The association of hepatocellular carcinoma with hepatitis C virus and its genotypes in Montenegrin patients

To the Editor,

It is reported that hepatocellular carcinoma (HCC) is the second leading cause of cancer mortality in the world [1]. Chronic hepatitis B (CHB) and chronic hepatitis C (CHC) account for the majority of HCC cases and their prevalence differs geographically. Worldwide, approximately 30% of HCC cases can be attributed to CHC [2]. The poor prognosis and considerable mortality associated with this cancer are mainly due to the late detection of the virus, inadequate monitoring of patients and the absence of significant clinical symptoms in early stages of the disease. We are presenting our investigation on the prevalence of CHC-related HCC in the Republic of Montenegro in order to evaluate their association and to establish the different hepatitis C virus genotypes in relation to this cancer.

Our study included 655 CHC patients during a 13-year period (January 2002 - January 2015): 490 were males (male to female ratio 2.9:1). The demographic, epidemiological and laboratory data was analyzed. Hepatitis was previously diagnosed based on histological reports (METAVIR score). The patients were followed-up according to current EASL and AASLD recommendations [3, 4]. The mean interval from liver biopsy to HCC detection was 5 years (range 2-9). All patients with HCC had been previously treated with alpha interferon plus ribavirin, obtaining a sustained virologic response (SVR) only in three cases.

This study was approved by the Ethics Committee Clinical Centre of Montenegro.

The prevalence of HCC in patients with CHC was found to be 18/655 (2.75%). Applied Barcelona Clinic criteria (BCLC) revealed that 14/18 HCC patients belonged to the stage A, 2/18 to the stage B, and 2/18 to the stage C [5]. Patients with HCC were significantly older (63.44±3.33 years, range 58-69) than patients with CHC without HCC (38±9, range 20-69) ($p<0.05$) and among them, 13/18 patients were older than 60 years. Twelve HCC patients were males (males:females 2:1).

Genotyping was performed in 522 CHC patients (Fig.1). Genotype 1 (GT-1) occurred most frequently in both groups, but more so in HCC patients (49% vs. 77.8%; $p<0.05$).

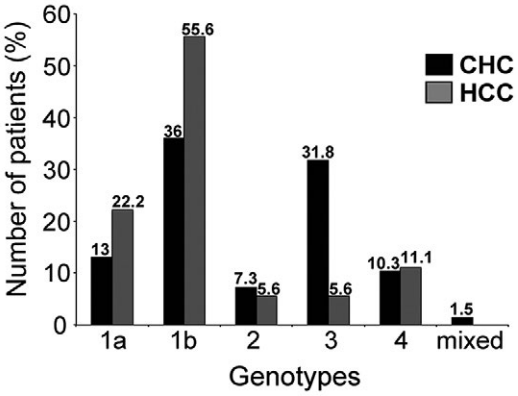

Fig. 1. The distribution of hepatitis C virus genotypes in CHC and HCC patients.

The characteristics of the HCC patients in relation to HCV genotypes are presented in Table I. Most of the patients were infected via iatrogenic routes. Mean values for serum alanine aminotransferase (ALT) and α-fetoprotein (AFP) were 142±46.5 IU/L and 138.94±60.43 ng/mL, respectively. Twelve patients exhibited increased AFP levels during follow-up. The initial histological findings revealed CHC with severe fibrosis in 6 patients and cirrhosis in 12. Viral reactivation occurred in 3 patients with previous SVR. A high viral load (> 800,000 IU/mL) was found in 12 patients.

Our results are generally in agreement with data from the literature [6, 7]. Patients with HCC are older, mostly males, and HCV infection results from iatrogenic transmission routes. We also observed a lower prevalence of GT-3 in comparison to GT-1 and a small number of drug abusers (4/18).

In conclusion, our findings confirm the association of HCC and HCV infection as well as the predominant genotype (GT-1b) in association with this cancer. The limitation of our study is the small number of patients, which might have caused some

Table I. The prevalence of clinical, laboratory and epidemiological characteristics of HCC patients in relation to HCV genotype

HCV genotype	1a	1b	2	3	4	Total (%)
Number of patients (%)	4	10	1	1	2	18 (100)
Transmission						
Iatrogenic[1]	3	10	-	1	-	14 (77.8)
IVDU[2]	1	1	-	-	2	4 (22.2)
Fibrosis[3]						
F3	2	3	1	-	-	6 (33.3)
F4	2	7	-	1	2	12 (66.6)
ALT elevation[4]	4	9	1	1	2	17 (94.4)
AFP elevation[5]	3	10	-	1	2	16 (88.9)
HIGH RNA[6]	3	5	1	1	2	12 (66.6)
SVR[7]	1	2	-	-	-	3 (16.7)

[1]Severe medical interventions, blood transfusion, etc.; [2]Intravenous drug use; [3]METAVIR scoring system; [4]>40 IU/L; [5]>10 ng/mL; [6]>800,000 IU/mL; [7]Sustained virologic response

bias in the statistical analysis. Further research is required to bring more information from this region.

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Influence of *MDR1* C3435T, *CYP2C19*2* and *CYP2C19*3* gene polymorphisms and clinical characteristics on the severity of gastric lesions: a case-control study

To the Editor,

Despite the marked progress in understanding the role of environmental and genetic factors in the etiopathogenesis of gastro-duodenal diseases, studies are frequently inconclusive [1]. It was suggested that *MDR1* C3435T and CYP2C19 gene polymorphisms might play a role in the gastro-duodenal lesion occurrence [2 ,3]. Our study aims to evaluate the possible association of *MDR1* C3435T, *CYP2C19*2* and *CYP2C19*3* single nucleotide polymorphisms (SNPs) with the severity of gastro-duodenal endoscopic lesions.

We screened consecutive patients referred for upper digestive endoscopy, in whom at least four biopsy specimens were obtained for routine histology. The study included 302 patients with no prior *H. pylori* eradication therapy, who were divided into 3 groups according to the severity of endoscopic lesions (Lanza score) [4]: mild (Lanza score 1 / 2,

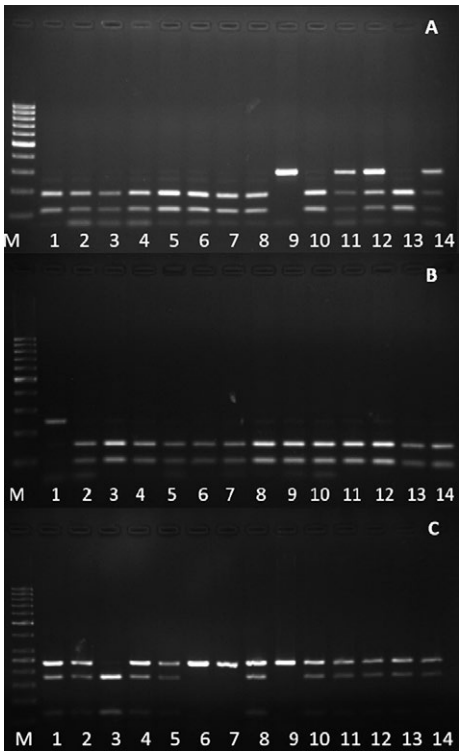

Fig. 1. Eletrophoregrams for the studied gene polymorphisms. A) CYP2C19*2 gene polymorphism. M: molecular marker 100 bp, lane 9 variant homozygous genotype *2/*2, lanes 1-8, 10, 13 homozygous wild-type genotype*1/*1, lanes 11, 12, 14 variant heterozygous genotype *1/*2; B) CYP2C19*3 gene polymorphism. M: molecular marker 100 bp, lane 1 variant homozygous genotype *3/*3, lanes 2-14 homozygous wild-type genotype *1/*1; C) MDR1 C3435T gene polymorphism. M: molecular marker 100 bp, lanes 6, 7, 9 variant homozygous genotype TT, lanes 3 homozygous wild-type genotype CC, lanes 1, 2, 4, 5, 8, 10-14 variant heterozygous genotype CT.

75 patients), severe (Lanza score 3 / 4, 48 patients) and controls (without lesions, Lanza score 0, 179 patients). Clinical and demographical data were collected in all patients. The *MDR1* C3435T, *CYP2C19*2* and *CYP2C19*3* gene polymorphisms were investigated using the PCR-RFLP technique as described previously [5] (Fig.1). The statistical analysis was performed using R software version 3.2.2.

On bivariate analysis a statistically significant correlation was observed between the presence or severity of the endoscopic lesions and certain comorbidities (coronary artery disease, p=0.04 and kidney disease, p=0.04) or antithrombotic therapies (low-dose aspirin, LDA, p=0.001 and anticoagulants, p=0.03). No association was found with proton pump inhibitors (PPI) therapy (p=0.55).

The distribution of *MDR1* C3435T genotypes was 17.5% wild-type CC, 52.3% heterozygous CT and 30.1% variant homozygous TT.

The *CYP2C19*2* genotyping revealed 216 (71.5%) genotype 1*/1* patients, 73 (24.2%) heterozygous 1*/2* and 13 (4.3%) variant homozygous 2*/2*. The *CYP2C19*3* genotype frequency indicated 99% (n=299) wild-type 1*/1* patients, 0.7% (n=2) heterozygous 1*/3* and 0.3% (n=1) variant homozygous 3*/3*. The gastro-duodenal lesions were correlated to *CYP2C19*3*, but not with *MDR1* C3435T and *CYP2C19*2*. Due to their reduced frequency [6], the *CYP2C19*3* genotypes were not used in multivariable analysis.

Active *H. pylori* infection (p=0.12), inactive gastritis (p=0.58), intestinal metaplasia and/or gastric atrophy (p=0.78) were not associated with the severity of gastro-duodenal lesions, while reactive gastropathy was less frequent in patients with severe mucosal lesions (p=0.05).

In the multinomial logistic regression analysis, LDA consumption, anticoagulant treatment and *H. pylori* infection were associated with severe endoscopic lesions. Mild gastric lesions were more frequently associated with comorbidities (coronary artery disease, kidney and respiratory diseases) as well as with age, LDA, anticoagulant treatment, but not with *H. pylori* infection (Table I).

In adjusted analysis of multinomial regression, independent risk factors for gastric lesions were LDA consumption (mild lesions: OR=2.52, 95%CI:1.45-4.40; severe lesions: OR=2.54, 95%CI:1.31-4.91), anticoagulant treatment (mild lesions: OR=2.15, 95%CI:1.06-4.38; severe lesions: OR=2.57, 95%CI:1.13-5.86). *H. pylori* infection increased the risk only for severe gastric lesions (mild lesions: OR=1.07, 95%CI:0.58-1.96; severe lesions: OR=2.10, 95%CI:1.06-4.13).

This is the first Romanian population-based study which has investigated the potential role of *MDR1* C3435T, *CYP2C19*2* and *CYP2C19*3* gene polymorphisms in the development of mucosal lesions, adjusted for the presence of concomitant PPI therapy and the most important clinical and histological known factors.

Table I. Univariate multinomial logistic regression between variables of interest and gastric lesions

	Mild gastric lesions		Severe gastric lesions	
Exogenous variables	p+	Crude OR (95% CI)	p+	Crude OR (95% CI)
Male gender	0.190	0.70 (0.40-1.20)	0.063	0.54 (0.29-1.03)
Mean age, years	0.022	1.03 (1.004-1.05)	0.32	1.01 (0.99-1.04)
LDA treatment	0.0009	2.54 (1.46-4.40)	0.003	2.645 (1.38-5.05)
Anticoagulant	0.0298	2.14 (1.08-4.26)	0.042	2.26 (1.03-4.96)
NSAIDs	0.191	0.54 (0.59-1.37)	0.306	0.56 (0.40-1.70)
Coronary artery disease	0.042	1.83 (1.02-3.29)	0.052	1.96 (0.99-3.86)
Kidney disease	0.014	2.47 (1.20-5.07)	0.25	1.68 (0.69-4.12)
Respiratory disease	0.056	1.88 (0.98-3.60)	0.16	1.72 (0.80-3.70)
Reactive gastropathy	0.386	0.78 (0.44-1.37)	0.021	0.41 (0.19-0.87)
Gastric atrophy/intestinal metaplasia	0.52	1.25 (0.64-2.44)	0.84	0.92 (0.39-2.15)
H. pylori infection	0.99	0.99 (0.56-1.79)	0.05	1.91 (0.99-3.65)
***CYP2C19*2* genotype**				
Heterozygous variant 1*/2*	0.68	1.14 (0.61-2.14)	0.74	1.13 (0.54-2.39)
Homozygous variant 2*/2*	0.44	1.68 (0.46-6.20)	0.35	1.98 (0.47-8.36)
***MDR1* C3435T genotype**				
Heterozygous variant CT	0.76	0.89 (0.43-1.86)	0.66	1.22 (0.51-2.95)
Homozygous variant TT	0.90	0.95 (0.43-2.09)	0.60	0.76 (0.28-2.09)
***CYP2C19*2* genotype**				
Hetero or homozygous variant (1*/2* or 2*/2*)	0.53	1.21 (0.67-2.18)	0.54	1.24 (0.62-2.48)
***MDR1* C3435T genotype**				
Hetero or homozygous variant (CT or TT)	0.80	0.91 (0.45-1.83)	0.91	1.05 (0.45-2.46)

LDA: low-dose aspirin, NSAIDs=non-steroidal anti-inflammatory drugs; +: crude p-values obtained from univariate multinomial logistic regression. The logistic regression analysis was used to highlight the independent risk factors for mild and severe gastro-duodenal lesions.

Our study found no association between presence or severity of endoscopic lesions and the *MDR1* C3435T, *CYP2C19*2* and *CYP2C19*3* gene polymorphisms. In our patients, the most important independent risk factors for both severe and mild endoscopic gastro-duodenal lesions were antithrombotic therapies and for severe gastric lesions *H. pylori* active infection.

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Tuberculin skin test and Quantiferon TB Gold in Romanian BCG vaccinated, immunosuppressed patients with moderate-to-severe Crohn's disease: a comparison with a Hungarian cohort

To the Editor,

We read with great interest the article published by Kurti et al., which presented data from 166 moderate-to-severe IBD patients (122 with Crohn's disease, CD) prospectively enrolled, treated with immunosupresives and/or biologicals [1]. As mentioned by Kurti et al., the diagnosis of latent tuberculosis (TB) remains problematic, particularly in patients treated with immunosuppressives and in countries with a high proportion of BCG vaccination, as tuberculin skin test (TST) positivity is not well-defined in BCG vaccinated patients. The authors found a TST positivity rate of 23.5%, 21.1%, 14.5% and 13.9%, for cut-off values of 5, 10, 15 and 20 mm, respectively. The interferon-gamma release assay (IGRA) positivity rate was 8.4%, and they concluded that TST and IGRA are partly complimentary methods, so an additional testing by TST with a cut-off >15 mm was recommended to identify patients at risk for latent TB.

Hungary belongs to the low incidence countries in Europe ($1.2/10^5$ inhabitants/year), while Romania has a moderate incidence ($20/10^5$ inhabitants/year) (WHO report) [2]. Data about latent TB in immunosuppressed patients in Romania are missing. Therefore, we want to report our recently published data from a retrospective study enrolling all CD patients (265) in Romania who were treated with Infliximab or Adalimumab for a period of 5 years (2008 - 2014 [3]. All patients were naïve for biologicals; 208 (78.5%) were treated with Azathioprine at the time of the evaluation for biologic therapy initiation and were treated in excellence centers [4]. All data were collected from the files of the archive of the National Insurance Agency.

Screening for latent TB (TST and/or IGRA) was performed in 96% of our patients before starting anti-TNF therapy: TST in 59.6% and IGRA in 30.6% patients. Ten (4%) performed only a chest X-ray, which was suggestive for latent tuberculosis in 2 patients.

The median age was 23 years in the Hungarian cohort and 38 in our cohort. A positive TST was defined if ≥ 5 mm, according to Romanian guidelines: recommendations for TST interpretation in BCG-vaccinated individuals are similar to those in non-BCG-vaccinated ones in Romania, a country of higher endemicity in active TB [5]. Only 16 patients (6%) performed both TST and IGRA in the same month. All the Hungarian patients were tested by both methods. We found a concordance of both tests in 14 out of 16 (87.5%); in 2 cases TST was positive and IGRA negative, similar to an Italian study (6). The correlation was better than that in the Hungarian study, where the TST positivity rate was 23.6% at the cut-off value of 5 mm and the IGRA positivity rate was only 8.4%.

In our study, 52 patients (20.4%) were proved to have latent TB, while in the Hungarian cohort TB incidence was much lower (8.4%). IGRA has a better diagnostic performance than TST in diagnosing latent TB in BCG vaccinated subjects, so the difference between the TST positivity rate and the IGRA positivity rate in the Hungarian cohort might be due to the high proportion of TST false positive results in their young BCG-vaccinated population.

Our data confirm that there is no correlation between the TST/IGRA positivity and the disease phenotype characteristics of CD, but patients on Azathioprine might have a higher risk of latent TB (22.8%) as compared with those not on Azathioprine (13.8%) ($p = 0.12$).

Regarding the follow-up of the patients under biologic therapy, TST and/or IGRA were performed only in 36 (13.6%),

and 4 patients became positive. We found 2 cases of active TB (1 located in lymph nodes, 1 in the small bowel), both with positive TST and/or IGRA testing at the initiation of biologic therapy. In the Hungarian cohort the incidence of active TB was also very low (1 in 98 patients treated with biologics).

In our opinion, the cut-off for positive TST testing in the two populations should be different because of the different TB incidence in Hungary and in Romania: 15 mm for Hungary, 5 mm for Romania, and this is demonstrated by a good correlation between TST and IGRA in our patients. The incidence of latent TB in our cohort was 20.4%, quite different compared to the Hungarian prospective cohort (8.4%). We strongly advise monitoring the risk of TB reactivation during biologic therapy by TST and/or IGRA, as isoniazid prophylaxis has good results. Fortunately, the risk of active TB under biologic therapy is very low (0.7%-1% in both countries cohorts).

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NUDT15: a novel player in thiopurine metabolism

To the Editor,

Thiopurines (i.e. azathioprine, mercaptopurine and thioguanine) play a key role in the maintenance therapy of inflammatory bowel disease (IBD). Firstly described in the 1950s, thiopurines were initially used in treating acute childhood leukemia [1]. Currently, thiopurines are used in treating a variety of autoimmune disorders, hematologic malignancies and preventing transplant rejections [2].

Over the years, the complex metabolism of thiopurines has been partly elucidated. The pharmacologically active end-products, 6-thioguaninenucleotides (6-TGN), consisting of 6-thioguanine-monophosphate (6-TGMP), 6-thioguanine-diphosphate (6-TGDP) and 6-thioguanine-triphosphate (6-TGTP), are formed by several enzymatic conversions [3]. In the past decade, it has been shown that the activity of one of these enzymes, thiopurine-methyltransferase (TPMT), correlates with the efficacy and toxicity of thiopurine treatment. Apart from this well-investigated influence, some studies describe the relationship between 6-TGN concentrations and other enzymes in the thiopurine metabolism, such as hypoxanthine guanine phosphoribosyl transferase (HGPRT), glutathione-s-transferases (GSTs), xanthine oxidase (XO) and inosine triphosphate pyrophosphatase (ITPase). However, the role of measuring activity of these enzymes before starting thiopurine therapy remains controversial in daily practice [3].

Interestingly, recent reports describe an important role of another key gene in the metabolism of thiopurines: the nucleoside diphosphate-linked moiety X motif 15 (NUDT15) gene codes for an enzyme in the regulation of 6-TGN concentrations by converting 6-TGTP into 6-TGMP (Fig. 1) [4]. One of the effects of thiopurines in oncology settings is acquainted by the incorporation of 6-TGTP in DNA, leading to DNA strand breakage and direct cytotoxicity. In patients with low NUDT15 expression, higher levels of 6-TGTP are measured, accounting for a higher number of strand breakage and higher cytotoxicity. NUDT15 regulates 6-TGTP concentration by downregulation to 6-TGMP, thus accounting for less cytotoxicity (in oncology) and most likely lower induction of apoptosis in activated T-lymphocytes when administered in dosages used in IBD treatment [4].

A recent review compares the expression of TPMT and NUDT15 in different ethnic groups (i.e. Caucasian and Asian) amongst thiopurine-using IBD patients [5]. In the Caucasian population, the incidence of an aberrant TPMT activity was ~10% compared to ~3% in the Asian population. Interestingly, the occurrence of leukopenia was significantly higher amongst Asians. In this subgroup, reduced NUDT15 activity was found in almost 90% of the cases, compared to 7% in the general Asian population, suggesting that screening for NUDT15-activity may play a role in the prevention of early leukopenia. In Caucasian patients with leukopenia, this association was identical; however, the frequency of this risk allele is much lower in Caucasian populations with an occurrence of only 0.4% [5].

With this letter, we conclude that the discovery of NUDT15 is an important next step in the further unravelment of the complex thiopurine metabolism, possibly leading to new clinical strategies of tailored medicine and prevention of early adverse events in IBD patients.

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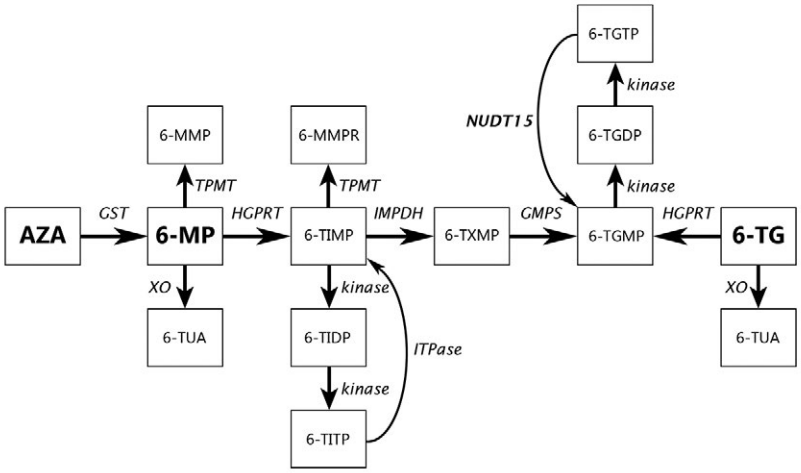

Fig. 1. Simplified scheme of thiopurine metabolism. AZA: azathioprine; 6-MP: 6-mercaptopurine; 6-TG: 6-thioguanine; 6-MMP: 6-methylmercaptopurine; 6-TUA: 6-thiouric acid; 6-MMPR: 6-methylmercaptopurine ribonucleotides; 6-TIMP: 6-thioinosine monophosphate; 6-TIDP: 6-thioinosine diphosphate; 6-TITP: 6-thioinosine triphosphate; 6-TXMP: 6-thioxanthosine monophosphate; 6-TGMP: 6-thioguanine monophosphate; 6-TGTP: 6-thioguanine diphosphate; 6-TGTP: 6-thioguanine triphosphate
Enzymatic conversions: GST: glutathione S-transferase; TPMT: thiopurine S-methyl transferase; XO: xanthine oxidase; HGPRT: hypoxanthine-guanine phosphoribosyl transferase; IMPDH: inosine monophosphate dehydrogenase; GMPS: guanosine monophosphate synthetase; ITPase: inosine triphosphate pyrophosphohydrolase; NUDT15: nucleoside diphosphate-linked moiety X motif 15 (Adapted from van Asseldonk et al, Curr Drug Metabolism, 2009;9:981-97).

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