

SUPPLEMENTARY MATERIAL

Impact of extended use of ablation techniques in cirrhotic patients with hepatocellular carcinoma: a cost-effectiveness analysis

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Markov Model

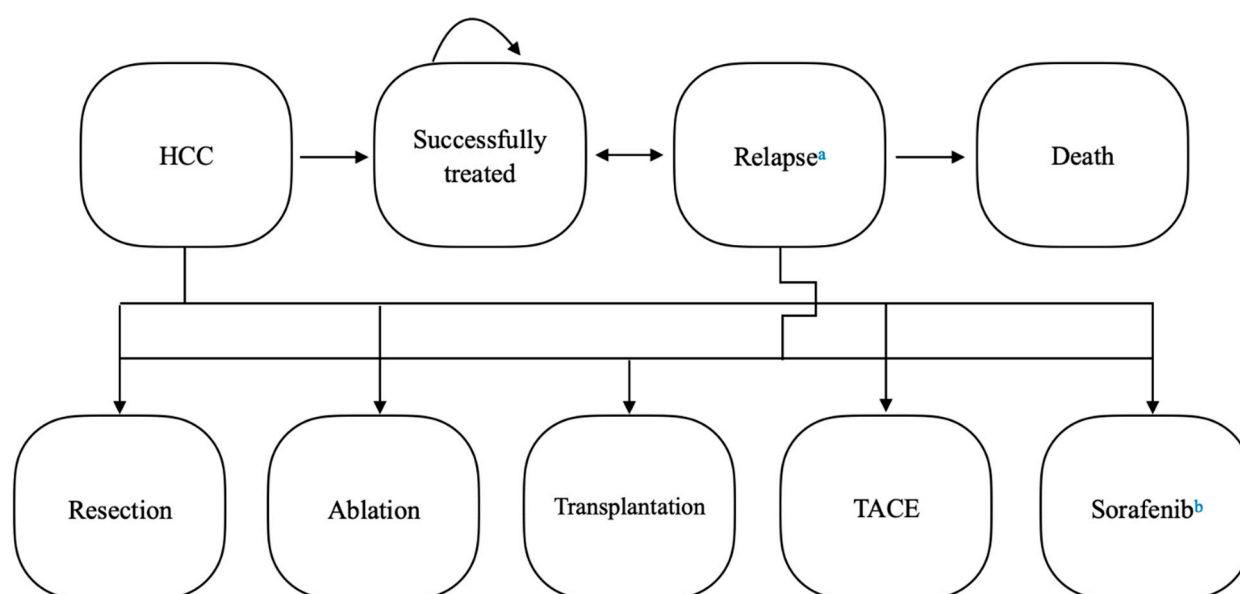
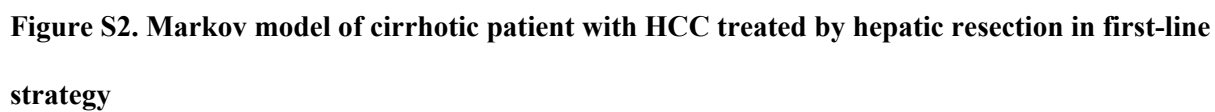


Figure S1. Simplified state transition model illustrating the progression of the disease and possible interventions.

^aRecurrence refers to development of new HCC lesions, relapse at the site of previous treatment, or non-response, necessitating repeated treatment at least 3 months after the previous one or switching to another treatment modality.

^bTARE and Sorafenib are combined into one group. HCC, Hepatocellular carcinoma; TACE, trans-arterial chemoembolization; TARE, trans-arterial radioembolization.



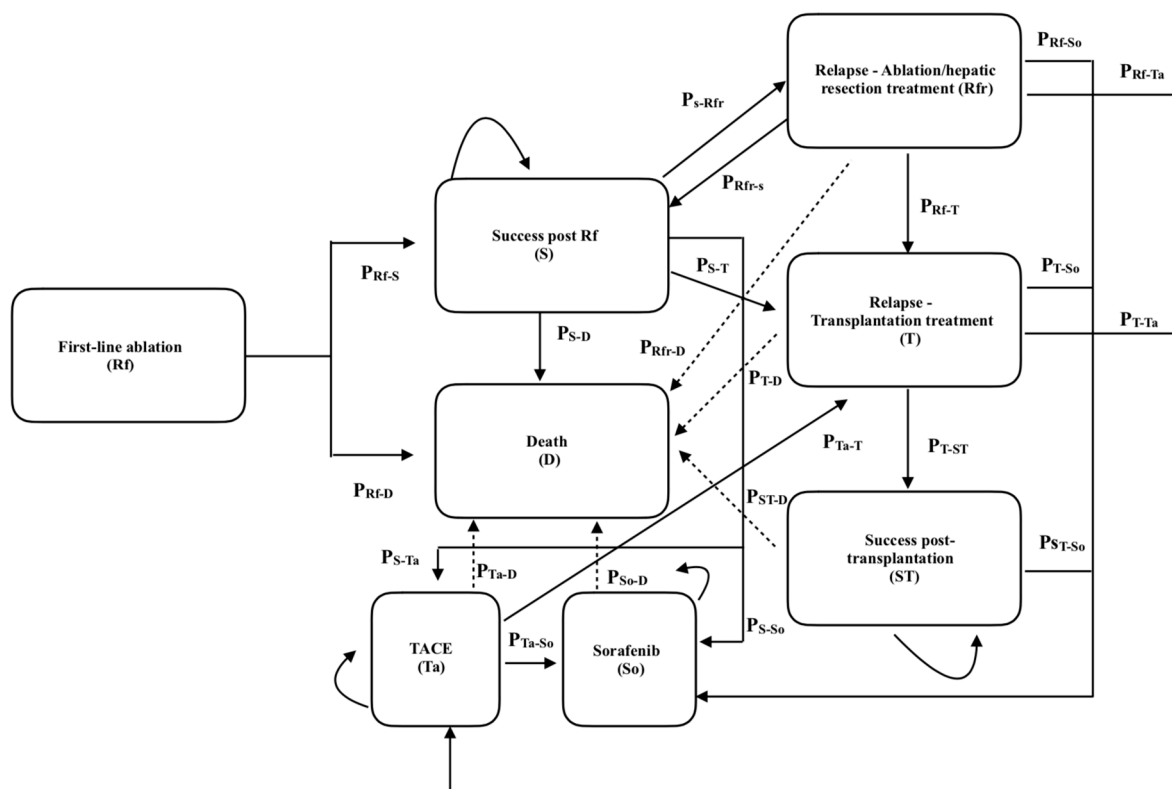


Figure S3. Markov model of cirrhotic patient with HCC treated by ablation in first-line strategy.

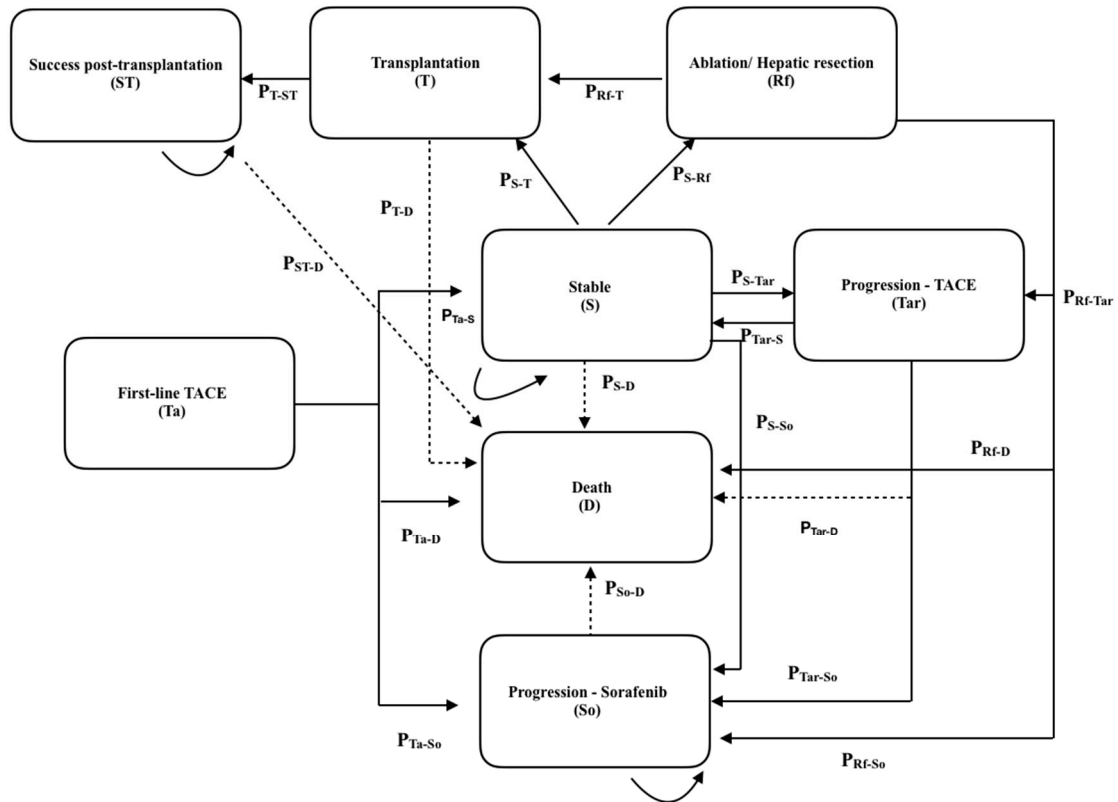


Figure S4. Markov model of cirrhotic patient with HCC treated by TACE in first-line strategy.

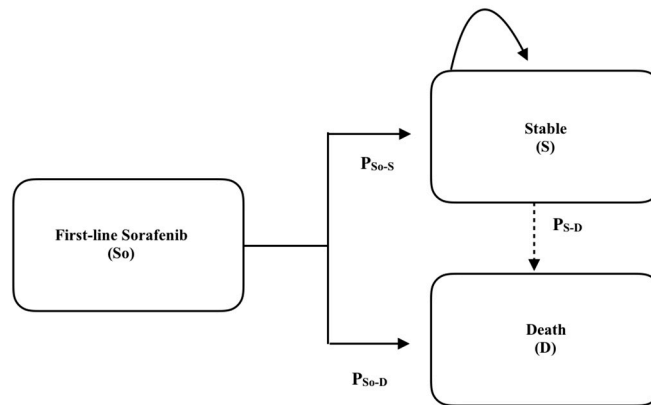


Figure S5. Markov model of cirrhotic patient with HCC treated by Sorafenib in first-line strategy

Table S1. Transition probabilities of cirrhotic patient with HCC treated by hepatic resection in first-line strategy

Transition probabilities	Bondy group	SOC group
p(He-D)	0.00%	0.00%
p(S-Rfr)	4.73%	4.73%
p(S-T)	0.00%	0.00%
p(S-So)	0.00%	0.00%
p(S-D)	2.99%	2.99%
p(S-Ta)	0.00%	0.00%
p(Rfr-T)	14.13%	14.13%
p(Ta-T)	0.00%	0.00%
p(ST-So)	0.00%	0.00%
p(ST-D)	0.00%	0.00%
p(Rfr-D)	0.00%	0.00%
p(T-D)	0.00%	0.00%
p(Rfr-So)	0.00%	0.00%
p(T-So)	0.00%	0.00%
p(Rfr-Ta)	0.00%	0.00%
p(T-Ta)	0.00%	0.00%
p(So-D)	0.00%	0.00%
p(STa-D)	4.73%	4.73%
p(STa-Ta)	0.00%	0.00%
P(STa-So)	0.00%	0.00%
p(Ta-So)	2.99%	2.99%
p(Ta-D)	0.00%	0.00%

Table S2. Transition probabilities of cirrhotic patient with HCC treated by ablation in first-line strategy

Transition probabilities	Bondy group	SOC group
p(Rf-D)	1.11%	0.93%
p(S-Rfr)	12.89%	12.60%
p(S-T)	0.73%	0.61%
p(S-So)	1.25%	1.52%
p(S-D)	4.97%	4.50%
p(S-Ta)	2.05%	2.01%
p(Rfr-T)	0.87%	0.73%
p(Ta-T)	0.00%	0.00%
p(ST-So)	2.70%	2.61%
p(ST-D)	5.26%	5.09%
p(Rfr-D)	1.27%	1.77%
p(T-D)	0.00%	0.00%
p(Rfr-So)	0.85%	1.08%
p(T-So)	0.00%	0.00%
p(Rfr-Ta)	0.87%	0.73%
p(T-Ta)	0.00%	0.00%
p(So-D)	34.34%	30.62%
p(STa-D)	10.67%	9.14%
p(STa-Ta)	7.54%	5.65%
P(STa-So)	3.10%	3.56%
p(Ta-So)	3.56%	2.56%
p(Ta-D)	0.00%	0.00%

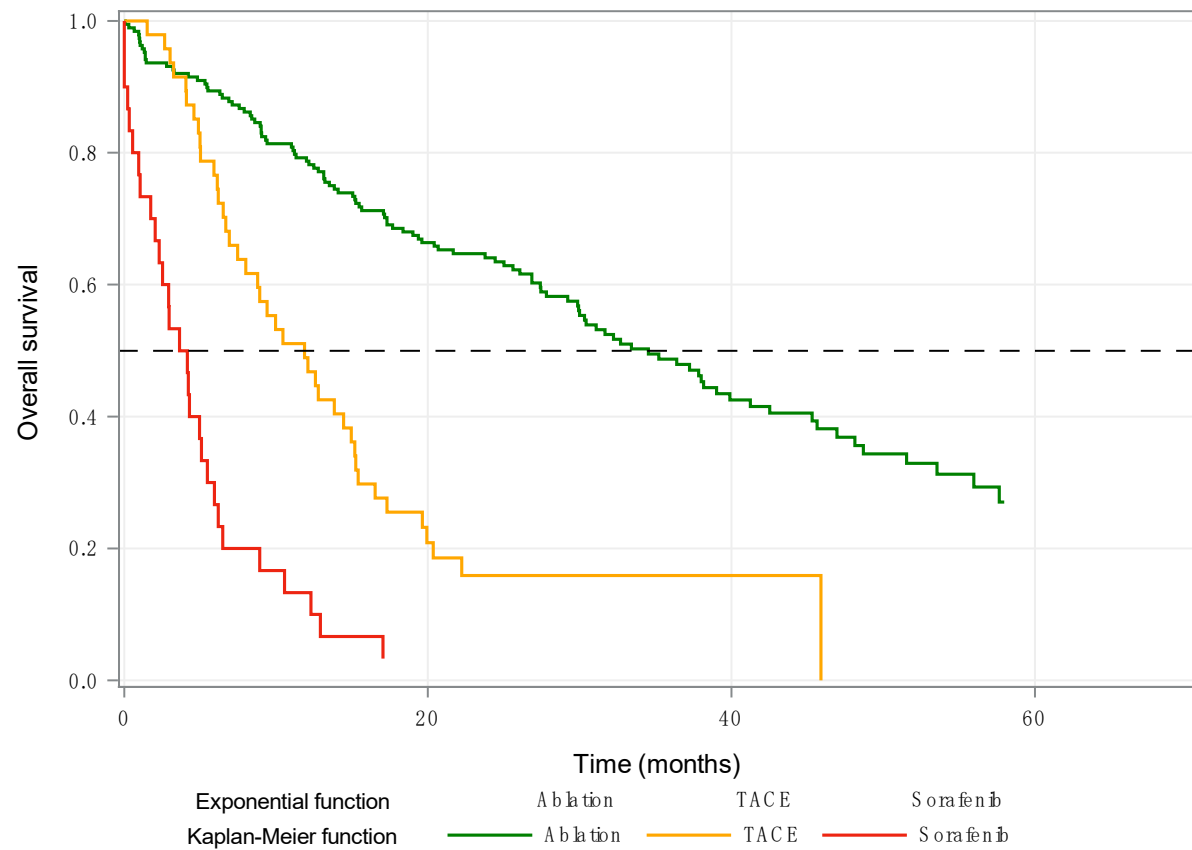
Table S3. Transition probabilities of cirrhotic patient with HCC treated by TACE in first-line strategy

Transition probabilities	Bondy group	SOC group
p(Ta-D)	1.69%	1.59%
p(Ta-So)	1.69%	0.35%
p(S-RF)	12.30%	3.13%
p(RF-S)	22.84%	17.92%
p(RF-T)	0.00%	0.00%
p(S-T)	0.00%	3.67%
p(T-D)	0.00%	3.55%
p(ST-D)	0.00%	1.20%
p(RF-Tar)	0.00%	0.00%
p(RF-Sor)	3.85%	0.00%
p(S-D)	12.29%	8.67%
p(So-D)	56.05%	26.52%
p(S-Tar)	15.61%	16.00%
p(Tar-So)	9.44%	4.61%
p(Tar-D)	8.63%	3.85%
p(S-So)	8.31%	6.76%

Table S4. Transition probabilities of cirrhotic patient with HCC treated by Sorafenib in first-line strategy

Transition probabilities	Bondy group	SOC group
p(So-D)	34.72%	7.14%
p(S-D)	38.47%	27.96%

A. Bondy group



B. SOC group

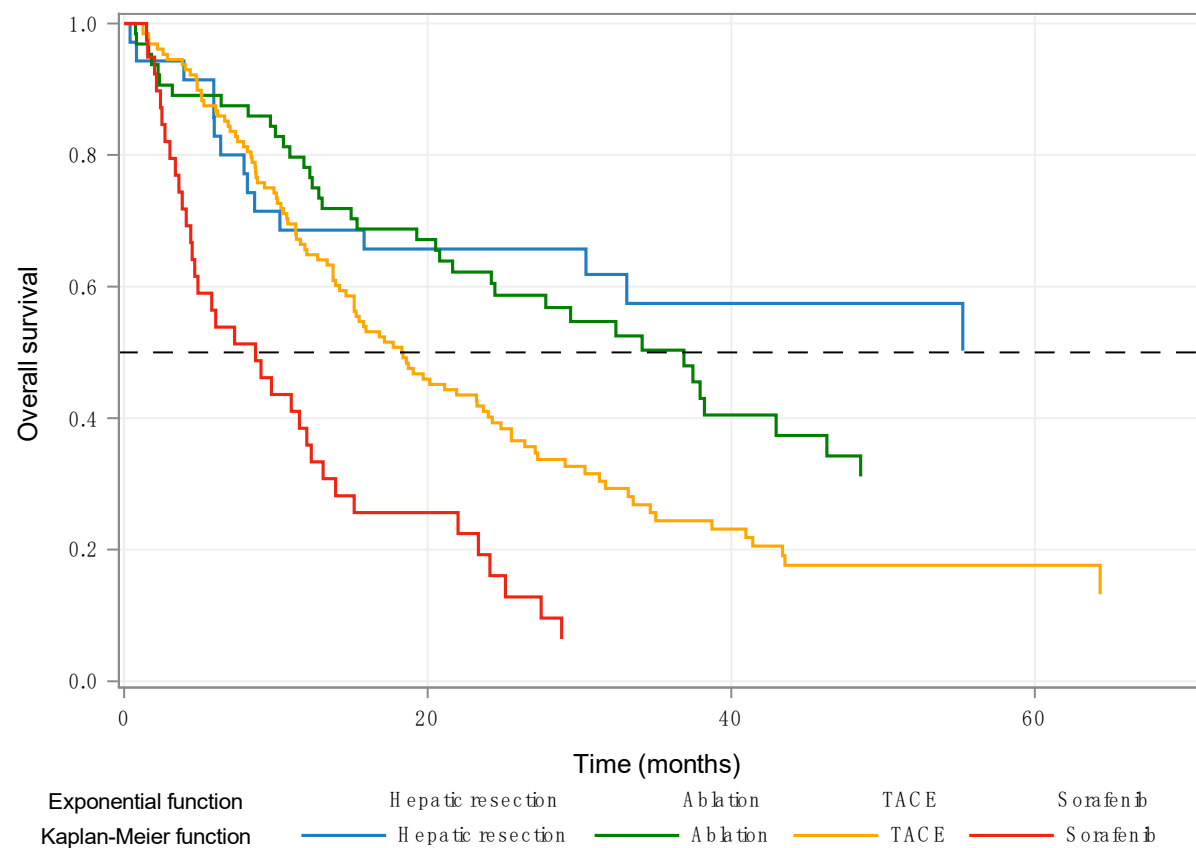


Figure S6. Model calibration by first-line treatment in the (A) Bondy and (B) SOC. Dash lines represent the Markov model results (derived from exponential function) while segmented lines represent patient-level data (Kaplan-Meier function)

Propensity Score Analysis

$$P(z_i=1|X_i) = b_0 + b_1 \times \text{age} + b_2 \times \text{gender} + b_3 \times \text{comorbidity_index} + b_4 \times \text{cause_of_cirrhosis} + b_5 \times \text{pugh_child_score} + b_6 \times \text{tumor_size} + b_7 \times \text{number_of_tumor} + b_8 \times \text{vascular_invasion} + b_9 \times \text{htp_signs} + b_{10} \times \text{location} + b_{11} \times \text{afp}$$

where,

z_i , the probability between 0 and 1 of group assignment assumption derived from the logit model,

b_0 , the intercept,

b_i , regression coefficients estimated by maximum likelihood,

X_i , the set of variables (age, sex, Pugh-Child score, number of tumors...).

Table S5. Characteristics of variables including in the model used for propensity score

Set of variables	Type	Values	Reference
Age	Continuous	31-92	-
Gender	Binary	Male Female	Female
Comorbidity index	Ordinal	≤ 1 > 1	≤ 1
Cause of cirrhosis	Category	Alcoholic Hepatitis C Hepatitis B NASH Others	Others
Child-Pugh score	Binary	A B	B
Size of the largest tumor (mm)	Continuous	0-220	-
Number of tumor	Ordinal	Unique (=1) Oligo (2-3) Multi (≥ 4)	Multi
Vascular invasion	Binary	Present Absent	Absent
HTP signs	Binary	Present Absent	Absent
Location	Binary	Unilobar Bilobar	Unilobar
AFP	Ordinal	≤ 100 100-1000 $> 1000 \text{ ng/mL}$	≤ 100

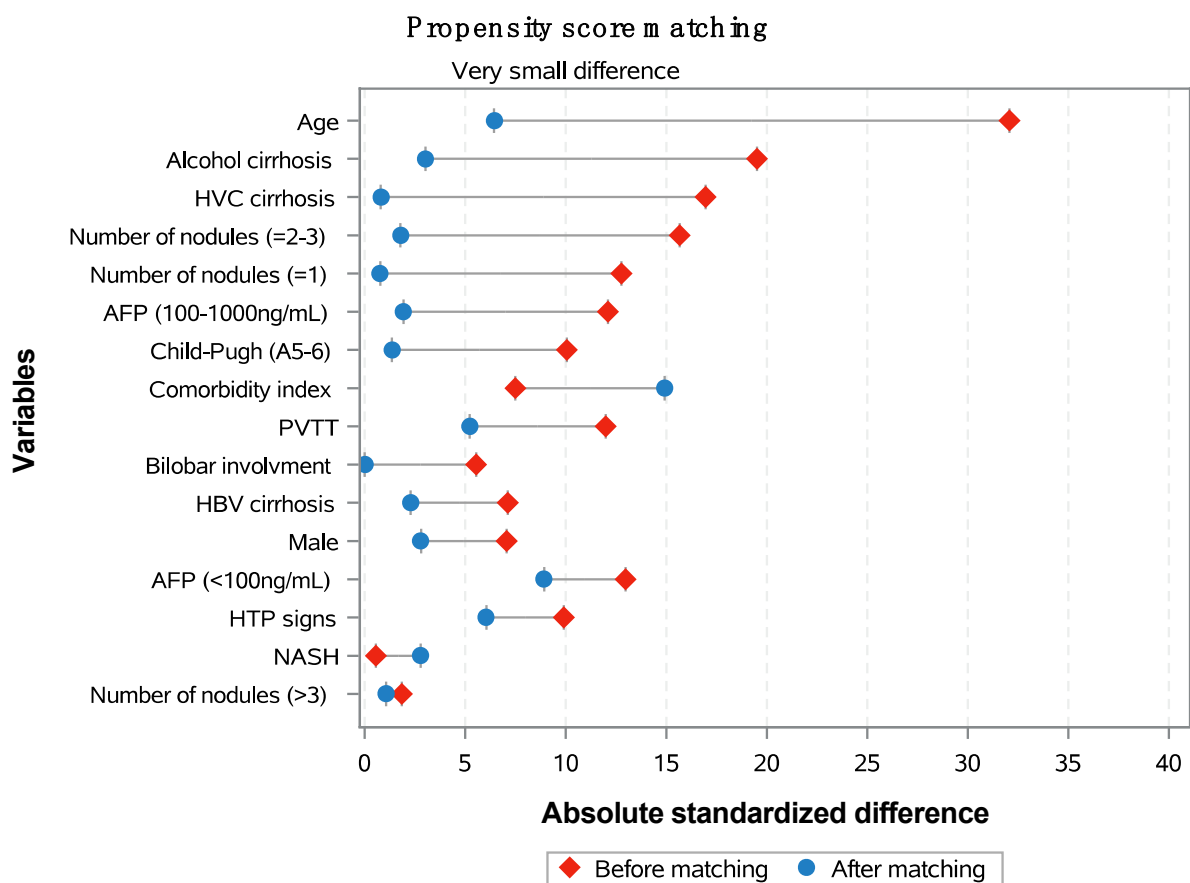


Figure S7. Balance assessment on the covariates after propensity score matching

Costs Evaluation

Table S6. Costs of in-patient HCC treatment from PMSI. Costs are valued in Euro.

In-patient HCC treatment	N (n)	Mean	SD	Minimum	Maximum	IC 95-	IC 95+
Hepatic resection	976 (976)	17 129.77 €	10 764.35 €	7 543.21 €	160 357.05 €	16 454.44 €	17 805.10 €
Ablation	1549 (1714)	3 939.35 €	5 117.75 €	413.93 €	160 357.05 €	3 684.49 €	4 194.21 €
Liver transplantation	343 (343)	51 252.89 €	22 015.90 €	21 130.20 €	176 167.11 €	48 922.95 €	53 582.83 €
TACE	2486 (3470)	3 705.61 €	3 443.79 €	404.58 €	70 480.60 €	3 570.23 €	3 840.99 €
Care after liver transplantation	16 (70)	10 528.43 €	20 273.21 €	712.16 €	95 193.01 €	594.56 €	20 462.30 €
Palliative care	89 (133)	4 343.64 €	2 474.60 €	714.56 €	20 579.54 €	3 829.52 €	4 857.76 €

N (n)=Number of patients (number of distinct treatments, patient may have received multiple procedures). SD, Standard deviation. IC 95-/+ : Confidence interval 95%.

Table S7. Costs of pre-operative examinations. Costs are valued in Euro.

Pre-operative examinations	Cost per unit	Sources
Hepatologist consultation	28.00 €	AMELI
Liver ultrasonography	52.45 €	AMELI
Liver MRI	69.00 €	AMELI
Liver CT-scan	50.54 €	AMELI
Liver biopsy	196.18 €	AMELI
Nurse consultation	4.26 €	Micro-costing
Multidisciplinary meeting	91.96 €	Micro-costing
Anesthetic consultation	46.00 €	AMELI
Biology	50.83 €	Biolam

AMELI : <https://www.ameli.fr/accueil-de-la-ccam/index.php>; Biolam : <https://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donnees-statistiques/actes-de-biologie-medicale/biolam/biolam-2013-2015.php>

Table S8. Direct medical costs of out-patient HCC treatment. Costs are valued in Euro.

Out-patient treatment	Cost per unit	Sources
Cortancyl 5mg (SANOFI AVENTIS)	1.85 €	CEPS
Advagraf 5mg (ASTELLAS PHARMA)	298.28 €	CEPS
Cellcept 500mg (ROCHE)	55.73 €	CEPS
Sorafenib 200mg (BAYER)	3 261.64 €	CEPS

CEPS: Comité Economique des Produits de Santé, <http://medicprix.sante.gouv.fr/medicprix>.

Table S9. Costs of follow-up surveillance after curative or palliative treatment. Costs are valued in Euro.

Follow-up examinations	Cost per unit	Sources
Hepatologist consultation	28.00 €	AMELI
Liver ultrasonography	52.45 €	AMELI
Liver MRI	69.00 €	AMELI
Liver CT-scan	50.54 €	AMELI
Biology	50.83 €	Biolam

AMELI : <https://www.ameli.fr/accueil-de-la-ccam/index.php>; Biolam : <https://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donnees-statistiques/actes-de-biologie-medicale/biolam/biolam-2013-2015.php>

Table S10. Costs of in-patient follow-up (care after liver transplantation, palliative care) from PMSI. Costs are valued in Euro.

In-patient follow-up	N (n)	Mean	SD	Minimum	Maximum	IC 95-	IC 95+
Care after LT	16 (70)	10 528.43 €	20 273.21 €	712.16 €	95 193.01 €	594.56 €	20 462.30 €
Palliative care	89 (133)	4 343.64 €	2 474.60 €	714.56 €	20 579.54 €	3 829.52 €	4 857.76 €

N (n)=Number of patients (number of distinct treatments, patient may have received multiple procedures). SD, Standard deviation. IC 95-/+ : Confidence interval 95%.

LT, liver transplantation.

Table S11. Direct medical costs of HCC management from French Insurance. Costs are valued in Euro.

Health states	Pre operative examinations ^a	In-patient procedures	Follow-up exams ^b	Outpatient medications ^c	Average total (3-months cycle)
Transplantation	536 €	51 253 €	-	-	51 789 €
Resection	536 €	17 130 €	-	-	17 666 €
Ablation	536 €	4 359 €	-	-	4 895 €
TACE	536 €	5 172 €	-	-	5 708 €
Sorafenib	536 €	-	-	5 870 € ^d	6 407 €
Death	-	-	-	-	0 €
Follow-up after LT	-	134 € ^e	79 €	1 301 € ^f	1 515 €
Follow-up after resection	-	-	146 €	-	146 €
Follow-up after ablation	-	-	146 €	-	146 €
Follow-up after TACE	-	232 € ^g	146 €	-	379 €

^aPre-operative examinations include specialist consultation in hepatology, liver ultrasound, abdominal CT-scan or MRI, liver biopsy, multidisciplinary consultation meeting, anesthesia consultation and biological exams. ^bFollow-up exams include specialist consultation, biology exams, and a CT scan or a liver MRI. ^c2.1% VTA rate was applied. ^dCompliance rate of Sorafenib was 60% of daily planned dose in SHARP trial. This rate was applied to the cost of outpatient medications. ^eIn-patient procedure refers to « Care after liver transplantation » DRG. ^fOutpatients medications after liver transplantation were immunosuppressive drugs (Cortancyl®, Advagraf® and Cellcept®). ^gIn-patient procedure refers to « Palliative care » DRG. TACE, trans-arterial chemoembolization; LT, liver transplantation.

Table S12. Results of the cost-effectiveness analyses, by first-line treatment on a 5-year horizon.

These results were weighted by the probabilities of each first-line treatment in the Bondy and standard of care groups and used to calculate the final ICER. The respective mixes of first-line treatments in each group used to estimate the average ICER came from the cohort distribution.

Probability of first-line treatment		Bondy group		SOC group	
Hepatic resection		0.4 %		13.2 %	
Ablation		70.7 %		24.0 %	
TACE		17.7 %		48.1 %	
Sorafenib		11.2 %		14.7 %	

First-line	Costs and	Bondy group	SOC group	Net effects	ICER (€/LYG)
	life-years per patient				
Hepatic resection	Cost	€101 (\$111)	€3,513 (\$3,864)	€-3,412 (\$-3,753)	
	Life-years	0.1	1.7	-2.5	
Ablation	Cost	€12,187 (\$13,406)	€4,101 (\$4,511)	€8,086 (\$8,895)	
	Life-years	7.7	2.7	7.3	
TACE	Cost	€2,266 (\$2,493)	€12,098 (\$13,308)	€-9,832 (\$-10,815)	
	Life-years	0.7	3.5	-3.6	
Sorafenib	Cost	€1,322 (\$1,454)	€2,694 (\$2,963)	€-1,372 (\$-1,509)	
	Life-years	0.2	0.5	-0.3	
Average total	Cost	€15,876 (\$17,464)	€22,406 (\$24,647)	€-6,530 (\$-7,183)	Dominant
	Life-years	8.7	8.4	0.3	

Costs and life years are expressed as average for a patient and were discounted by 3%. The net effect could be a reduction in costs (negative values) or an increase in costs (positive values).

TACE, trans-arterial chemoembolization; ICER, incremental cost-effectiveness ratio; LYG, life-years gained.

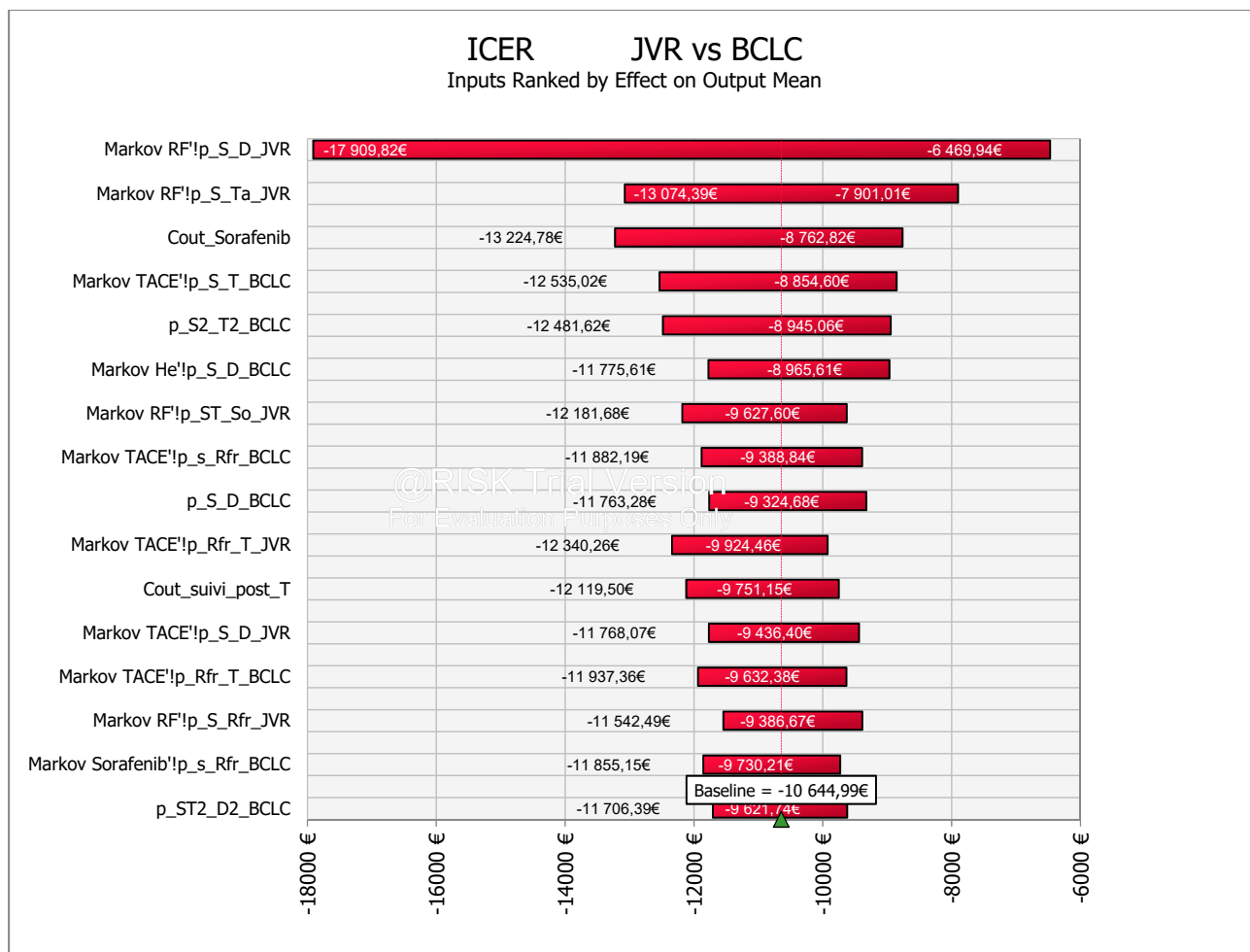


Figure S8. Results of the deterministic univariate analysis.