THE RISKS OF HEPATOCELLULAR CARCINOMA AND VARICEAL BLEEDING AFTER HCV ERADICATION WITH DIRECT-ACTING ANTIVIRAL THERAPY: A PROPENSITY SCORE ANALYSIS

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THE RISKS OF HEPATOCELLULAR CARCINOMA AND VARICEAL BLEEDING AFTER HCV ERADICATION WITH DIRECT-ACTING ANTIVIRAL THERAPY: A PROPENSITY SCORE ANALYSIS (Abstract): The combination paritaprevir/ritonavir, ombitasvir, and dasabuvir (PrOD), which achieves a high sustained virologic response (SVR) rate and few side effects, has dramatically changed the outcome of hepatitis C virus (HCV) infection. The risk of hepatocellular carcinoma (HCC) and variceal bleeding in patients treated with interferon (IFN)-free direct-acting antivirals (DAAs) is unknown. The aim of this prospective study was to evaluate the rate of HCC and variceal bleeding and identify prognostic factors for decompensation/complications in HCV-1b-infected patients with compensated liver cirrhosis following treatment with PrOD with or without ribavirin. **Material and methods:** A total of 483 HCV patients received PrOD treatment. Patients with a history of HCC were excluded from the study. Prior antiviral therapy was identified in 59% of patients. Patient data were collected at baseline, at the end of treatment (EoT), at 3 months after EOT (SVR) and during an 18-month surveillance period. Patients were divided into two age groups: <60 years (233 patients) and ≥60 years (250 patients). **Results:** The median observation period was 540 days. During this period, HCC developed in 18 patients (3.7%) and variceal bleeding developed in 9 patients (1.9%). A Propensity score matching analysis found no significant difference in the incidence of HCC (p= 0.078) or variceal bleeding (p=0.426) between the two groups. The mean serum AFP levels decreased in the young group (baseline=19.44 ng/dL, SVR=4.57 ng/dL) and the elderly group (baseline=4.52 ng/dL, SVR=10.69 ng/dL). Edge of decompensation and previous esophageal varices were significantly associated with the risk of variceal bleeding. **Conclusions:** The risk of HCC (5.3%) and variceal bleeding (2%) development in elderly patients (≥60 years) following viral eradication by IFN-free DAA therapy may follow a specific pattern. **Keywords:** DIRECT ACTING ANTIVIRALS, HEPATITIS C VIRUS, HEPATOCELLULAR CARCINOMA, VARICEAL BLEEDING.
The treatment of hepatitis C virus (HCV) with direct-acting antivirals (DAAs) has significantly changed the approach to patient selection. Interferon (IFN)-free regimens offer an important benefit for patients who are difficult to treat such as liver cirrhosis (1). DAAs have been found to be safe and effective in all patients, including those with hypoalbuminemia or thrombocytopenia, with the exception of patients with decompensated cirrhosis (2, 3). For the 1b genotype, which represents approximately 75% of all infections, an IFN-free therapeutic regimen achieved a sustained virologic response (SVR) in more than 95% of cases considered difficult to treat (elderly patients and those with compensated or decompensated liver cirrhosis, renal failure, or obesity) (4, 5). Based on data reported by clinical trials, SVR correlates with a decrease in mortality, a survival rate in formerly HCV-infected patients comparable to that of the general population, amelioration of portal hypertension, and reduced risks of hepatic disease decompensation and hepatocellular carcinoma (HCC) (6). Among cirrhotic patients with HCV, an annual incidence of HCC of up to 7% was reported (7). Some studies found that IFN- and DAA-based antiviral treatments reduced the risk of HCC (7-9), whereas others found no effect (9). The risk of variceal bleeding after DAA treatment remains unknown.

The aim of this study was to evaluate the risk of HCC and variceal bleeding and identify prognostic factors for decompensation/complications in HCV-1b-infected patients with compensated liver cirrhosis following treatment with paritaprevir/ritonavir, ombitasvir, and dasabuvir (PrOD) with or without ribavirin.

**MATERIAL AND METHODS**

**Patients selection**

Between December 1, 2015 and July 31, 2016, patients eligible for the National Insurance House reimbursement programme on PrOD treatment were prospectively enrolled via a regional antiviral therapy register. Patients with compensated HCV cirrhosis (Child-Pugh class A), genotype 1a or 1b, and severe liver fibrosis (METAVIR score 4) were eligible. Patients previously treated with IFN and ribavirin who recorded a lack of virologic response, virologic breakthrough or relapses were considered for PrOD treatment. Patients with decompensated HCV cirrhosis (defined as the presence of ascites, jaundice, variceal bleeding, hepatic encephalopathy; Child-Pugh class B or C) or the presence of HCC or dysplastic liver nodules were excluded. Only patients who achieved SVR were included in this study. We further defined a subgroup of patients who, at the time of therapy initiation, had characteristics that indicated potential decompensation-edge of decompensation group - Child-Pugh class A, score 6 and/or esophageal varices.

**Treatment**

Patients received the PrOD regimen, with or without ribavirin, for 12 weeks (in the case of genotype 1b HCV cirrhotic patients). The PrOD regimen administered daily included 25 mg ombitasvir, 150 mg paritaprevir, and 100 mg ritonavir in combination with 500 mg dasabuvir. Ribavirin doses of up to 1200 mg daily, adjusted according to hemoglobin level, were added.

**Patients evaluation**

Patients were evaluated at baseline, at the end of treatment (EoT), at SVR (12 weeks after the completion of treatment) and every 12 weeks until the end of the
follow-up (18 months post-SVR). Data collected prospectively included demographics, medical history, blood tests (full blood count, INR, ALT, AST, bilirubin, creatinine, AFP and HCV RNA quantitative test) and abdominal ultrasonography. The METAVIR score was evaluated using FibroMax™ or liver biopsy. FibroMax™ is a combination of five non-invasive diagnostic tests including FibroTest, ActiTest, SteatoTest, NashTest and AshTest. This method is used to diagnose hepatic fibrosis, viral necro-inflammatory activity, hepatic steatosis, severe alcoholic steatohepatitis (in alcoholic patients) and non-alcoholic steatohepatitis (in overweight, diabetic, or Insulin-resistant patients) (10). The FibroMax™ score is calculated using an algorithm based on a patients’ sex, age, weight, height, and specific blood biomarkers (ALT, AST, GGT, haptoglobin, blood glucose, lipids, apolipoprotein A1, alpha-1-macroglobulin) (11).

Liver enzymes and quantitative viral load for HCV were re-evaluated at EoT and SVR (12). SVR was defined as undetectable HCV RNA at 12 weeks after the completion of treatment (11).

Patients found to have high AFP levels (≥20 ng/mL) underwent computed tomography (CT) and/or magnetic resonance imaging (MRI). Patients without suspicion of HCC according to the Liver Imaging Reporting and Data System (LI-RADS) criteria, or evidence of dysplastic nodules requiring surveillance, received antiviral treatment. During follow-up, HCC diagnosis required either a positive ultrasound with confirmation on a second dynamic imaging modality CT or MRI or a diagnostic biopsy (13). Patients who developed variceal bleeding were treated according to the current clinical guidelines (14). The diagnosis of variceal bleeding was confirmed by upper digestive endoscopy, performed in all patients in the first 12 hours from the bleeding event.

Patients were stratified into two groups based on age (<60 years and ≥60 years).

**Outcomes**

HCC occurrence and variceal bleeding were considered events of interest in both study groups.

**Statistical analysis**

Continuous variables were evaluated by descriptive statistics and described as the mean (±SD) or median.

Categorical values were expressed as percentages. Student’s t-test was performed to compare the mean of continuous variables.

A propensity analysis was performed to match the patients one-to-one by age group (<60 years and ≥60 years (15, 16). Variables entered in the propensity model included BMI, serum albumin, platelet counts, leukocyte counts, AST, ALT, AFP and GGT levels, gender, edge of decompensation status, esophageal varices, comorbidities, T2DM and arterial hypertension.

The risks of HCC and variceal bleeding were analyzed using Cox multivariate analysis in the subgroup of patients matched by propensity score.

Statistical analysis was performed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). A p-value ≤0.05 was considered statistically significant.

This prospective study was performed according to the Declaration of Helsinki and international guidelines for observational studies. Written inform consent was obtained from each patient before starting the study. The study was approved by the National Ethics Committee of Medicines and Medical Devices (17).
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RESULTS

Patient characteristics

A total number of 483 consecutive patients who completed the PrOD regimen were evaluated. The baseline characteristics of these patients are described in tab. I. All patients were diagnosed with severe liver fibrosis (F4 METAVIR score), and in 59.0% of cases, patients were previously treated with IFN. One hundred ninety-nine of cases (41.2%) were identified to be on the edge of decompensation. None of the patients were lost during the follow-up.

TABLE I

Baseline Characteristics of HCV Patients (n = 483)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male (n = 220)</td>
<td>45.5%</td>
</tr>
<tr>
<td></td>
<td>Female (n = 263)</td>
<td>54.5%</td>
</tr>
<tr>
<td>Age (yrs.) (mean ± SD)</td>
<td>59.18 ± 8.30</td>
<td></td>
</tr>
<tr>
<td>Weight (kg) (mean ± SD)</td>
<td>76.79 ± 14.94</td>
<td></td>
</tr>
<tr>
<td>Height (cm) (mean ± SD)</td>
<td>165.96 ± 0.19</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²) (mean ± SD)</td>
<td>27.77 ± 4.19</td>
<td></td>
</tr>
<tr>
<td>Edge of Decompensation</td>
<td>Yes (n = 199)</td>
<td>41.2%</td>
</tr>
<tr>
<td></td>
<td>No (n = 284)</td>
<td>58.8%</td>
</tr>
<tr>
<td>Esophageal Varices</td>
<td>Yes (n=135)</td>
<td>28.0%</td>
</tr>
<tr>
<td></td>
<td>No (n=348)</td>
<td>72.0%</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Yes (n=215)</td>
<td>44.5%</td>
</tr>
<tr>
<td></td>
<td>No (n=268)</td>
<td>55.5%</td>
</tr>
</tbody>
</table>

Patient characteristics by age group (<60 years and ≥60 years) are found in tab. II. There were no statistically significant differences between the two groups except for gender, comorbidities and arterial hypertension.

TABLE II

Clinical Characteristics of Young (<60 years) vs. Elderly (≥60 years) Groups in 483 Unmatched Cases

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Young Group (&lt;60 years old)</th>
<th>Elderly Group (≥60 years old)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Male/Female)</td>
<td>128/105</td>
<td>92/158</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.30 (16.80-41.40)</td>
<td>27.12 (19.50-40.63)</td>
<td>0.367</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.06 (3.10-5.25)</td>
<td>3.91 (3.04-4.97)</td>
<td>0.248</td>
</tr>
<tr>
<td>Platelet Count (x 10³/mm³)</td>
<td>142 (34-466)</td>
<td>128 (40-362)</td>
<td>0.44</td>
</tr>
<tr>
<td>RNA VHC (log/UI/mL)</td>
<td>5.71 (1.26-6.86)</td>
<td>5.64 (1.06-7.18)</td>
<td>0.473</td>
</tr>
<tr>
<td>Leukocyte (x 10³/mm³)</td>
<td>6030 (2280-10990)</td>
<td>5270 (1880-12140)</td>
<td>0.571</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>94 (29-381)</td>
<td>86 (31-342)</td>
<td>0.776</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>97 (23-412)</td>
<td>86 (24-382)</td>
<td>0.074</td>
</tr>
<tr>
<td>AFP (ng/mL)</td>
<td>9.72 (1.57-131.20)</td>
<td>8.33 (1.13-53.37)</td>
<td>0.483</td>
</tr>
<tr>
<td>GGT (IU/L)</td>
<td>92 (17-455)</td>
<td>62 (12-279)</td>
<td>0.379</td>
</tr>
</tbody>
</table>
Parameter | Young Group (<60 years old) n = 233 | Elderly Group (≥60 years old) n = 250 | p-value
---|---|---|---
International Normalized Ratio (INR) | 1.16 (0.90-4.07) | 1.12 (0.92-7.79) | 0.307
Edge of Decompensation (Yes/No) | 36.6% / 61.4% | 43.6% / 56.4% | 0.262
Esophageal varices (Yes/No) | 25.7% / 74.3% | 30.0% / 70.0% | 0.298
Comorbidities (Yes/No) | 18.01% / 30.23% | 26.50% / 25.26% | 0.002
T2DM (Yes/No) | 6.21% / 42.03% | 9.73% / 42.03% | 0.082
Arterial Hypertension (Yes/No) | 8.49% / 39.75% | 17.60% / 34.16% | <0.001

The propensity score analysis found 461 matched cases (16 patient variables), where 230 were young patients and 231 were elderly patients (tab. III).

| Parameter | Young Group (< 60 years old) N=230 | Elderly Group (≥ 60 years old) N=231 | p-value
---|---|---|---
Gender (Male/Female) | 126/104 | 92/139 | 0.002
BMI (kg/m²) | 28.10 (16.80-41.40) | 27.05 (19.50-40.63) | 0.32
Albumin (g/dL) | 4.04 (3.10-5.25) | 3.92 (3.04-4.97) | 0.249
Platelet Count (x 10³/mm³) | 141.5 (34-466) | 134 (45-362) | 0.472
RNA VHC (log/UI/mL) | 5.72 (1.26-6.86) | 5.66 (1.06-7.15) | 0.489
Leukocyte (x 10³/mm³) | 5990 (2280-10990) | 5330 (2610-12140) | 0.616
AST (IU/L) | 94 (29-381) | 81 (31-342) | 0.776
ALT (IU/L) | 97 (23-412) | 84 (24-382) | 0.096
AFP (ng/mL) | 9.67 (1.57-131.20) | 7.69 (1.13-53-37) | 0.505
GGT (IU/L) | 91 (17-455) | 63 (12-279) | 0.373
International Normalized Ratio (INR) | 1.16 (0.90-4.07) | 1.12 (0.92-7.79) | 0.187
Edge of Decompensation (Yes/No) | 19.52 % / 30.37 % | 21.04 % / 29.07 % | 0.57
Esophageal Varices (Yes/No) | 13.02 % / 36.88% | 14.10 % / 36.01% | 0.675
Comorbidities (Yes/No) | 18.66 % / 31.24% | 23.64 % / 26.46% | 0.038
T2DM (Yes/No) | 6.51 % / 43.39 % | 7.81 % / 42.30 % | 0.506
Arterial Hypertension (Yes/No) | 8.49 % / 39.75 % | 14.32 % / 35.80 % | 0.004

There was no significant intergroup difference in any of the analyzed parameters except gender and concomitant diseases. Ninety young patients and 109 elderly patients were on the edge of decompensation (p = 0.262).

**HCC and variceal bleeding incidence**

During the observation period, HCC developed in five out of 233 (2.14%) patients in the <60-year-old group and 13 out of 250 (5.2%) patients in the ≥60-year-old group (p=0.077). An analysis of the effect of gender revealed no significant differences between the ≥60-year-old group (p=0.39) and the <60-year-old group (p=0.45). The **male : female ratio** of HCC incidence was 2.5 : 1. The distribution of
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...events of interest (HCC and variceal bleeding) in different study subgroups are presented in tab. IV and V.

The incidence of HCC was significantly elevated in patients with high levels of AFP (> 7 ng/mL). Mean serum AFP levels decreased in the < 60-year-old group from baseline (19.44 ng/mL) to SVR (4.57 ng/mL). The corresponding mean serum AFP levels found in the ≥60-year-old group were moderate (baseline 14.52 ng/mL, SVR 10.69 ng/mL).

### TABLE IV
Annual risk rate of HCC post SVR

<table>
<thead>
<tr>
<th>Age</th>
<th>N (%)</th>
<th>Edge of decompensation</th>
<th>Compensated</th>
<th>Previous IFN</th>
<th>No previous IFN</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (N; %)</td>
<td>483 (100%)</td>
<td>199 (41.20%)</td>
<td>284 (58.59%)</td>
<td>285 (59%)</td>
<td>198 (40.99%)</td>
</tr>
<tr>
<td>HCC (N; %)</td>
<td>18 (3.72%)</td>
<td>9 (4.52%)</td>
<td>9 (3.16%)</td>
<td>10 (3.05%)</td>
<td>8 (4.04%)</td>
</tr>
<tr>
<td>Annual Risk Rate</td>
<td>0.41 (0.145; 1.207)</td>
<td>1.15 (0.687; 1.929)</td>
<td>0.89 (0.568; 1.411)</td>
<td>0.39 (0.166; 0.927)</td>
<td>1.91 (1.435; 2.546)</td>
</tr>
<tr>
<td>(ARR; 95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60 years old</td>
<td>233 (48.24%)</td>
<td>90 (18.63%)</td>
<td>143 (29.60%)</td>
<td>143 (29.60%)</td>
<td>90 (18.63%)</td>
</tr>
<tr>
<td>HCC</td>
<td>5 (2.14%)</td>
<td>1 (1.11%)</td>
<td>4 (2.79%)</td>
<td>4 (2.79%)</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>Annual Risk Rate</td>
<td>0.59 (0.281; 1.238)</td>
<td>0.51 (0.088; 2.967)</td>
<td>1.31 (0.839; 2.065)</td>
<td>0.98 (0.475; 2.019)</td>
<td>1.03 (0.348; 3.056)</td>
</tr>
<tr>
<td>(ARR; 95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60 years old</td>
<td>250 (51.76%)</td>
<td>109 (22.56%)</td>
<td>141 (29.19%)</td>
<td>142 (29.39%)</td>
<td>108 (22.36%)</td>
</tr>
<tr>
<td>HCC</td>
<td>13 (5.2%)</td>
<td>8 (7.33%)</td>
<td>5 (3.54%)</td>
<td>6 (4.22%)</td>
<td>7 (6.48%)</td>
</tr>
<tr>
<td>Annual Risk Rate</td>
<td>1.40 (1.023; 1.940)</td>
<td>1.37 (0.830; 2.264)</td>
<td>0.72 (0.368; 1.430)</td>
<td>0.14 (0.022; 0.929)</td>
<td>2.22 (1.766; 2.800)</td>
</tr>
<tr>
<td>(ARR; 95% CI)</td>
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</tbody>
</table>

### TABLE V
Annual risk rate of variceal bleeding post SVR

<table>
<thead>
<tr>
<th>Age</th>
<th>N (%)</th>
<th>Edge of decompensation</th>
<th>Compensated</th>
<th>With esophageal varices</th>
<th>Without esophageal varices</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (N; %)</td>
<td>483 (100%)</td>
<td>199 (41.20%)</td>
<td>284 (58.79%)</td>
<td>135 (27.95%)</td>
<td>348 (72.04%)</td>
</tr>
<tr>
<td>Variceal Bleeding (N; %)</td>
<td>9 (1.86%)</td>
<td>9 (4.52%)</td>
<td>0</td>
<td>9 (6.66%)</td>
<td>0</td>
</tr>
<tr>
<td>Annual Risk Rate</td>
<td>0.71 (0.148; 3.453)</td>
<td>0.56 (0.349; 0.907)</td>
<td>2.65 (0.746; 9.476)</td>
<td>0.52 (0.285; 0.970)</td>
<td></td>
</tr>
<tr>
<td>(ARR; 95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 years old</td>
<td>233 (48.24%)</td>
<td>90 (18.63%)</td>
<td>143 (29.60%)</td>
<td>60 (12.42%)</td>
<td>173 (35.81%)</td>
</tr>
<tr>
<td>Variceal Bleeding (N; %)</td>
<td>4 (1.71%)</td>
<td>4 (4.44%)</td>
<td>0</td>
<td>4 (6.66%)</td>
<td>0</td>
</tr>
<tr>
<td>Annual Risk Rate</td>
<td>0.81 (0.327; 2.045)</td>
<td>3.00 (0.525; 17.149)</td>
<td>0.33 (0.088; 1.256)</td>
<td>1.50 (0.520; 4.323)</td>
<td>0.50 (0.106; 2.355)</td>
</tr>
<tr>
<td>(ARR; 95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60 years old</td>
<td>250 (51.75%)</td>
<td>104 (21.53%)</td>
<td>141 (29.19%)</td>
<td>75 (15.52%)</td>
<td>175 (36.23%)</td>
</tr>
<tr>
<td>Variceal Bleeding (N; %)</td>
<td>5 (2.0%)</td>
<td>5 (4.8%)</td>
<td>0</td>
<td>5 (6.66%)</td>
<td>0</td>
</tr>
<tr>
<td>Annual Risk Rate</td>
<td>1.14 (0.590; 2.226)</td>
<td>0.11 (0.007; 1.177)</td>
<td>0.64 (0.435; 0.950)</td>
<td>0.33 (0.027; 4.186)</td>
<td>0.50 (0.296; 0.844)</td>
</tr>
<tr>
<td>(ARR; 95% CI)</td>
<td></td>
<td></td>
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<td></td>
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</table>
Multivariate analysis revealed that the probability of HCC development at 540 days was higher in the ≥60-year-old group (5.4%) than in the <60-year-old group (1.7%) (Figure 1).

Propensity scores matching analysis found an increased probability of HCC development in the ≥60-year-old group (5.3%) compared to the <60-year-old group (1.8%), with no significant differences observed between the groups (p=0.078) (fig. 2).

Fig. 1. Cumulative HCC Development-Before Propensity Score Matching

Fig. 2. Cumulative HCC Development in Propensity Score Matched Patients

Variceal bleeding was recorded in nine (1.9%) of all cases. None of the patients without previous described esophageal varices has bled. Esophageal varices at
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Baseline were found in 25.7% of <60-year-old patients and 30.0% of ≥60-year-old patients. There was no difference regarding the variceal bleeding rate between elderly group and the young group (2.0% versus 1.7%, p=0.818). Evolution of variceal bleeding was favorable under standard treatment and no mortality was recorded.

The edge of decompensation had significant influence on HCC development in elderly group. Eight patients (14.50%) in the elderly group were at the edge of decompensation and developed HCC vs. 1 patient (1.8%) in the young group (p=0.011).

DISCUSSION

Our study included a homogeneous large cohort of HCV genotype 1b liver cirrhosis patients, followed-up for 18 months in tertiary academic centers, aiming to evaluate the incidence and the risk factors of HCC and variceal bleeding development. Hepatocellular carcinoma (HCC) remains the most important life-threatening complication of HCV cirrhosis. IFN significantly reduced the risk of HCC in this category of patients; however, usage was limited by contraindications (depression, immune diseases). The development of new DAAAs surpassed these limitations imposed by IFN usage. The risk of HCC associated with DAA therapy remains unclear. Several studies found that DAAAs increased the risk of HCC recurrence (19, 20). These studies investigated HCC recurrence and not incidence, had a limited follow-up period and were underpowered. An extensive retrospective study included more than 3,000 HCV cirrhotic patients treated with either IFN or DAAAs or a combination. During a 6.1-year follow-up period, DAA treatments reduced the risk of HCC up to 71%, with no difference between IFN and DAAAs (9).

The most important risk factors associated with HCC in HCV cirrhotic patients were age, gender, excessive alcohol consumption, comorbidities (diabetes, obesity, renal diseases, lymphoma, HIV coinfection) (21).

Our study investigated the risk of HCC development in young (<60 years) and elderly (≥60 years) patient groups. During the 18-month follow-up period only 3.7% of cases developed HCC. The male : female ratio of HCC incidence was 2.5:1; however, the difference was not statistically significant, likely due to the relatively small sample size.

To overcome the bias due to differences in the distribution of covariates among young and elderly patients treated with PrOD, we created one-to-one matches using propensity score analysis. The model was used to obtain a one-to-one match according to the nearest neighbor matching method, resulting in a sample size of 230 patients per cohort.

The propensity score matching analysis showed an increased probability of HCC development in the elderly patients (5.3%) compared to the young patients (1.8%). The lack of statistical significance may be due to the higher number of females in the elderly patient group. Alpha-fetoprotein is considered an important risk factor for HCC in cirrhotic patients irrespective of cause (22). Long-term follow-up studies have found that approximately 1-8% of patients with cirrhosis develop HCC per year, 2% in HBV-infected cirrhotic patients and 3-8% in HCV-infected cirrhotic patients (23). We found a significant correlation between AFP values and the incidence of HCC (64% of HCC cases were noted in patients with a baseline AFP of more than 7
ng/mL). Edge of decompensation had a significant influence on HCC development.

The second most common cause of death in cirrhotic patients is gastrointestinal bleeding produced by esophageal varices effraction (24).

IFN prevented or delayed the development of de novo esophageal varices; however, its efficacy against gastrointestinal bleeding was not established (25). There was a lack of information regarding effectiveness of DAAs in prevention of variceal bleeding.

In Romania between 2015-2016, a single oral antiviral medication was available for the treatment of HCV, and National Insurance House reimbursement conditions were limited to patients with compensated liver cirrhosis (Child-Pugh class A) (26). The limiting condition for PrOD treatment was related to the demonstration of F4 fibrosis by FibroMax™ or liver biopsy. The majority of patients were evaluated by FibroMax™, and we included only patients with a value of over 0.75, considered a cut-off for an F4 METAVIR score. Patients who were at the limit of F4 on the FibroMax™ examination usually had hepatic stiffness values evaluated with Fibroscan in the clear liver cirrhosis spectrum. Using the FibroMax™ method permitted the inclusion of a population of patients with cirrhosis, sometimes at the edge of decompensation. In this case, the mean value of Fibroscan is above the limit that the Baveno VI (13) consensus considers indicative of clinically significant portal hypertension.

Furthermore, some patients already had esophageal varices (included in the Baveno II stage), some had platelet counts indicating portal hypertension or albumin values indicating a deficiency in liver albumin synthesis. The cohort of patients approved for PrOD treatment due to compensated status as defined by Child-Pugh scores allowed the admission of a wide spectrum of stages of liver cirrhosis into the study. Considering the grading of patients after FibroMax™ and Fibroscan, and adopting the proposed Baveno staging (13), we found that we treated compensated liver cirrhosis patients in a lower proportion than those at the limit of edge of decompensation.

In cirrhotic patients without varices, the rate of developing them was estimated at 5-8% per year (13, 27). Patients with small varices develop large varices at an annual rate of 8% as well (27). The risk of first variceal bleeding is higher in patients with larger varices, with red-signs and decompensated liver cirrhosis, and range between 6-15% per year (28). In our study the annual rate of the first variceal bleeding in patients who already had esophageal varices was 2.65% per year, with no significant difference between the elderly and the young group (p=0.918). No patient without previous described varices had any bleeding. The lower percentage of variceal bleeding after SVR than reported data from literature and the fact that none of patients without esophageal varices developed bleeding could suggest a tendency of improving portal hypertension after SVR and the risk of bleeding which, however, is not eliminated.

Our study has some strengths such as large number of patients, homogeneous groups of cirrhotic genotypes 1b cases, a high proportion at edge of decompensation and excellent adherence. However, the main limitation is due to short period of follow-up.

**CONCLUSIONS**

The risk of HCC (5.3%) and the vari-
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...teral bleeding (2.0%) in elderly patients following viral eradication by IFN-free DAA therapy may follow a specific pattern, comprised of factors like the edge of de-compensation, AFP levels, age, esophageal varices.

However, further larger cohort studies with longer follow-up are needed to characterize this pattern.

**CONFLICT OF INTERESTS AND FUNDING**

The authors declare that there is no conflict of interest and they received no specific funding regarding this scientific research.

**REFERENCES**


**NEWS**

COVID-19: EVEN THROUGH DEATH WE ARE NO LONGER EQUAL?

A recent research paper entitled “Racial disparities in COVID-19 mortality are driven by unequal infection risks” made by a group of researchers led by Jon Zelner, after analyzing COVID-19 incidence and mortality data in the state of Michigan, signals a surprising paradigm shift: the unequal distribution of the risks of infection between different race-ethnic groups. The black population was the most affected group of all, with an age-standardized incidence of 1,626/100,000 and a mortality rate of 244/100,000. Using Hierarchical models of Bayesian regression for the data analysis and the posterior predictive controls for the results validations, dramatic disparities were found, the age-standardized incidence being 5.5 (95% CrI= 5.4, 5.6) and the mortality 6.7 (95% CrI= 6.4, 7.1) times higher for the Blacks, compared with the Whites. Zelner J, Trangucci R, Naraharisetii R, *et al.* Racial disparities in COVID-19 mortality are driven by unequal infection risks. *Clin Infect Dis* 2020. doi:10.1093/cid/ciaa1723).