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RAPID COMMUNICATION



Direct-acting antiviral therapy decreases hepatocellular carcinoma recurrence rate in cirrhotic patients with chronic hepatitis C

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Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy[☆]

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Letters to the Editor



 **EASL | JOURNAL OF
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**Unexpected high incidence of hepatocellular carcinoma
in cirrhotic patients with sustained virologic response
following interferon-free direct-acting antiviral treatment**

Research Article



Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals

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Inclusion criteria

- First HCC diagnosed by invasive or non-invasive criteria following AASLD guidelines
- Complet remission after HCC treatment defined by EASL guidelines

Exclusion criteria

- Prior history of HCC before January 2009
- Liver transplantation before HCC diagnosis
- Presence of non-characterized nodules after HCV treatment
- History of DAA treatment before HCC diagnosis
- Hepatic decompensation
- HIV coinfection

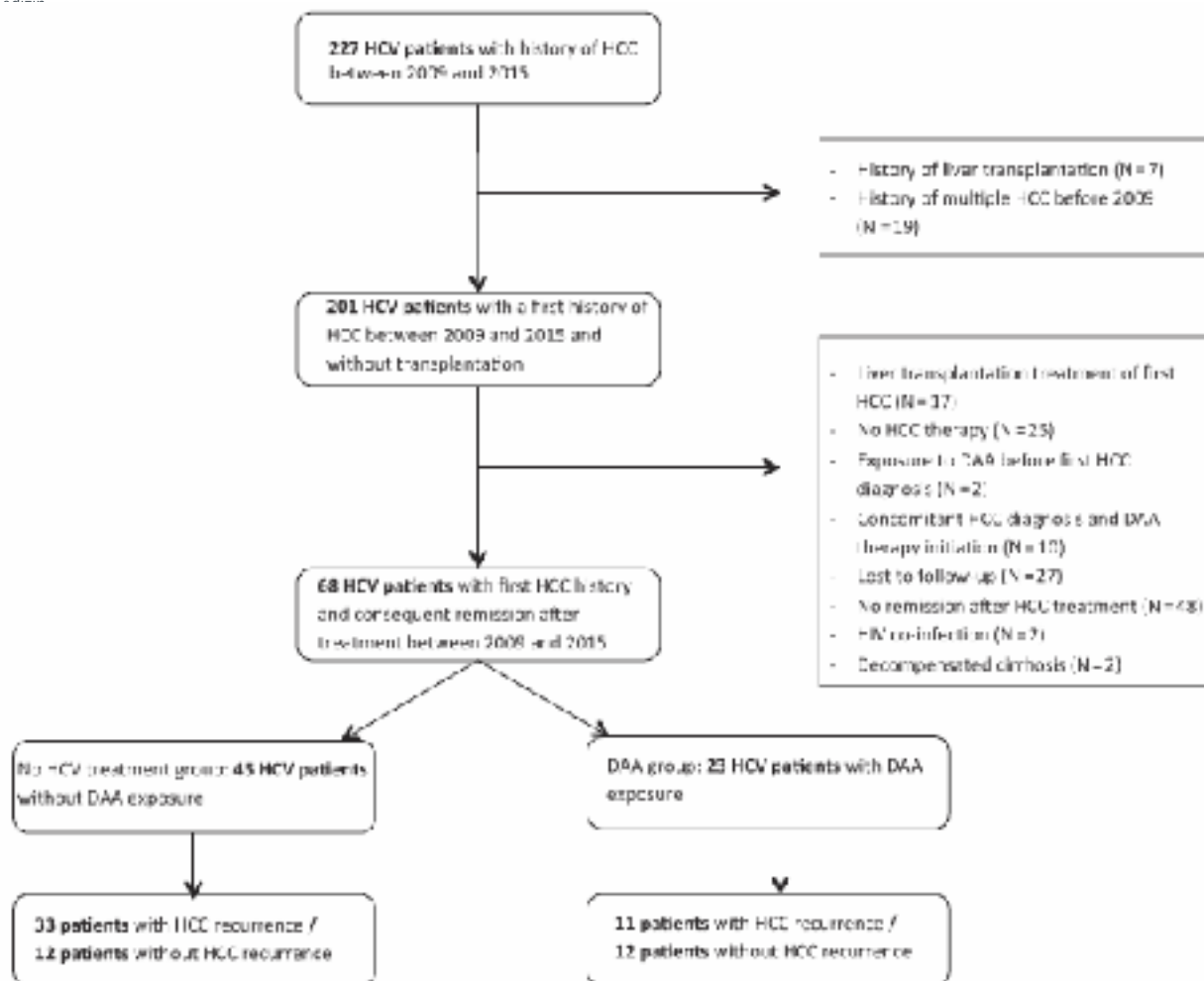


FIGURE 1 Flow chart showing patient selection. HCC: hepatocellular carcinoma, DAA: direct-acting antiviral drug

| Characteristics | DAA-exposed (N=23) | Non-exposed (N=45) | Total (N=68) | p-value |
|---|--------------------|--------------------|--------------|--------------|
| Age (years); median (range) | 58 (51 - 84) | 66 (51 - 90) | 62 (51 - 90) | 0.002 |
| Male gender – n (%) (N=68) | 20 (87) | 32 (71) | 52 (76) | 0.248 |
| BMI; median (range) | 25 (19 - 34) | 25 (18 - 50) | 25 (18 - 50) | 0.721 |
| Genotype – n (%) (N=61) | | | | |
| 1 | 13 (62) | 28 (70) | 41 (67) | 0.475 |
| 2 | - | 1 (2) | 1 (2) | |
| 3 | 5 (24) | 10 (25) | 15 (25) | |
| 4 | 2 (9) | 1 (2) | 3 (5) | |
| 6 | 1 (5) | - | 1 (2) | |
| Previous treatment response – n (%) (N=66) | | | | 0.395 |
| Naïve | 5 (23) | 15 (34) | 20 (30) | |
| Non-responder | 17 (77) | 29 (66) | 46 (70) | |
| Previous triple therapy ¹ – n (%) (N=46) | 6 (35) | 5 (17) | 11 (24) | 0.282 |
| Diabetes – n (%) (N=68) | 4 (17) | 14 (31) | 18 (26) | 0.356 |
| Previous alcohol abuse – n (%) (N=68) | 15 (63) | 17 (38) | 32 (47) | 0.060 |
| Non-alcoholic steatohepatitis (NASH) – n (%) (N=68) | 2 (9) | 6 (13) | 8 (12) | 0.707 |
| Cryoglobulinemia – n (%) (N=68) | 1 (4) | 4 (9) | 5 (7) | 0.656 |
| Portal hypertension – n (%) (N=68) | 14 (61) | 22 (49) | 36 (53) | 0.497 |
| Esophageal varices – n (%) (N=36) | 13 (97) | 19 (86) | 32 (89) | 0.389 |
| Coinfection ² – n (%) (N=68) | 1 (4) | 1 (2) | 2 (3) | 1.000 |

Supplementary Table 2. Patients' characteristics at first HCC diagnosis, first HCC treatment (all patients) and DAA treatment (treated group) characteristics.

| Characteristics | DAA-exposed (N=23) | Non-exposed (N=45) | Total (N=68) | p-value |
|---|--------------------|--------------------|------------------|---------|
| MELD Score; median (range) | 7.9 (6.4 - 14.0) | 8.5 (6.4 - 15.6) | 8.5 (6.4 - 15.6) | 0.168 |
| Child Pugh Score – n (%) (N=68) | | | | |
| A | 20 (87) | 38 (84) | 58 (85) | 1.000 |
| B | 3 (13) | 7 (16) | 10 (15) | |
| AFP level at HCC diagnosis; median (range) | 15 (3 - 48) | 12 (2 - 170) | 13 (2 - 170) | 0.690 |
| BCLC staging – n (%) (N=68) | | | | |
| 0 | 7 (30) | 18 (40) | 25 (37) | 0.584 |
| A | 14 (61) | 21 (47) | 35 (51) | |
| B | 2 (9) | 6 (13) | 8 (12) | |
| Number of HCC lesions – n (%) (N=68) | | | | |
| 1 | 16 (70) | 32 (71) | 48 (71) | 0.155 |
| 2 | 3 (13) | 11 (24) | 14 (21) | |
| 3 | 4 (17) | 2 (4) | 6 (9) | |
| Size of the largest HCC lesion (mm); median (range) | 26 (11 - 55) | 21 (11 - 90) | 22 (11 - 90) | 0.832 |
| Imaging diagnosis of HCC – n (%) (N=68) | | | | |
| CT | 2 (9) | 11 (24) | 13 (19) | 0.082 |
| MRI | 18 (78) | 22 (49) | 40 (59) | |

| Characteristics | DAA-exposed (N=23) | Non-exposed (N=45) | Total (N=68) | p-value |
|---|--------------------|--------------------|----------------|--------------|
| Abdominal Ultrasound | 3 (13) | 12 (27) | 15 (22) | |
| Delay between HCC diagnosis and treatment (days); median (range) | 59 (24 - 269) | 43 (17 - 440) | 51 (17 - 440) | 0.683 |
| HCC treatment – n (%) (N=68) | | | | 0.181 |
| Radiofrequency ablation | 14 (61) | 29 (64) | 43 (63) | |
| Chemoembolization-CBR | 0 (0) | 5 (11) | 5 (7) | |
| Chemoembolization | 0 (0) | 2 (5) | 2 (3) | |
| Resection | 6 (26) | 4 (9) | 10 (15) | |
| Other³ | 3 (13) | 5 (11) | 8 (12) | |
| Viral load at DAA initiation (treated) or first HCC diagnosis (untreated; log IU/mL); median (range) ⁴ | 5.7 (3.1 - 6.5) | 5.8 (4.2 - 7.1) | - | |
| DAA combination⁵ (N=23) | | | | |
| SOF | 3 (13) | - | - | |
| SOF/DCV | 11 (48) | - | - | |
| SOF/LEDI | 4 (17) | - | - | |
| SOF/SIME | 4 (17) | - | - | |
| 3D ⁶ | 1 (4) | - | - | |
| Use of RBV – n (%) (N=23) | 10 (43) | - | - | |
| Treatment duration (N=23) | | | | |
| 12 weeks | 13 (57) | - | - | |
| 24 weeks | 10 (43) | - | - | |

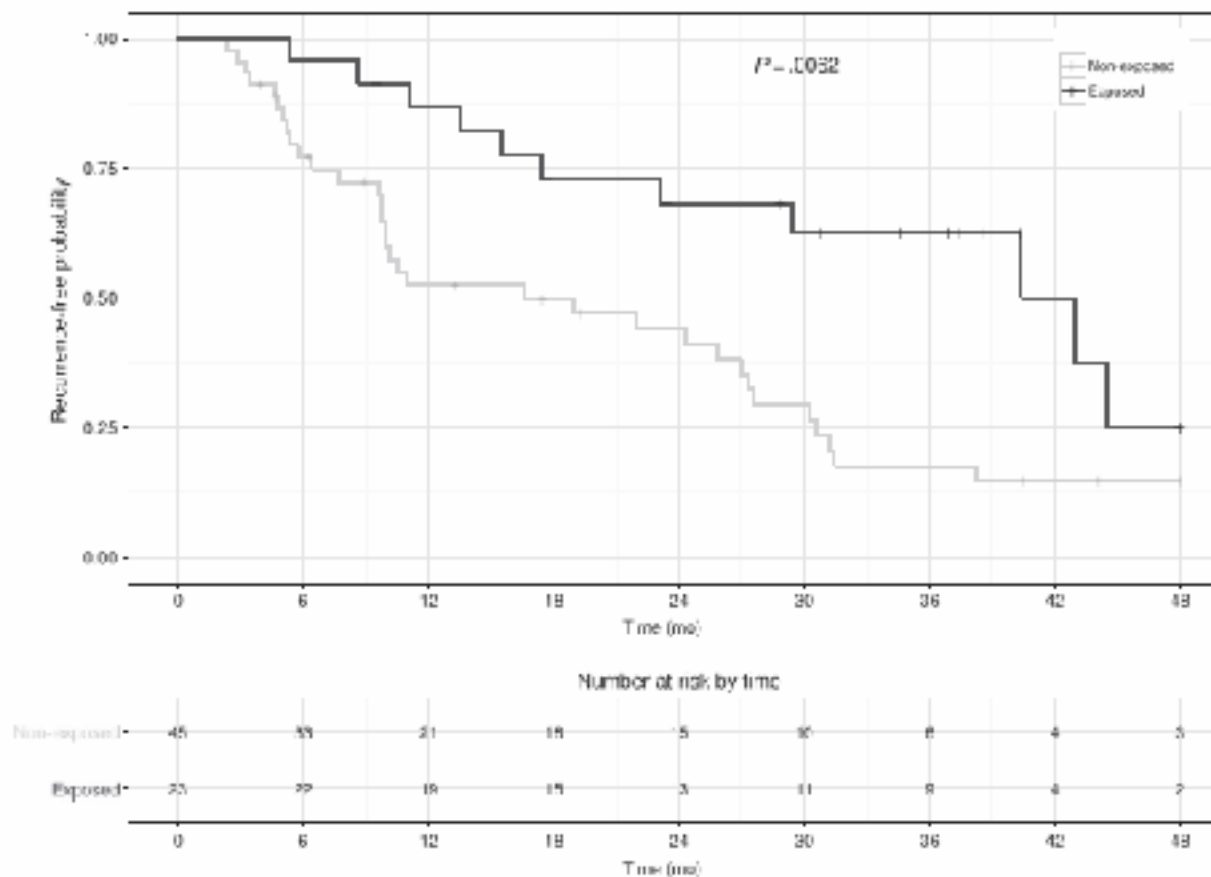


FIGURE 2 Hepatocellular carcinoma recurrence over time among HCV patients according to direct acting antiviral therapy exposure. Time zero is the date of HCC remission for all patients. Censored subjects are indicated on the Kaplan-Meier curve as tick marks. The number of patients at risk in each group (i.e. without HCC recurrence and/or not lost to follow up) is indicated at the bottom of the figure

| Characteristics | HCC recurrence (N=11) | No HCC recurrence (N=12) | p-value |
|----------------------------------|-----------------------|--------------------------|---------|
| Age (years); median (range) | 61 (55 - 76) | 56 (51 - 84) | 0.073 |
| Male gender – n (%) | 11 (100) | 9 (75) | 0.217 |
| BMI; median (range) | 25 (19 - 34) | 26 (19 - 30) | 0.975 |
| Genotype – n (%) | | | |
| 1 | 7 (70) | 6 (55) | 0.635 |
| 2 | - | - | |
| 3 | 2 (20) | 3 (27) | |
| 4 | - | 2 (18) | |
| 6 | 1 (10) | - | |
| Diabetes – n (%) | 2 (18) | 2 (17) | 1.000 |
| Previous alcoholic abuse – n (%) | 7 (64) | 8 (67) | 1.000 |
| MELD Score; median (range) | 7.2 (6.4 - 14.0) | 8.5 (6.4 - 13.1) | 0.215 |
| Portal hypertension – n (%) | 6 (55) | 8 (67) | 0.680 |
| Child Pugh Score – n (%) | | | |
| A | 9 (82) | 11 (92) | 0.590 |
| B | 2 (18) | 1 (8) | |

Supplementary Table 4. Characteristics of patients receiving DAA combination with/without HCC recurrence during follow-up.

| Characteristics | HCC recurrence (N=11) | No HCC recurrence (N=12) | p-value |
|--|-----------------------|--------------------------|---------|
| BCLC staging – n (%) | | | |
| 0 | 3 (27) | 4 (33) | 1.000 |
| A | 7 (64) | 7 (58) | |
| B | 1 (9) | 1 (8) | |
| Number of HCC lesions – n (%) | | | |
| 1 | 8 (73) | 8 (67) | 1.000 |
| 2 | 1 (9) | 2 (17) | |
| 3 | 2 (18) | 2 (17) | |
| Size of the largest HCC lesion (mm); median (range) | 28 (11 - 55) | 24 (16 - 36) | 0.915 |
| HCC treatment – n (%) | | | |
| Radiofrequency ablation | 7 (64) | 7 (58) | 1.000 |
| Resection | 3 (27) | 3 (25) | |
| Other ¹ | 1 (9) | 2 (16) | |

| Characteristics | HCC recurrence (N=11) | No HCC recurrence (N=12) | p-value |
|--|-----------------------|--------------------------|---------|
| DAA combination | | | |
| SOF | 2 (18) | 1 (8) | 0.433 |
| SOF/DCV | 4 (36) | 7 (58) | |
| SOF/LEDI | 3 (27) | 1 (8) | |
| SOF/SIME | 1 (9) | 3 (25) | |
| 3D ² | 1 (9) | 0 (0) | |
| Use of RBV – n (%) | 5 (45) | 5 (42) | 1.000 |
| Viral load at DAA initiation (log IU/mL); median (range) | 5.7 (4.2 - 6.3) | 5.7 (3.1 - 6.5) | 0.824 |
| Treatment duration | | | |
| 12 weeks | 8 (73) | 5 (42) | 0.214 |
| 24 weeks | 3 (27) | 7 (58) | |

Discussion

- Potential decrease of HCC recurrence after DAA regime
- contradictory with the recently published study
- Difference: control group

limitation

- Small number of patients treated with DAA
- Not randomized (retrospective cohort study)
- no histological information regarding HCC grade for all patients and the severity of HCC
- Only cirrothic patients

strengths

- Propensity score as a covariate in the multivariate analysis
- two sensitivity analyses in subgroups of patients without HCC recurrence within the first 6 months following remission or with a curative treatment option for their HCC
- exclusion of patients with multiple history of HCC
- single centre study
- **Control group**

conclusion

- no increased rate of HCC recurrence
- On the contrary >> beneficial effect of DAA treatment

➤ **large-scale prospective cohort studies are needed**