Definition of high risk of disease recurrence following curative treatment for early-stage hepatocellular carcinoma: a comparison of three approaches.

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Background

Hepatocellular carcinoma (HCC):

- Around 80% of primary liver cancer cases and is the third leading cause of cancer-related mortality globally (1).
- Early detection offers the possibility of disease curation with surgical resection (SR) or percutaneous ablation (PA), with promising survival benefits for early-stage HCC patients.
- Disease recurrence (DR) following SR/PA remains a main challenge, with rates reaching up to 70% within five years (2).

Challenges:

- Real-world data from early HCC patients in France are sparse
- No consensus on the definition of high-risk (HR) of DR following SR/PA.

Objectives:

- (i) Describe the characteristics of early HCC patients who received SR/PA in two regional centers in France
- (ii) Explore and compare three different approaches in defining HR of disease recurrence (two existing definitions + a data-driven definition)

Methods

Data:

- A retrospective cohort of patients with early-stage HCC who received their first SR or PA between 2017 and 2021 in two French regional centers - CHU Lyon and CHU Saint-Etienne.
- Inclusion at the date of their first SR or PA and follow-up for up to two years (until December 2023 at latest)
- Variables collected at baseline: socio-demographic, clinical and biological characteristics, HCC etiology and related comorbidities.

High risk of disease recurrence:

- Two existing definitions for high risk (HR) of DR, one from the IMbrave-050 (IM) clinical trial (3) and another based on the recommendations of the Study's Scientific Committee (SC). Both definitions were based on the following variables: tumor type (infiltrative vs. nodular) and size, the number and location of tumor nodules, the type of vascular invasion (microvascular vs. macrovascular), tumor differentiation grade, and alpha-fetoprotein levels.
- A third, data-driven definition of HRDR developed using machine learning methods

Analyses:

- Median and two-year recurrence-free survival (RFS) by HRDR status based on SC and IM definitions were estimated using Kaplan-Meier method. RFS was defined as a time from the first CT until the death or disease recurrence.
- The performance of the three definitions (sensitivity, specificity and overall accuracy) in classifying the patients in the study was estimated with respect to their observed DR status.

Machine learning method:

- Penalized Logistic Regression (Lasso) was used to identify variables associated with DR. Included were all aforementioned variables from the existing IM and SC definitions + sex, BMI, smoking status, diagnosed cirrhosis (yes/no), diagnosed diabetes (yes/no), hepatitis B (yes/no), hepatitis C (yes/no), hemochromatosis (yes/no), NAFLD, ASAT, ALAT, Gamma GT, tumor grade and macrotrabecular HCC (yes/no). Model robustness was ensured using cross-validation.

Results

Table 1: Baseline characteristics of patients included in the study

Characteristics	Patients			
	Overall N=371	Curative treatment groups		
		Ablated patients N=237	Resected patients N=117	Ablated and resected patients N=17
Average age in years (SD)	67.3 (10.4)	67.8 (9.8)	65.9 (11.5)	70.0 (11.0)
Male Sex	317 (85.4%)	209 (88.2%)	93 (79.5%)	15 (88.2%)
BMI (kg/m²)				
<25	98(27.4%)	60 (26.0%)	34 (30.9%)	4 (23.5%)
25-29.9	133 (37.2%)	92 (39.8%)	37 (33.6%)	4 (23.5%)
>= 30	128 (35.5%)	79 (34.2%)	39 (35.4%)	9 (53.0%)
Comorbidities diagnosis				
Cirrhosis	199 (53.6%)	147 (62.0%)	45 (38.5%)	7 (41.2%)
Suspected cirrhosis	88 (23.7%)	63 (26.6%)	17 (14.5%)	8 (47.1%)
Diabetes	166 (46.2%)	114 (48.3%)	49 (46.2%)	3 (17.6%)
Dyslipidemia	38 (10.6%)	25 (10.6%)	12 (11.3%)	1 (5.9%)
Smoking habits				
Former	141 (38.0%)	94 (39.7%)	42 (35.9%)	5 (29.4%)
Current	76 (20.5%)	56 (23.6%)	17 (14.5%)	3 (17.6%)
Alcohol consumption				
Weaned	155 (41.8%)	102 (43.0%)	45 (38.5%)	8 (47.1%)
Current	99 (26.7%)	70 (29.5%)	26 (22.2%)	3 (17.6%)
Liver Disease Etiology				
Hepatitis C only	53 (14.3%)	36 (15.2%)	13 (11.1%)	4 (23.5%)
Hepatitis B only	18 (4.9%)	11 (4.6%)	6 (5.1%)	1 (5.9%)
Alcohol only	35 (9.4%)	25 (10.5%)	10 (8.5%)	0 (0.0%)
NAFLD only	31 (8.4%)	21 (8.9%)	9 (7.7%)	1 (5.9%)
Tumor type (N=367)				
Nodular	344 (93.7%)	218 (93.5%)	110 (97.3%)	16 (94.0%)
Infiltrative	18 (4.9%)	10 (4.3%)	7 (2.7%)	1 (7.0%)
Mixed (nodular and infiltrative)	5 (1.4%)	5 (2.1%)	0 (0.0%)	0 (0.0%)
Microvascular invasion	37 (10.0%)	15 (6.3%)	22 (19.0%)	0 (0.0%)
Macrovascular invasion	16 (4.3%)	1 (0.4%)	15 (13.0%)	0 (0.0%)
Disease recurrence within two years after the first SR/PA	174 (46.9%)	112 (47.3%)	52 (44.4%)	10 (58.8%)

Represented are n(%) unless indicated otherwise; SD, standard deviation; BMI, body mass index; NAFLD, non-alcoholic fatty liver disease; SR, surgical resection; PA, percutaneous ablation

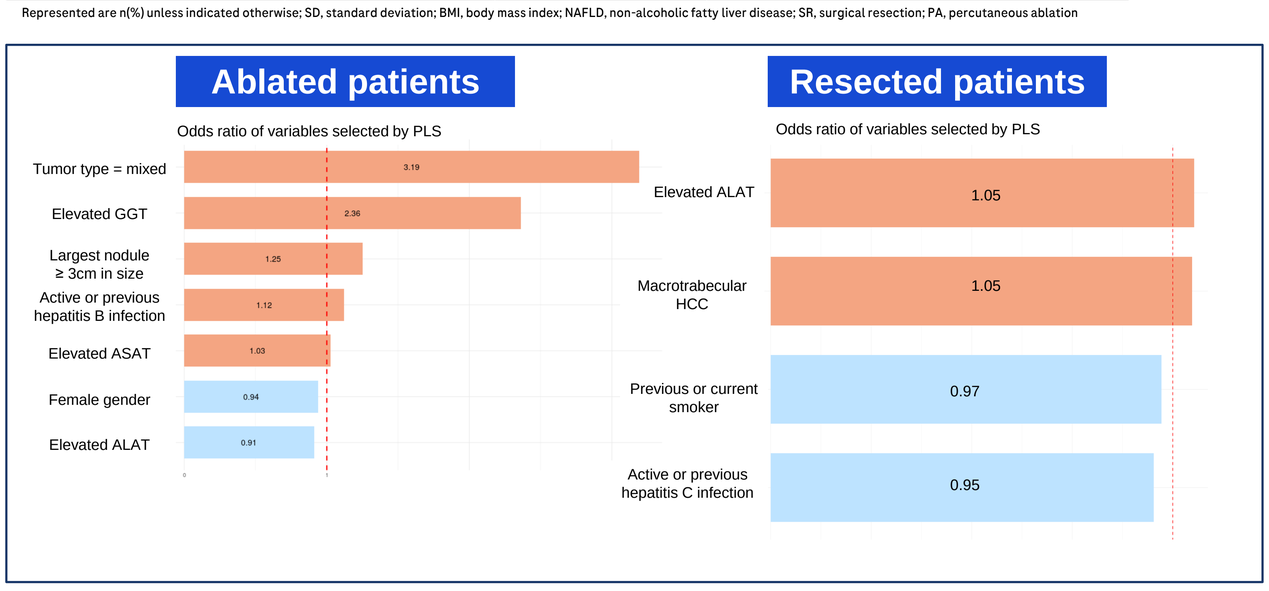

Figure 2: Variables selected in Penalised (Lasso) Logistic Regression (PLS) model for disease recurrence or death

Table 2: High risk of disease recurrence according to the two existing definitions

High risk of disease recurrence n(%)	Patients			
	Overall N=371	Curative treatment groups		
		Ablated patients N=237	Resected patients N=117	Ablated and resected patients N=17
IMbrave050	206 (55.5%)	135 (57%)	61 (52%)	10 (59%)
Scientific Committee (SC)	195 (52.6%)	103 (43%)	84 (72%)	8 (47%)
IMbrave-050 only	55 (14.8%)	52 (22%)	1 (0.9%)	2 (12%)
Scientific Committee only	44 (11.9%)	20 (8.4%)	24 (21%)	0 (0%)
IMbrave050 AND Scientific Committee	151 (40.7%)	83 (35%)	60 (51%)	8 (47%)
Imbrave-050 OR Scientific Committee	250 (67.4%)	155 (65%)	85 (73%)	10 (59%)
Not at high-risk (neither SC or IMbrave050)	121 (32.6%)	82 (35%)	32 (27%)	7 (41%)

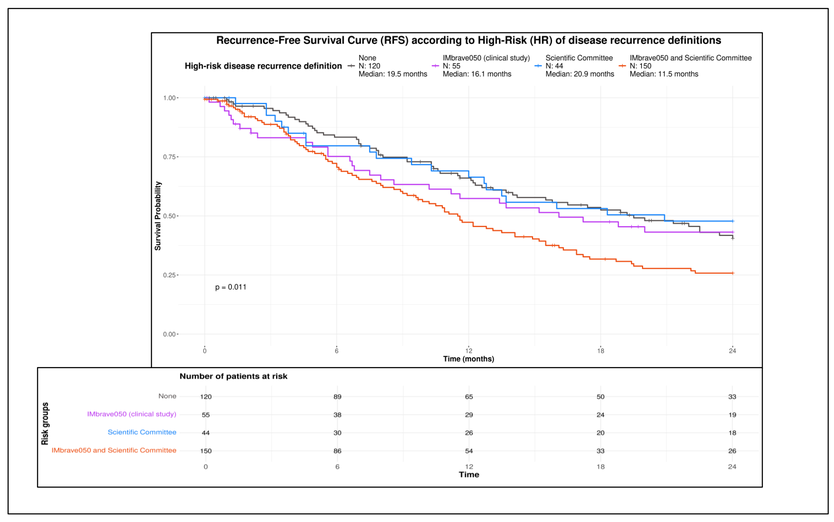

Figure 1: Recurrence-free survival according to different definitions of high risk of disease recurrence

Table 3: Performance of the three definitions for high risk of disease recurrence or death

High-risk of disease recurrence definition	Metrics			
	Accuracy	Sensitivity	Specificity	AUC
IMbrave-050 (IM)	0.53	0.58	0.48	N.A
Comité Scientifique (SC)	0.55	0.55	0.54	N.A
IM and SC	0.54	0.44	0.65	N.A
Data-driven (Ablation)	0.63	0.72	0.54	0.67
Data-driven (Resection)	0.63	0.69	0.53	0.65

Conclusion

While the two current definitions of high risk of disease recurrence (HRDR) following surgical resection or percutaneous ablation for HCC incorporate similar variables, a considerable discrepancy exists, with over 40% of patients classified as HRDR by only one definition. A data-driven approach reduced the number of variables defining HRDR and improved patient classification compared to existing definitions, offering a promising alternative. We need further analyses to confirm these results and evaluate how clinicians can use them for decision-making.

References

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