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## Profile of hepatocellular carcinoma in the Republic of Moldova: first-hand information on the presentation, distribution and etiologies

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**Introduction.** Moldova is the European country with the highest incidence of hepatocellular carcinoma (HCC) in both sexes. There is, however, no data comprehensively describing the presentation and the risk factors of HCC in the country. We decided to analyze cases of HCC recently received in a tertiary healthcare Institution from Chisinau, the Moldovan capital.

**Methods.** A series of 148 primary liver tumors including 139 cases of HCC were retrospectively analyzed for demographic features, serological and biochemical data, and clinical presentation.

**Results.** The mean age of patients was  $59 \pm 10$  years (range: 19-66) with a M:F sex ratio of 1.9. Tumors appeared on full-blown liver cirrhosis in 83% of cases and were composed of multiple nodules at diagnosis in 36% of patients. Serum Alpha-fetoprotein was exceeding 10ng/mL in 76% of cases. Liver tumor and hepatitis were co-discovered in 34% of cases. More than 81% of hepatocellular carcinomas were associated with at least one hepatitis virus. Carriers of anti-hepatitis C virus were predominating (55% of cases) over patients seropositive for hepatitis B virus surface antigen (36%). Half of the latter were also infected with hepatitis Delta virus. In total, dual or triple infections were present in 24% and 7% of cases.

**Conclusions.** The burden of infections with hepatitis viruses is particularly important in Moldova and corresponds to a situation commonly observed in countries of the Southern hemisphere. A pro-active policy of screening for persistent liver infection targeting population at risk of HCC (> 50 years) and coupled with the distribution of antivirals in positive cases should be rapidly implemented in Moldova to reduce incidence or primary liver cancer.

**Keywords:** Hepatocellular carcinoma, Hepatitis viruses, Multiple infections, Cirrhosis, Liver cancer, Moldova.

### INTRODUCTION

Primary liver cancer (PLC) became recently the second cause of mortality from malignancy in humans worldwide [1]. This tumor is, however, characterized by extensive geographical variations of incidence that range over three logs ( $0.1-100/10^5$  habitants). Historically, Eastern Asia and sub-Saharan Africa were the regions affected with the highest incidences (PLC) that can occasionally reach more than  $100/10^5$  habitants as in the case of men in Mongolia [2]. Within Europe, variations of PLC incidence are wide as well and extend in both sexes from  $1.6/10^5$  in the Netherlands to  $10.0/10^5$  in Moldova. Moldova is, actually, the European country with the highest PLC incidence both for men ( $12.5/10^5$ ) and women ( $5.4/10^5$ ).

Moldova is a small but densely populated country of 3.5 million habitants in the South Eastern

corner of Europe landlocked between Romania and Ukraine. Since medieval times and until sequential annexations of Moldova by the Russian Empire and the Soviet Union, Moldova and Romania shared most of their populations, destiny and culture, a situation that might explain some current commonalities between these countries in terms of Public Health. Moldova regained its independence in 1991 after 47 years of integration as a republic in the Soviet Union [3, 4]. Regarding infectious risk factors of HCC, Moldova was identified as soon as the 1970's decades as a hotspot for high endemicity of chronic infection with hepatitis B virus (HBV) [5]. Later on, the importance of other infectious factors of HCC in Moldova, such as hepatitis Delta (HDV) and hepatitis C viruses, were also singled out in the complex epidemiological context of the Soviet Union [6, 7]. Non-infectious risk factors of HCC are also particularly relevant in Moldova as well. It is primarily the case for alcohol abuse. Moldovan

populations have a centuries-old tradition of wine production and alcohol consumption. As a consequence, according to the World Health Organization in 2014, it is second country in Europe behind Belarus for alcohol consumption *per capita* [8]. Interestingly, a specificity of the country is the very high proportion of unrecorded alcohol consumption. Moldova is, indeed, the only European country where citizens consumed more unrecorded (62.5% vs. 37.5%) than recorded alcoholic beverages. Hence, in the recent years, several studies reported that consumption of unrecorded alcohol is a major risk factor of severe diseases such as liver cirrhosis, and head and neck carcinomas [9]. Moldova is indeed also the European country with the highest death rate from liver cirrhosis in Europe (98.5/10<sup>5</sup> habitants over 15 years) [10]. Considering this ominous accumulation of threats, other risk factors such as type 2 diabetes or obesity, although currently increasing in the country, might appear as only marginally important in the current HCC epidemiology [11]. Finally, the role of aflatoxin B1 in Moldovian cases of PLC is unknown but, due to the recent finding of an aflatoxin B1-associated *TP53* mutation in a HCC from neighboring Romania, it could be suspected as well [12].

The local forms taken by PLC as well as its mode of presentation in Moldova have been only barely, if ever, described in the medical literature. We conducted a retrospective study on 148 PLC cases diagnosed in the main University Hospital of Chisinau, to determine the tolls attributable to the different risk factors prevalent in Moldova and the different tumor features that result from their deleterious activities.

## MATERIAL AND METHODS

### PATIENTS

We conducted a retrospective study of patients diagnosed with primary liver cancer (PLC) in the Department of Gastroenterology of the “Timofei Mosneaga Republican Hospital attached to the “Nicolae Testemitanu” State University of Medicine and Pharmacy in Chisinau, Republic of Moldova between 2014 and 2017. This study was approved by the institutional review board of the “Nicolae Testemitanu” State University of Medicine and Pharmacy of the Republic of Moldova (No. 03-108). No informed consent was obtained due to the retrospective nature of the study. PLC diagnosis was multimodal and based on histopathological assessment, on the presence of a liver mass at imaging (CT or MRI, Siemens, 1.5T), on the

clinical context, notably the presence of a chronic liver disease or cirrhosis, on serological markers of viral infections, and on alpha-fetoprotein (AFP) levels (physiological level < 10 ng/mL, diagnostic level > 300 ng/mL). In brief, image-based diagnosis was performed by computerized tomography (CT scan) only in 64/139 cases (46%), MRI only in 36 cases (26%) and both in 39 cases (28%). Liver biopsy followed by histo-pathological assessment was performed for 18 patients with HCC (n = 18/139, 13%). All of them had a CT scan beforehand. Data about socio-demographic status, clinical symptoms, clinical biochemistry, blood cell count, serological data concerning the three major viruses responsible for persistent liver infections (hepatitis B, C and Delta virus), lifestyle-related and metabolic risk factors of HCC, risk factors of infections, non-tumor liver histology, tumor number and diameter, lymph nodes involvement, metastases, treatment and survival length were recovered from medical files and stored in a database.

### STATISTICAL ANALYSIS

Statistical analyses were performed using a Prism 6.0d statistical package (GraphPad Software, Inc, La Jolla, CA, USA). Numerical variables were summarized by their median, mean and range according to their types of distribution (normal or not). They were compared either by a Student T test or by a Mann-Whitney test as appropriate. Categorical variables were summarized as frequencies that were compared either by Fisher exact or Chi<sup>2</sup> tests. All tests were univariate and two-sided. Level of significance was set at  $p < 0.05$ .

## RESULTS

### PATIENT DEMOGRAPHY

A total of 148 primary liver malignancies were retrieved from pathological records in the period investigated. Beside 139 HCC, seven cholangiocarcinomas, a mucinous carcinoma and a carcinosarcoma were found. The clinical and demographical features of patients with HCC are described in Table 1. Briefly, the mean age of patients was 59.2 ± 10.1 and there were almost two men for a woman. Regarding the geographic distribution of patients within the country, we observed that patients were coming from 33 out of the 37 administrative divisions (*raions*) of the country. The four main geographical regions, North, Center (including Chisinau), South (including Gagauzia) and Transnistria

were represented in the series. However, the central region was significantly over-represented with regard to its demographic weight in the country (57% vs. 43%,  $P = 0.022$ , OR = 1.7, 95%CI: 1.1-2.9). By contrast, Transnistrian population (including Tighina/Bender) was underrepresented in this HCC

series ( $P = 2.8 \text{ E-}04$ , OR = 0.13, 95%CI: 0.02-0.46). A single district, located in the central part of the country, Ialoveni (15 km South-West from Chisinau), presented a significant excess of observed HCC cases (OR = 4.3, 95%CI: 1.2-15.5,  $P = 0.030$ ).

*Table 1*  
Clinico-biological features of patients

<b>Clinico-Biological features (n = 139)</b>	<b>Values</b>
<b>Age</b>	
Mean	59.2 ± 10.1
Median (IQR)	59 (35-66)
<b>Sex Ratio (M:F)</b>	1.9 (92:47)
<b>Region of origin (%)</b>	
Centre	56.8
North	23.0
South	17.2
Transnistria	2.1
<b>Education (%)</b>	
Primary	40.3
Secondary	37.4
Academy	22.3
<b>Family Income (%)</b>	
Low	57.2
Average	42.4
<b>Maternal language (%)</b>	
Bulgarian	7.9
Moldovan-Romanian	69.0
Russian-Ukrainian	23.0
<b>Serological markers (%)</b>	
HBs Ag	25.9
anti-HCV	42.4
HBsAg+anti-HCV	12.9
HBe Ag	1.6
anti-HBc	67.8
anti-HBe	22.6
anti-HBs	9.6
anti-Delta	18.5
nonB, nonC	17.9
Cancer-Hepatitis Co-discovery	33.7
<b>Other Risk Factors (%)</b>	
Alcohol intake	53.6
Tobacco use	30.0
Type 2 Diabetes	46.1
Overweight-Obesity (BMI ≥25)	34.7
Familial tumors	14.8
Previous personal tumors	12.2
Coffee consumption	48.2
<b>Liver histology (%)</b>	
Cirrhosis	82.9
Child-Pugh A	13.2
Child-Pugh B	42.4
Child-Pugh C	44.3
Steatosis	70.3
<b>Tumor Features</b>	
Multiples nodules (%)	35.5
Mean diameter (cm)	5.9 ± 3.5
Positive Lymph nodes (%)	79.3
Metastases (%)	83.7
<b>AFP (%)</b>	
>300ng/mL	45.8
10-300 ng/mL	30.8
<10 ng/mL	23.3

Table 1 (continued)

<b>Liver Biochemistry</b>		
	ASAT (IU/mL)	117 ± 83
	ALAT (IU/mL)	90 ± 91
	GGT (IU/mL)	187 ± 245
	ALP (IU/mL)	190 ± 170
	Plasma Proteins (g/L)	67 ± 9
	Albumin (g/L)	30 ± 7
	Urea (mmol/L)	9.7 ± 6.7
	Creatinine (micromol/L)	108 ± 74
	Total Bilirubin (micromol/L)	113 ± 173
	Leukocytes (Giga/L)	6.8 ± 3.9
	Erythrocytes (T/L)	5.6 ± 14.2
	Platelets (X10 <sup>3</sup> /mL)	135 ± 64
	INR	1.5 ± 0.3
<b>Infection Risk factors (%)</b>		
	IVDU	9.8
	Tatooes	12.7
	Transfusion-Injection	46.0
	Sex-transmitted infection	2.3
<b>Clinical Symptoms (%)</b>		
	Esophageal varices	78.4
	Portal thrombosis	58.7
	Digestive tract ulcers and inflammation	20.5
	Haemorrhagia	26.7
	Ascite	86.6
	Encephalopathy	75.0
	Loss of Weight	87.6
	Right Quadrant Pain	98.0
<b>Overall Survival (median, IQR in months)</b>		12.0 (7.0-24.0)
<b>Treatment (%)</b>		
	Chemotherapy	38.4
	Resection	41.5
	Abstention	16.9
	Tranplantation	3.0

### Risk factors distribution

The most frequent risk factor of HCC in Moldova is infection with HCV (55.3%), well above the level of infection with HBV (36.1%, OR = 1.9, 95%CI: 1.2-3.2, P = 0.007). In addition, two patients who developed a cholangiocarcinoma were infected with HCV (n = 2/7, 28.5%). A substantial proportion of the whole series (n = 26, 18.5%) was infected with the viroid Delta, a situation that concerned therefore almost one-half of HBsAg(+) patients (47.2%). Overall, at least one of the viruses responsible for persistent liver infectious (HBV, HCV or HDV) was present in more than 81% of cases. Moreover, HBV-HCV coinfections were found in 19 patients (13.6%). More strikingly, 10 out of these 19 patients (52.6%, i.e. 7.2% of the whole series) were, indeed, affected by a triple HBV-HCV-HDV infection. In total, one patient every four was infected with at least two viruses. The burden of infection pattern was, therefore, particularly severe in this series of Moldovan patients.

Lifestyle-related risk factors of HCC were rather prevalent in this series as alcohol intake and tobacco consumption was self-reported by patients

in 56.3 and 30.0% of cases. Finally, as shown in Table 1, metabolic risk factors of HCC such as overweight/obesity (34.7%) or Type 2 Diabetes (T2D, 46.1%) were also rather frequent.

### CLINICO-PATHOLOGICAL CORRELATIONS

Genders were not differing for the prevalence of liver infections but were drastically contrasting for exposure to toxic and metabolic risk factors. Both alcohol intake (62.4% vs. 34.0%, OR = 3.2 95% CI: 1.4-7.3, P = 0.0020) and tobacco consumption (39.5% vs. 10.2%, OR = 5.6, 95%CI: 1.7-23.9, P = 0.0011) were significantly more frequent among men than women (Figure 1A). On the opposite, Body Mass Index (BMI) was lower in men than in women (22.7 ± 3.7 vs. 24.6 ± 3.7, P = 0.010, Figure 1B). Male patients tended to be younger, albeit not quite significantly, than women (58.0 ± 10.3 vs. 61.9 ± 9.1, P = 0.070, Figure 1C).

HCV infected patients were characterized by a slightly higher BMI (24.0 ± 4.0 vs. 22.5 ± 3.5, P = 0.041) and smaller tumors (54.6 ± 32.8 vs. 65.9 ± 38.4 mm, P = 0.0766, ns) than other patients. Liver

disease stage as measured by Child-Pugh score was, as expected, more severe in anti-HCV carriers ( $P = 0.036$ ). In addition, noninvasive staging systems evaluating liver diseases progression such as aspartate aminotransferase-to-platelets ratio index (APRI), or Fibrosis-4 index (FIB-4) were significantly worsened in anti-HCV carriers (Figure 2A-B) [13, 14]. Likewise, using the staging systems for non-transplanted patients within Milan criteria, anti-HCV carriers were displaying more severe scores than other patients (Figure 2C).

Patients from southern Moldova were over-represented among HBV HBsAg carriers (27.7% vs. 10.2%, OR = 3.17, 95%CI: 1.17-9.05,  $P = 0.012$ ). The patients were more often tattooed than the others (22.2 vs. 6.1%, OR = 4.3, 95%CI: 1.1-20.2,  $P = 0.019$ ). Likewise, co-infected patients [HBsAg (+)/anti-HCV(-)] were more often coming from the Southern region (38.8 vs. 14.1%, OR = 3.80, 95% CI: 1.09-12.63,  $P = 0.0174$ ) and more often tattooed (31.2 vs. 9.5%,  $P = 0.0308$ ) and/or intravenous drug users (23.5 vs. 7.3%,  $P = 0.0022$ ) than others. These observations suggest that HBV/HCV co-infections occur primarily in grown-up individuals with at-risk behaviors.

Patients infected with Delta virus were characterized by a variety of salient features. HCC was diagnosed six years younger than other

patients ( $54.0 \pm 8.3$  vs.  $60.5 \pm 10.1$  years,  $P = 0.0041$ , Figure 2D). They were also affected with larger tumors ( $75.7 \pm 9.6$  vs.  $56.0 \pm 3.2$ , 0.0184, Figure 2E). Liver cirrhosis tended to be almost universally present in these patients (95.8 vs. 79.2%, OR = 5.96, 95%CI: 0.87-256.95,  $P = 0.074$ , ns). As expected, CLIP score (Cancer of the Liver Italian Program) was slightly higher in anti-delta carriers than in other patients (Figure 2F) [15]. Regarding risk factors of super-infection with Delta viroid, intravenous drug use was more frequent among seropositive patients than others (23.8 vs. 6.5%, OR = 4.34, 95%CI: 0.93-19.52,  $P = 0.0312$ ). Remarkably, patients with dual HBV and HCV infection were also more often anti-delta carriers than other subjects (66.6 vs. 12.5%, OR = 13.5, 95%CI: 3.6-57.9,  $P = 1.3 \text{ E-}05$ ) suggesting that at-risk behavior brings these patients in an environment characterized by an intense circulation of all hepatitis viruses.

Regarding the toxic risk factors of HCC, self-recognized alcohol intake was a hallmark of a lower level of education (see below), and low family income (67.1 vs. 48.3%, OR = 2.16, 95%CI: 1.00-4.47,  $P = 0.0330$ ). Habitants from Southern Moldova were more prevalent among alcohol drinkers than in abstinent ones (24.6 vs. 9.6%, OR = 3.0, 95%CI: 1.05-10.04,  $P = 0.0255$ ).

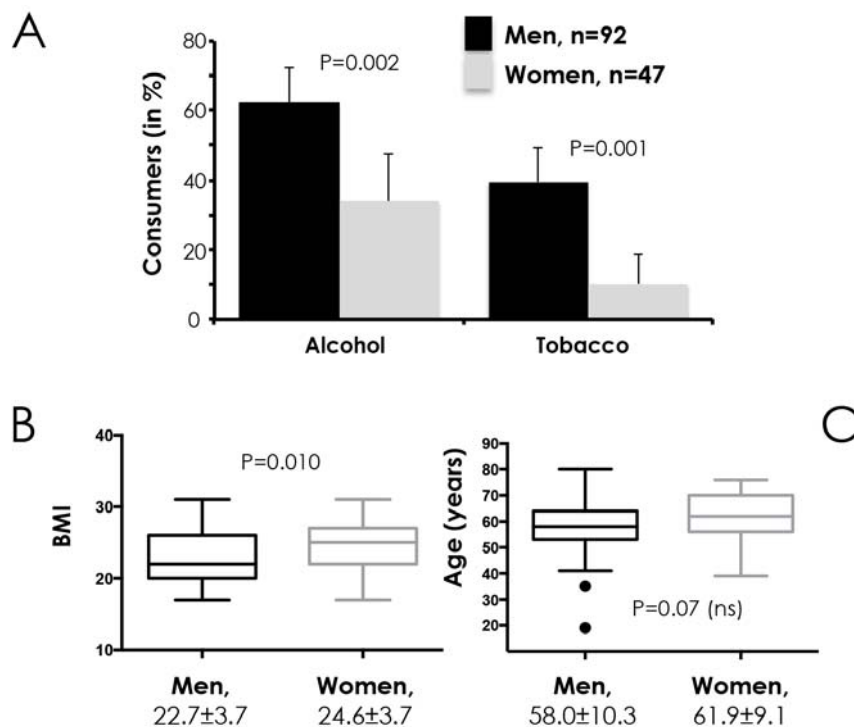


Figure 1. Clinico-biological differences between sexes. A\_ Men are significantly more exposed to toxic risk factors (alcohol and tobacco) of HCC. B\_ Women display a higher BMI than men. C\_ Men develop HCC slightly earlier than women.

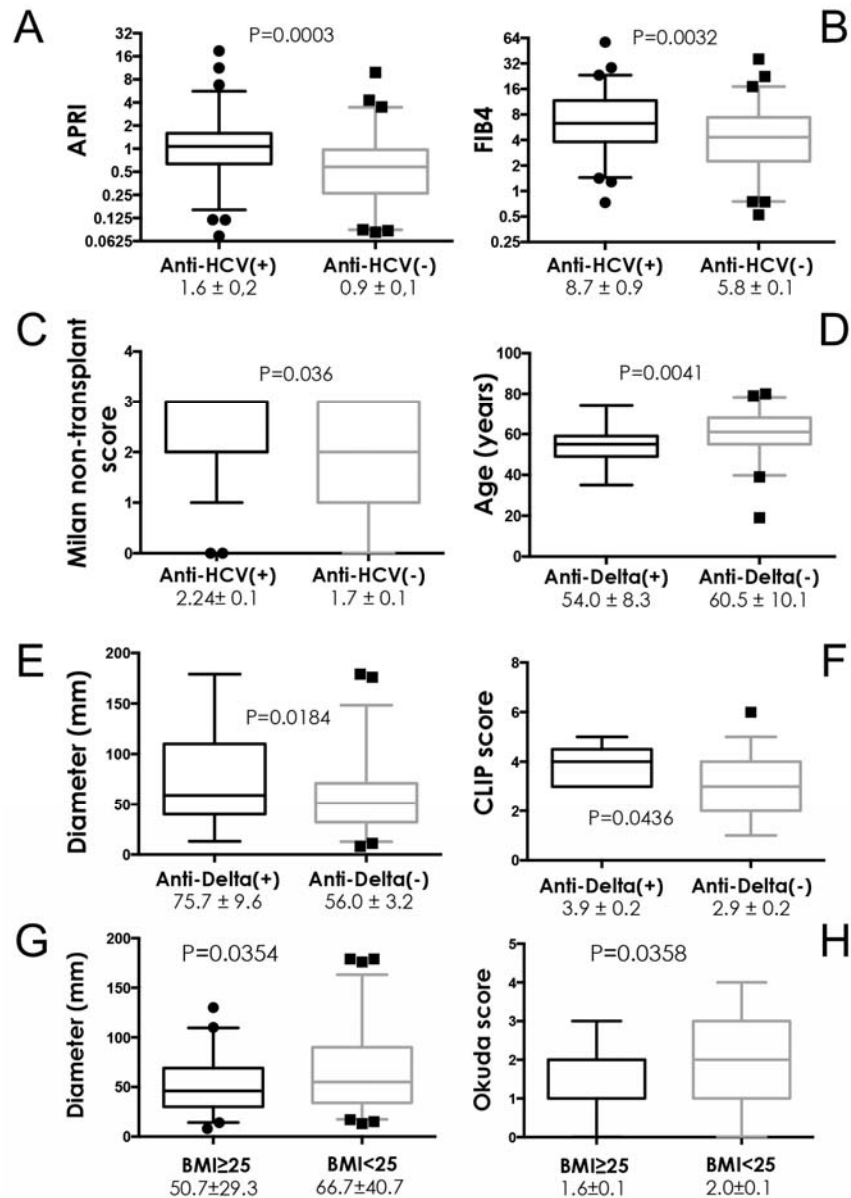


Figure 2. A-C\_ Anti-HCV(+) patients displayed worsened progression scores. D-F\_ Anti-Delta(+) patients are younger, affected with larger tumors and have more severe CLIP score than other patients. G-H\_ Patients with overweight have smaller tumors and better Okuda score than the rest of the series.

Metabolic risk factors such as T2D and BMI were associated with distinct clinical and biological features. Patients with T2D were less frequently infected with HBV (19.4 vs. 45.2%,  $P = 0.018$ ) or HDV (2.7 vs. 23.0%,  $P = 0.0147$ ) than other patients. As expected, they were significantly older ( $63.4 \pm 8.4$  vs.  $57.6 \pm 10.8$ ,  $P = 0.0126$ ) and affected by a higher mean Body Mass Index ( $26.4 \pm 3.4$  vs.  $22.7 \pm 3.1$ ,  $P = 1.72 \text{ E-}05$ ) than the rest of the series. Liver steatosis was universal among them (100% vs. 42.8%,  $P = 7.16 \text{ E-}06$ ). Women were strongly represented (46.9 vs. 23.8%,  $P = 0.005$ ) among

patients from the upper median for BMI ( $> 22$ ). Liver steatosis was as in the case of T2D highly prevalent in case of high BMI (96.6 vs. 43.3%,  $P = 7.9 \text{ E-}06$ ). Interestingly, mean tumor diameter was significantly lower among those patients with overweight (BMI $>25$ ) suggesting that they were diagnosed either earlier than others, a doubtful hypothesis, or that they were submitted to a less aggressive/more indolent tumor process ( $50.7 \pm 29.3$  vs.  $66.7 \pm 40.7$  mm,  $P = 0.0354$ , Figure 2G). As a consequence, Okuda score was significantly more favorable in overweight or obese patients than in others (Figure 2H) [15].

## SURVIVAL

Overall survival of patients was known for 108 of them. As mentioned in Table 1 the median survival was 12 months (inter-quartile range 7-24). No risk factor was significantly associated with poor survival. Tobacco use and T2D were tumor risk factors only marginally associated with a difference of survival (Log rank test,  $P = 0.059$ , and  $P = 0.073$ ). By contrast, academic education level was significantly associated with a better survival ( $P = 0.0036$  Logrank test, Figure 3A) when compared with secondary or primary school levels (median overall survival 23.4 vs. 12 months). This difference was not depending on treatments (surgical resection, chemotherapy or palliative care) that were evenly distributed between education

groups ( $P > 0.05$ ). We observed, however, that toxic risk factors (alcohol intake and tobacco consumption) were significantly less prevalent in the subset of patients with an academic education than in the rest of the series (Figure 3B). Of note, these patients were, in addition, more often coffee consumers than the rest of the series and it is sometimes considered that coffee is a hepatoprotective beverage.

Other features associated with survival length variation were tumor diameter, presence of clinical symptoms of severity (eg. portal thrombosis, hemorrhage, hepatic encephalopathy), few biochemical markers (AST, urea), high scores in three staging systems (CLIP, Tokyo and ALBI scores, see Figure 3C for ALBI score) and of course surgical treatment [15, 16].

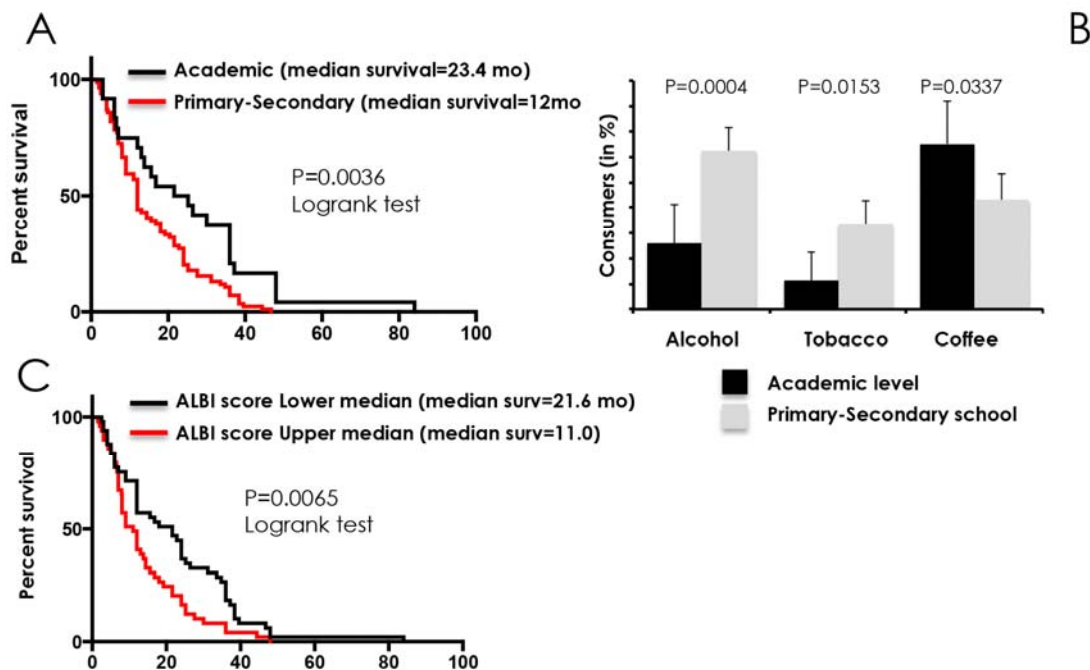


Figure 3. A\_ Patients who reached academic education have a better survival than patients who stopped schooling at primary or secondary levels. B\_ Patients who reached an academic level of education are more alcohol and/or tobacco abstinent than others. In addition, a larger proportion consumes coffee, a beverage considered as hepatoprotective. C\_ ALBI score is a good predictor of overall survival for Moldovian patients.

## DISCUSSION

Although it is a direct neighbor of the large and developed area covered by European Union, Moldova remains the poorest country of the continent (Gross domestic product *per capita*, GDP, 1960 € vs. 27660 € in European Union) and consequently has to face serious Public Health issues. Among these, liver diseases occupy a worrying position as

the country displays both the highest rates of primary liver cancer and the highest death rate of liver cirrhosis in Europe [1, 10]. This situation prompted us to conduct a retrospective study of PLC cases treated in the main University Hospital of Chisinau, the national capital. The aim of this survey was to estimate the tolls taken by the different risk factors of PLC in Moldova to provide National and European Public Health decision



makers more insights into the worrying local situation.

Regarding the risk factors of HCC, the most salient feature of the Moldovian situation was, of course, the importance taken by the three viruses responsible for persistent liver infections. Indeed, at least one of these viruses (HBV, HCV or HDV) was present in more than 80% of cases in the current series. Such a situation that is not commonly observed throughout the European continent where heavy alcohol intake and plausibly dysmetabolic conditions (T2D, obesity) often represent important causes of HCC. In a recent paper de Martel *et al.* observed that Italy was the European country with the highest rate of virus-associated HCC cases (78.4%) [17]. Although our results deserve further confirmation, it seems that Moldova might even exceed this rate. Moreover, as we did not have the opportunity to explore using molecular methods for the presence of occult B infection in the nonBnonC patients (9 of them were positive for anti-HBc), we are, thus, entitled to hypothesize that the real proportion of virus-associated cases might be even higher than currently reported. The Moldovian situation is, thus, for chronic hepatitis more akin to those observed in sub-Saharan Africa or Far Eastern Asia than to the usual European epidemiology [17-19]. Furthermore, we observed that one-fourth of the series was co-infected (either HBV/HDV or HBV/HCV) a situation apparently rarely observed in HCC cases from Europe. As an illustration, the rate of HBV/HCV co-infection in HCC patients (13%) was higher than what is currently reported from the rest of the European continent where the highest prevalence was observed in Belgium (8.5%) [17].

The problem of viral hepatitis burden in Moldova is known for a long time as it has been reported as early as the Soviet Union period [4, 7, 20]. Interestingly, it can only be compared in Europe with the situation observed in neighboring Romania that is known for high endemicities concerning both for HBV and HCV with regards to the European Union standards [21, 22]. Overall, infection risk factor distribution observed in patients with HCC from Chisinau is similar to that recently reported by a large Tertiary Institution of Bucharest [23]. In this survey, Grigorie *et al.* reported that 90% of the 670 patients with serological records have been infected with a hepatitis virus. As in Chisinau, HCV was predominant in Bucharest (54% vs. 55%) whereas HBV infection was slightly more frequent in HCC patients from Bucharest (42% vs. 36%). HDV was, however, somewhat less prevalent in HBsAg carriers from Bucharest than in

those from Chisinau (34% vs. 47%). Likewise, dual (16% vs. 24%) or triple (0.8% vs. 7.2%) infections were less prevalent in the Bucharest series than in the present one. Beyond epidemiology of HCC *sensu stricto*, triple infections are considered as a frequent hallmark of patients with delta infections in Central Europe [24, 25].

A striking feature of the present series was the frequent presence of HDV as this agent used to be usually marginally present in HCC cases from European patients. As a risk factor, it represents undoubtedly the hallmark of Moldova and Romania in Europe. After an initial phase of controversies, HDV is known to be associated with a more rapid progression of the liver disease and higher rate of conversion to HCC [25-27]. Its role in liver tumorigenesis is known to be particularly detrimental for populations living in Central Africa, Eastern Turkey or Mongolia where it is found in 27-80% of all HCC cases [28-30].

Our study suffers, of course, from some limitations. Important data such as HBV DNA loads, clinical annotations concerning T2D or liver steatosis or even the nature of the treatments received by the patients were far to be complete. However, this first analysis of Moldovian primary liver cancer cases has the merit to establish the landscape of risk factors responsible for what should be considered as the most worrisome situation concerning liver health on the European continent.

## CONCLUSION

In conclusion, we described therein the epidemiological situation in a European country where incident cases of HCC are greatly dependent on the infectious burden. A remarkable feature is that all three viruses responsible for persistent liver infections, i.e. HBV, HCV and HDV, are highly prevalent and often acting together through dual or triple associations. Although the rate of multiple infections does not reach the dreadful levels observed in Mongolia, the country with the highest incidence of primary liver cancer in the world, we consider that this heavy burden of multiple liver infections that affects Moldovian patients with HCC is presumably responsible for the particularly high incidence of this disease in the country with regards to current European standards. The establishment of viral hepatitis endemicities at such high levels is, of course, reminiscent of the situation still currently observed in neighboring Romania and differentiates both countries from their surrounding neighbors (Bulgaria, Hungary, Serbia, Ukraine).

However, and despite their conspicuous cultural proximity, Moldovians and Romanians have lived since 1812 most of the times in separated political entities (the only exception is the short 1918-1940 period of Greater Romania/Romania Mare). This observation suggests that the circulation of hepatitis viruses in the ancestral Dacian populations, rather than being the recent outcome of poor public health policies or defective medical practices, might have been initiated more than two centuries ago according to modalities that remain to be discovered.

For the times going, energetic measures of screening should be implemented in Moldova to detect patients infected with hepatitis viruses and still unaware of their conditions. Availability of

efficient direct-acting antivirals, particularly those targeting HCV, might hopefully reduce the number of incident HCC cases in a near future. At risk behaviors (tattooing, intravenous drug use), especially responsible for the spread of HDV, should be clearly advertised as dangerous and discouraged in the concerned subgroups of populations. Finally, field studies should be conducted in southwest Moldova to better understand the modalities of circulation of HBV and HDV.

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**Introducere.** Republica Moldova este țara europeană cu cea mai mare incidență de carcinom hepatocelular (HCC) la ambele sexe. Cu toate acestea, nu există date care descriu în mod cuprinzător prezentarea și factorii de risc ai HCC în țară. Am decis să analizăm cazurile de HCC obținute într-o instituție terțiară de asistență medicală din Chișinău, capitala Republicii Moldova.

**Metode.** O serie de 148 de tumori hepatice primare, incluzând 139 de cazuri de HCC, au fost analizate retrospectiv pentru caracteristici demografice, date serologice și biochimice și prezentări clinice.

**Rezultate.** Vârsta medie a pacienților a fost de  $59 \pm 10$  ani (interval: 19-66) cu un raport de sex M: F de 1,9. Tumorile au apărut pe fondul de ciroză hepatică în 83% din cazuri și au constituit formațiuni multiple la diagnostic la 36% dintre pacienți. Valoarea alfa-fetoproteinei serice a depășit 10 ng/mL în 76% din cazuri. Mai mult de 81% dintre carcinoamele hepatocelulare au fost asociate cu cel puțin un virus hepatitic. Au predominat persoanele cu infecția virală C (55% din cazuri) față de pacienții seropozitivi pentru HBsAg (36%). Jumătate dintre acestea din urmă au fost de asemenea infectați cu virusul hepatitic Delta. În total, infecțiile duble sau triple au fost prezente în 24% și 7% din cazuri.

**Concluzii.** Povara infecțiilor cu virusuri hepatitice este deosebit de importantă în Moldova și corespunde unei situații frecvent observate în țările din emisfera sudică. O politică proactivă de screening pentru infecția hepatică persistentă care vizează populația cu risc de HCC (> 50 de ani) și asociată cu distribuția antiviralelor în cazuri pozitive ar trebui implementată rapid în Moldova pentru a reduce incidența sau cancerul hepatic primar.

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