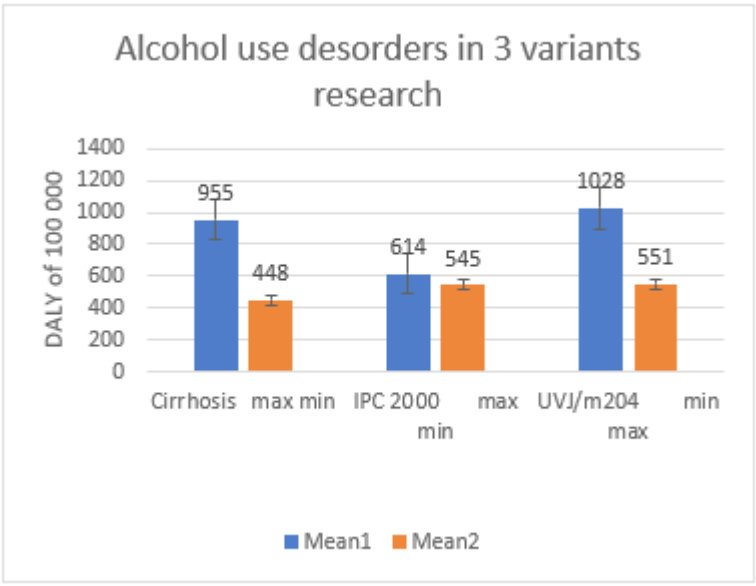

Figure 4: Burden of alcoholism in countries with maxi and mini cirrhosis: 2- alcoholism burden in countries with maxi and mini income; 3. The burden of alcoholism in countries with UV mini maxi.

Consumption Levels of Food, Including Alcoholic Beverages and Nutrients in Group 1 and 2 Countries

Food consumption levels

In group 1 of countries, in comparison with the second group of countries, the total daily food consumption was 1.3 times lower ($p \leq 0.022$); 1.3 times lower consumption of animal products ($p \leq 0.042$) *; there was no statistical difference between the groups of countries in the level of consumption of cereals and vegetables ($p = 0.3$) and alcoholic beverages (alcohol, spirits, wine and beer ($p = 0.5$) and was 1.5 times lower in consumption of fruits, coffee and sweeteners ($p \leq 0.001$) (Table 3).

Table 3: Comparative analysis of the levels of consumption of food, alcohol, and nutrients in the countries of the 1st and 2nd groups (Mann-Whitney U-test) (Figure 1). Per capita income and the general level of food consumption in the 1st and 2nd group of countries.

	U	Z	p-value	Mean	Median	Quartile	Mean	Median	Quartile
Total CL 2003-05	-	-	10,000						
AP	129,00	- 2,29	0,0221	1548	1514	1031	1957	2109	635
Bovine Meat	182,00	- 0,96	0,3391	31	27	36	40	34	44
Pigmeat	152,00	- 1,71	0,0872	27	12	30	51	53	58
Mutton & Goat Meat	114,00	- 2,67	0,0077	11	3	9	21	16	27
Red meat	139,00	- 2,04	0,0416	69	67	66	112	97	103
Poultry Meat	116,50	- 2,60	0,0092	38	40	40	72	54	64
Meat, Other	112,00	- 2,72	0,0066	31	33	12	40	43	16
Offals, Edible	199,00	- 0,53	0,5973	8	9	9	10	9	8
Milk, Whole	210,50	0,24	0,8111	268	223	253	241	227	95
Milk, Skimmed	126,00	- 2,36	0,0180	33	14	16	68	49	60
Eggs	147,00	- 1,84	0,0663	18	13	14	24	25	16
Cheese	101,00	- 2,99	0,0028	6	5	6	24	14	35
Butter, Ghee	117,00	- 2,59	0,0096	2	2	3	6	5	7
Fat animal	183,00	- 0,93	0,3520	5	4	4	7	6	10
Freshwater Fish	158,00	- 1,56	0,1188	3	2	2	6	4	4
Demersal Fish	94,50	- 3,16	0,0016	6	1	4	17	8	20
Pelagic Fish	141,00	- 1,99	0,0469	13	9	15	23	13	15
Marine Fish, Other	174,00	- 1,16	0,2472	5	2	1	7	3	5
Molluscs, Other	122,00	- 2,28	0,0225	1	0	2	4	1	8
Fish amount	106,00	- 2,87	0,0041	28	13	36	57	47	43
AP amount	139,00	- 2,04	0,0416	507	551	319	661	663	409
% AP	189,00	- 0,78	0,4355	33	31	6	34	33	8
GV	-	-	10,000						
Wheat	155,50	- 1,62	0,1047	236	162	248	292	273	171
Rice	203,50	0,42	0,6781	74	27	119	51	22	76
Maize	106,50	2,52	0,0119	92	63	117	21	8	33
Barley	180,50	0,99	0,3204	6	3	6	4	1	3
Beans	207,00	0,33	0,7436	9	4	12	4	3	5
Rye	152,50	0,22	0,8237	5	1	5	4	1	2
Nuts	80,50	- 3,51	0,0004	4	3	4	11	10	9
Grains and legumes	167,00	1,33	0,1824	421	419	121	385	395	155
Potatoes	177,50	- 1,07	0,2850	134	77	189	139	148	108
Tomatoes	135,50	- 2,13	0,0335	50	37	55	96	84	90
Onions	196,00	- 0,60	0,5460	28	29	31	31	27	25
Vegetables, Other	130,00	- 2,26	0,0236	161	150	104	229	212	123
Soyabean Oil2003-05	165,50	- 1,37	0,1704	8	3	9	10	10	9
Sunflowerseed Oil	183,50	- 0,92	0,3585	7	2	9	6	5	5
Olive Oil	61,00	- 3,74	0,0002	0	0	0	2	2	2
Oil amount	163,50	- 1,42	0,1552	15	11	17	18	16	7
% Oil	213,00	- 0,18	0,8602	1	1	1	1	1	1
GV amount	175,00	- 1,13	0,2576	809	745	513	899	820	425

% GV	159,00	1,53	0,1249	53	55	10	47	49	19
FS	-	-	10,000						
Oranges	51,00	- 4,01	0,0001	24	16	35	78	69	54
Lemons, Limes	132,00	- 2,02	0,0432	6	4	5	9	5	9
Apples	118,00	- 2,57	0,0103	28	20	24	48	44	52
Honey	147,00	- 1,84	0,0663	1	0	1	1	1	2
Sugar (Raw Equivalent)	109,50	- 2,78	0,0054	69	72	41	99	107	34
Coffee2003-05	104,50	- 2,91	0,0037	4	4	5	11	10	9
Tea	215,50	0,11	0,9099	3	3	2	2	2	2
FS amount	65,00	- 3,90	0,0001	131	122	64	249	267	131
% FS	88,00	- 3,32	0,0009	9	8	4	13	13	3
AB 2003-05	-	-	10,000						
Beverages, Alcoholic	148,50	1,80	0,0721	12	7	10	5	5	9
Wine	155,00	- 1,64	0,1020	8	2	12	24	21	43
Beer	189,00	- 0,78	0,4355	66	50	80	103	70	142
AB amount	194,50	- 0,64	0,5212	87	67	90	132	92	192
% AB	206,00	- 0,35	0,7247	5	5	4	6	6	9
BA 2016-18	-	-	10,000						
both sexes	208,50	0,29	0,7724	6	5	4	6	7	9
male	206,00	0,35	0,7247	10	8	7	9	11	13
female	212,00	0,20	0,8405	3	2	2	3	3	4
TCL g / person / day	129,00	- 2,29	0,0221	1548	1514	1031	1957	2109	635
AP amount	139,00	- 2,04	0,0416	507	551	319	661	663	409
GV amount	175,00	- 1,13	0,2576	809	745	513	899	820	425
FS amount	65,00	- 3,90	0,0001	131	122	64	249	267	131
AB amount	194,50	- 0,64	0,5212	87	67	90	132	92	192
% AP	189,00	- 0,78	0,4355	33	31	6	34	33	8
% GV	159,00	1,53	0,1249	53	55	10	47	49	19
% FS	88,00	- 3,32	0,0009	9	8	4	13	13	3
% AB	206,00	- 0,35	0,7247	5	5	4	6	6	9
Nutrients	-	-	10,000						
1990-92									
AP Energy% 1990-92	127,00	- 2,34	0,0193	17	17	12	23	21	14
AP Protein% 1990-92	124,50	- 2,40	0,0163	36	37	10	48	50	27
AP Fat% 1990-92	207,00	- 0,33	0,7436	46	45	24	48	46	22
2003-05									
AP Energy %20 03-05	134,50	- 2,15	0,0315	18	18	7	24	22	13
AP Protein% 2003-05	112,00	- 2,72	0,0066	40	42	8	51	53	21
AP Fat% 2003-05	194,00	- 0,65	0,5131	45	48	19	48	48	23
1990-92									
Carboh%E 1990-92	66,50	3,86	0,0001	67	66	7	58	55	12
Proteins%E 1990-92	118,00	- 2,57	0,0103	11	11	2	12	12	2

Fats%E 1990-92	68,50	- 3,81	0,0001	22	22	5	30	32	12
2003-05									
Carboh%E 2003-05	73,00	3,70	0,0002	66	64	8	57	56	12
Proteins%E 2003-05	135,50	- 2,13	0,0335	11	11	2	12	12	2
Fats%E 2003-05	66,00	- 3,87	0,0001	23	24	5	31	32	10
1990-92									
Energy (kcal / person / day) 1990-92	31,00	- 3,72	0,0002	2366	2310	680	3033	3100	400
Proteins (g/person / day) 1990-02	31,50	- 3,70	0,0002	62	59	19	91	96	25
Fats (g/person / day) 1990-02	22,00	- 4,04	0,0001	54	50	18	103	112	55
2003-05									
Energy (kcal / person / day) 2003-05	99,00	- 3,04	0,0023	2742	2830	750	3184	3150	280
Proteins (g/person / day) 2003-05	92,00	- 3,22	0,0013	78	79	27	98	97	20
Fats (g/person / day) 2003-05	62,00	- 3,97	0,0001	71	68	30	109	111	46
Diversification Energy %	96,50	- 3,11	0,0019	49	50	12	60	63	20
Smoking smgaret	-	-	10,000						
m Daily Age	87,50	1,00	0,3184	34	32	19	30	26	15
f Daily Age	77,50	- 1,66	0,0969	8	5	18	15	17	15
ba/w	177,00	1,08	0,2794	2,04	0,50	2,20	0,35	0,18	0,27
ba/b	89,50	3,28	0,0010	0,29	0,17	0,16	0,04	0,05	0,07
ba/ab	69,00	3,80	0,0001	0,21	0,14	0,18	0,03	0,03	0,05
ba/%ab	94,00	3,17	0,0015	2,70	1,62	2,35	0,73	0,73	1,15
ba/tdc	113,00	2,69	0,0071	0,01	0,00	0,01	0,00	0,00	0,00
ba/ap	109,00	2,79	0,0052	0,03	0,02	0,03	0,01	0,01	0,01
red meat/g and l	137,00	- 2,09	0,0368	0,18	0,16	0,15	0,35	0,24	0,46
fat an./Oil am.	83,00	3,45	0,0006	0,34	0,08	0,27	0,02	0,02	0,03

Legend	
Total CL	Total CL Daily food intake
AP	AP Animal Products
GV	GV Cereals, vegetables
FS	FS Fruit, sweeteners
AB	AB Alcoholic drinks (hard alcohol, wine, beer, pure alcohol)
ba/w	Beverages, Alcoholic/
ba/b	Beverages, Alcoholic/
ba/ab	Beverages, Alcoholic/
ba/%ab	Beverages, Alcoholic/
ba/tcl	Beverages, Alcoholic/
ba/ap	Beverages, Alcoholic/
red meat/g and l	red meat/
fat an./Oil am.	Fat animal

Macronutrient Intake Levels in Group 1 and Group 2

1990-02 years

In the 1st group of countries in comparison with the 2nd group, the consumption of total energy, total proteins and total fats was 1.5-2 times lower ($p \leq 0.001$). At the same time, the percentage of carbohydrates was higher in the 1st group of countries ($p \leq 0.001$). But the percentage of protein and fat was slightly higher in group 2 countries ($p \leq 0.001$). The share (%) of consumption of animal products (energy and protein) was 1, 5 times higher in the 2nd group of countries ($p \leq 0.019$). The proportion of animal fat consumption was not statistically different between group 1 and group 2 ($p = 0.7$).

2003-2005 years

The analysis of nutrient consumption showed that in the 1st group of countries the consumption of total nutrients increased by 24% ($p \leq 0.001$). In group 2 of countries, the increase in consumption of total nutrients was 5% compared to 1990-02 ($p \leq 0.001$) (Table 3).

Discussion

The WHO considers the use of tobacco, alcohol, unhealthy diet and physical inactivity to be the main risk factors for NCDs [28]. The research results were unexpected. The 12-fold gradient in the burden of liver cirrhosis between country groups 1 and 2 was not accompanied by statistically significant differences in the main risk factors for NCDs (Tables 2 & 3). We have not found statistically significant differences in the burden of incidence of viral hepatitis B and C between group 1 and group 2 of countries. This hepatitis is considered the main risk factors for non-alcoholic cirrhosis of the liver [2, 29]. Higher consumption of animal products, including animal fat, was higher in group 2 countries with a low burden of cirrhosis. Overweight, obesity and hyperlipidemia were 2 times higher in group 2 countries. Thus, the risk factors for non-alcoholic cirrhosis in the 1st group of countries were lower than in the 2nd group of countries [2, 29]. Consequently, the 12-fold gradient of liver cirrhosis in group 1 of countries cannot be justified by lower risk factors for non-alcoholic cirrhosis of the liver than in group 2 of countries [2, 29].

It should be noted that in the GBD database of 2004 [20] there is no division of cirrhosis into alcoholic and non-alcoholic forms. The GBD 2004 database [20] provides a summary indicator of the burden of liver cirrhosis. It is known that alcoholic cirrhosis of the liver is caused by the abuse of alcoholic beverages by patients [3, 8]. However, in our studies, the consumption of alcoholic beverages (spirits, wine and beer) did not statistically significantly differ in group 1 of countries from group 2 of countries.

Thus, the absence of statistically significant differences between groups 1 and 2 countries in alcohol consumption (the third risk factor for liver cirrhosis) could not explain the striking difference in the burden of liver cirrhosis between groups 1 and 2 countries [3, 8]. We have undertaken several validations of our original data: the 2004 GBD disease burden database [20], the FAO food and alcohol consumption rate database [27], and the statistics program. To check our results, we used the list of countries by consumption of pure alcohol for 2016-18 [30].

There were no statistically significant differences between the countries of the 1st and 2nd groups in the consumption of pure alcohol in 2016-18. As a result, we have come to believe that our results are not an error. Thus, we have no reason to assert that the high burden of liver cirrhosis in group 1 of countries is due to a higher incidence of viral hepatitis, alcohol abuse and malnutrition. It should be noted that I was unable to obtain a model of liver cirrhosis using only alcohol in studies on Wistor rats and outbred rats. Against the background of alcohol consumption, rats always had to inject carbon tetrachloride or D-galactosamine in a certain regimen [31]. However, in the modern literature, this model is called alcoholic cirrhosis of the liver [32].

We noted that in group 1 there were statistically significantly more countries with the phenotype of rapid NAT2 - acetylation (Table 2). Back in the second half of the 20th century, textbooks on hepatology wrote that the NAT2 enzyme system suffers in liver cirrhosis [33]. It has been argued that patients who are fast in the NAT2 phenotype can become slow NAT2 - acetylators and vice versa in the development of liver cirrhosis [33]. We conducted a study of the stability of the NAT2-acetylation system in 82 patients with liver cirrhosis at the Center of Surgery of the Academy of Sciences. The control consisted of 150 men and women of the Moscow population [34]. As a result of research, we found that with the phenotype fast NAT2 in the control group was 45% of Muscovites. In total, the control group and the group of patients with liver cirrhosis did not statistically differ in NAT2 phenotype. But among patients with active liver cirrhosis, that is, with a severe form of liver cirrhosis, there were statistically significantly more rapid NAT2 phenotypes [34].

Among patients with inactive cirrhosis, there were 22% of rapid NAT2 phenotypes; with active cirrhosis of the liver - 61% of rapid NAT2 phenotypes; with decompensated liver cirrhosis - 100% of slow NAT2 phenotypes [34]. None of the 82 patients showed a change in the rate of NAT2 acetylation during 12 months of follow-up. Among patients with cirrhosis of the liver of fast NAT2 acetylators, the mortality rate was 2 times higher than among slow NAT2 acetylators [34]. Patients with cirrhosis of the liver with the rapid NAT2 phenotype were on average 3-4 years younger and had a more severe course of LC than patients with the slow NAT2 phenotype [34]. The reason for the more severe course of LC and higher mortality from liver cirrhosis in patients with a rapid NAT2 phenotype may be associated with the mechanism of accelerated NAT2-dependent collagen synthesis. During the development of liver cirrhosis, this mechanism can contribute to the development of fibrosis of the liver parenchyma and impairment of portal microcirculation [19,34].

In several studies, we have shown that mortality from liver cirrhosis is significantly higher in countries with a high percentage of the population of rapid NAT2 phenotypes [18, 19]. Recently, new surgical methods for the treatment of liver cirrhosis have appeared with the use of bariatric surgery. Bariatric surgery contributes to the reduction of the Body Mass Index and the prevention of liver cirrhosis [35-37].

Earlier, we also proposed a surgical method for the treatment of chronic hepatitis and cirrhosis of the liver. The method was developed on models of chronic hepatitis and liver cirrhosis in rats [38-40]. We noticed that ischemia, or stenosis of the left or right branch of the portal vein in rats, is accompanied by a reduction in the lobe of the liver, devoid of portal inflow. In this case, all the adductor and discharge vessels in portal ischemia of the liver lobes should be preserved. Reduction of the liver lobe occurs by apoptosis.

But the complete reduction of the liver lobe never occurs and does not depend on the duration of ischemia of the portal vein branch. Even the maximum degree of reduction of the lobe to 10% of the initial mass does not cause disturbances in the reduced lobe of the liver of its bar structure of the parenchyma. In addition, there are many stem cells in the parenchyma of the reduced lobe [40-43]. Cessation of portal ischemia (reperfusion) restores the lobe of the liver by stimulating hepatocyte division. Histological preparations and morphometry of the parenchyma structure indicated complete organotypic liver renewal [39, 40]. So, returning to the goal set in our work and the results obtained, we cannot answer the question about the reason for the 12-fold difference in the burden of liver cirrhosis in 1 and 3 groups of countries of the world.

In conclusion, we would like to note that the burden of liver cirrhosis, cardiovascular diseases, diabetes mellitus and alcoholism exhibits a specific dependence on per capita income, latitude, and "pure" UV. This is shown in Figures 1-4. The figures combine the results of this study of liver cirrhosis and data from our other work [44].

Conclusion

In accordance with the set goal, in our studies it was found that in group 1 of countries in comparison with group 2 of countries, the burden of Cirrhosis of the liver is 12 times higher (p≤0,001). The burden of comorbid liver cirrhosis is alcoholism and cardiovascular disease was also 2 times higher in 1 group of countries in comparison with 2 group of countries (p≤0.001). The burden of diabetes was not statistically significant between groups 1 and 2 countries. Major risk factors for liver cirrhosis - The burden of viral hepatitis B and C did not differ statistically between groups 1 and 2. Consumption levels of food, including animal fats, red meat, animal energy and total energy were, on average, 1.5 to 2 times higher in Group 2, with a low burden of liver cirrhosis and comorbid diseases (p≤0.003). Consumption of all types of alcoholic beverages: pure alcohol, strong alcohol, wine and beer were not statistically different between the two study groups of countries (p = 0.7). The results obtained do not allow us to draw a conclusion about the risk factors for liver cirrhosis in this study. Further research on risk factors for liver cirrhosis is needed.

Acknowledgment

Authors are grateful For ongoing consultations, Alexander Nemtsov, M.D. National Center for Addiction Medicine.

Conflict of Interest

No conflict of interest.

References

1. Zhou WC, Zhang QB, Qiao L (2014) Pathogenesis of liver cirrhosis. World J Gastroenterol 20(23): 7312-7324.
2. Smith A, Baumgartner K, Positis C (2019) Cirrhosis: Diagnosis and Management. Am Fam Physician 100(12): 759-770.
3. Roerecke M, Vafaei A, Hasan OSM, Chrystoja BR, Cruz M, et al. (2019) Alcohol Consumption and Risk of Liver Cirrhosis: A Systematic Review and Meta-Analysis. Am J Gastroenterol 114(10): 1574-1586.
4. Jonas DE, Amick HR, Feltner C, Bobashev G, Thomas K, et al. (2014) Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA 311(18): 1889-1900.
5. Kaner EF, Beyer FR, Muirhead C, Campbell F, Pienaar ED, et al. (2018) Effectiveness of brief alcohol interventions in primary care populations. Cochrane Database Syst Rev 2(2): CD004148.
6. Millwood IY, Walters RG, Mei XW, Guo Y, Yang L, et al. (2019) Collaborative Group. Conventional and genetic evidence on alcohol and vascular disease aetiology: a prospective study of 500 000 men and women in China. Lancet 393(10183): 1831-1842.
7. Asrani SK, Devarbhavi H, Eaton J, Kamath PS (2019) Burden of liver diseases in the world. J Hepatol 70(1): 151-171.
8. Rehm J, Taylor B, Mohapatra S, Irving H, Baliunas D, et al. (2010) Alcohol as a risk factor for liver cirrhosis: a systematic review and meta-analysis. Drug Alcohol Rev 29(4): 437-445.
9. Pierantonelli I, Svegliati-Baroni G (2019) Nonalcoholic Fatty Liver Disease: Basic Pathogenetic Mechanisms in the Progression From NAFLD to NASH. Transplantation 103(1): e1-e13.
10. Møller S, Danielsen KV, Wiese S, Hove JD, Bendtsen F (2019) An update on cirrhotic cardiomyopathy. Expert Rev Gastroenterol Hepatol 13(5): 497-505.
11. Lopez-Delgado JC, Ballus J, Esteve F, Nelson L Betancur Zambrano, Vicente Corral Velez, et al (2016) Outcomes of abdominal surgery in patients with liver cirrhosis. World J Gastroenterol 22(9): 2657-2667.
12. Rocco A, Compare D, Angrisani D, Sanduzzi Zamparelli M, et al. (2014) Alcoholic disease: liver and beyond. World J Gastroenterol 20(40): 14652-14659.
13. Singh S, Osna NA, Kharbanda KK (2017) Treatment options for alcoholic and non-alcoholic fatty liver disease: A review. World J Gastroenterol 23(36): 6549-6570.
14. Marroni CA, Fleck AM, Fernandes SA, Galant LH, Marcos Mucenic, et al. (2018) Liver transplantation and alcoholic liver disease: History, controversies, and considerations. World J Gastroenterol 24(26): 2785-2805.
15. Niemelä O (2016) Biomarker-Based Approaches for Assessing Alcohol Use Disorders. Int J Environ Res Public Health 13(2): 166.
16. Ghosh Dastidar S, Warner JB, Warner DR, McClain CJ, Kirpich IA (2018) Rodent Models of Alcoholic Liver Disease: Role of Binge Ethanol Administration. Biomolecules 8(1): 3.

17. Suvichapanich S, Fukunaga K, Zahroh H, Taisei Mushiroda, Surakameth Mahasirimongkol, et al. (2018) NAT2 ultra-slow acetylator and risk of anti-tuberculosis drug-induced liver injury: a genotype-based meta-analysis. Pharmacogenet Genomics 28(7): 167-176.

18. Piruzyan LA, Radkevich LA, Morozova NV (2003) The use of ethnic metabolic portraiture for the choice of individual pharmacotherapy strategy as exemplified by N-acetylation and chronic liver diseases. Dokl Biol Sci 388: 45-48.

19. Radkevich LA, Korshunov IB, Pynko NE, Morozova NV (2005) The search for biochemical predictors of the NAT2 phenotype to optimize prophylaxis and pharmacotherapy of hepatic cirrhosis. Dokl Biochem Biophys 400: 52-55.

20. (2004) World Health Organization. The global burden of disease. Geneva, WHO (2008).

21. (2009) United Nations Department of Economic and Social Affairs / Population Division. World Population Prospects (2008).

22. (2004) World Health Organization. Average daily ambient ultraviolet radiation (UVR) level. World Health Data Platform / GHO / Indicator Metadata Registry List Average daily ambient ultraviolet radiation (UVR) level (2004).

23. World Population Prospects United Nations. 2005-2010.

24. Bhaven N Sampat (2009) Academic Patents and Access to Medicines in Developing Countries. American Journal of Public Health 99(1): 9-17.

25. Gross National Happiness Commission. Royal Government of Bhutan.

26. (2008) Global Health Observatory (GHO) data; Indicator and Measurement Registry version 1.7.0 BMI≥25; total cholesterol ≥ 5.0; blood glucose≥7.0; insufficiently active. 2008 // WHO (World Health Organization) Percentage of defined population Program Country.

27. Food and Agriculture Organization of the United Nations. Food Balance Sheets 2003-2005.

28. (2009) Global Health Risks: mortality and burden of disease attributable to selected major risks // Geneva, World Health Organization (WHO) p. 62.

29. Altamirano Barrera A, Barranco-Fragoso B, Méndez Sánchez N (2017) Management strategies for liver fibrosis. Ann Hepatol 16(1): 48-56.

30. (2020) Total per capita (15+) consumption (in litres of pure alcohol) with 95% CI, three-year average by country, WHO.

31. Radkevich LA, Pynko NE (1990) Morphometric characteristics of the hepatotoxic effect of ethanol. Gig Sanit (11): 78-80.

32. Rasineni K, Penrice DD, Natarajan SK, McNiven MA, Benita L McVicker, et al. (2016) Alcoholic vs non-alcoholic fatty liver in rats: distinct differences in endocytosis and vesicle trafficking despite similar pathology. BMC Gastroenterol 16: 27.

33. Bluger AF, Novinsky IN (1984) Practical Hepatology, Riga "Zinatne" p. 403.

34. Piruzyan LA, Korshunov IB, Morozova NV, Pynko NE, Radkevich LA (2004) Prediction of chronic liver diseases on the basis of the N-acetyltransferase 2 phenotype. Dokl Biochem Biophys 395: 84-87.

35. Hafeez S, Mohamed H Ahmed (2013) Bariatric surgery as potential treatment for nonalcoholic fatty liver disease: a future treatment by choice or by chance. J Obes 2013: 839275.

36. Hannes Hagström, Mattias Ekstedt, Torsten Olbers, Markku Peltonen, Lena Carlsson (2021) Bariatric Surgery Versus Standard Obesity Treatment and the Risk of Severe Liver Disease: Data From the Swedish Obese Subjects Study. Clin Gastroenterol Hepatol 19(12): 2675-2676.e2.

37. Daisuke Uehara, Yosuke Seki, Satoru Kakizaki, Norio Horiguchi, Hiroki Tojima, et al. (2019) Long-term Results of Bariatric Surgery for Non-alcoholic Fatty Liver Disease/Non-alcoholic Steatohepatitis Treatment in Morbidly Obese Japanese Patients. Obes Surg 29(4): 1195-1201.

38. Radkevich LA (2002) Stimulation of liver regeneration after atrophy in cirrhotic rats. Dokl Biol Sci 385: 326-328.

39. Piruzyan LA, Malenkov AG, Radkevich LA (2004) On the question of the mechanisms triggering apoptosis and proliferation of hepatocytes in partial portal ischemia of various duration in rats. Dokl Biochem Biophys 395: 75-79.

40. Radkevich LA (1980) Membrane potential of liver cells during certain hemodynamic changes]. Fiziol Zh SSSR Im I M Sechenova 66(10): 1566-1570.

41. Kerr JF (1971) Shrinkage necrosis: a distinct mode of cellular death. J Pathol 105(1): 13-20.

42. Kerr JFR, AH Wyllie, AR Currie (1972) Apoptosis: a basic biological phenomenon with wideranging implications in tissue kinetics. Brit J Cancer 126: 239-257.

43. Kerr JF (2002) History of the events leading to the formulation of the apoptosis concept. Toxicology 181-182: 471-474.

44. Radkevich LA, Radkevich DA (2018) Ecological Determinants of the Happiness Index, Life Expectancy, Incidence and Dietary Patterns in Different Countries. Journal of Obesity and Chronic Diseases 2(1): 26-36.