External validation of LCR1-LCR2, a multivariable HCC risk calculator, in patients with chronic HCV

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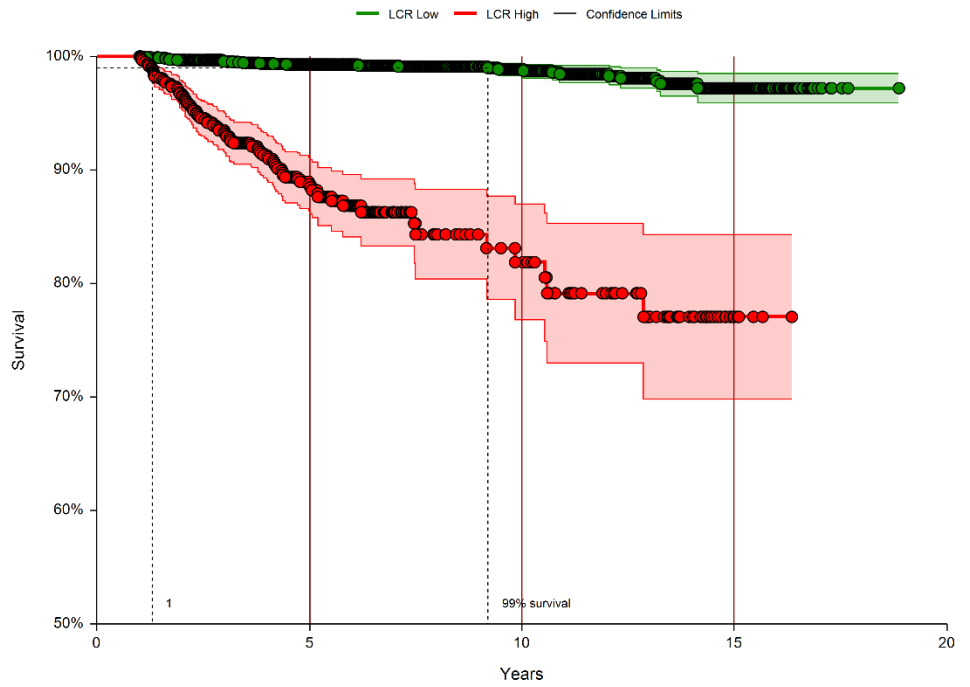
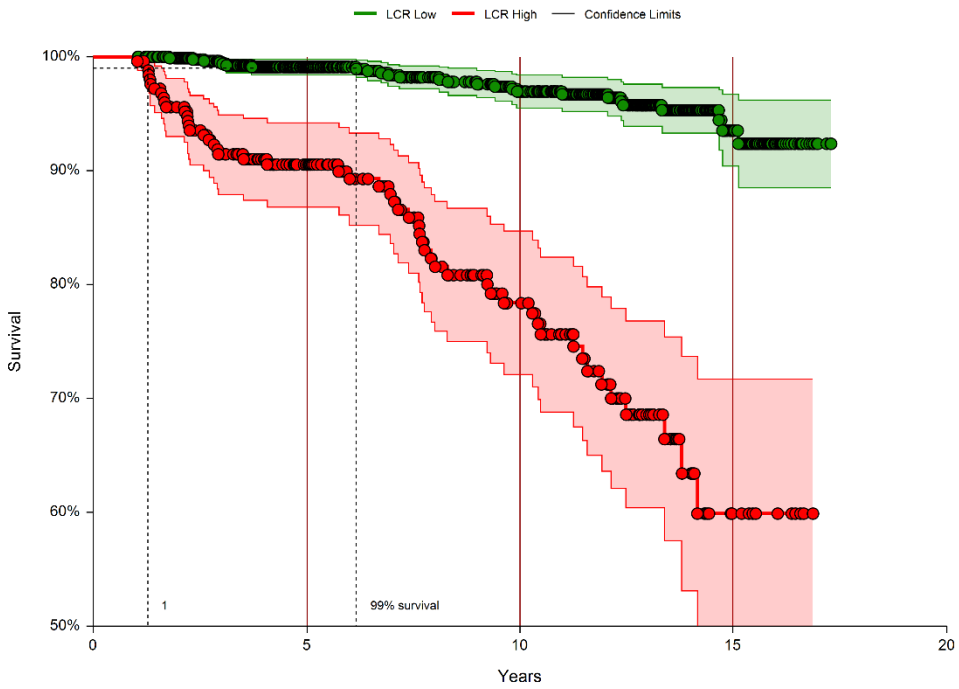
Fig. S1. 20-years survival without HCC according to LCR1-LCR2 cut-offs and SVR subsets.

Fig. S1A. Survival without HCC according to LCR1-LCR2 cut-offs, among the subset of patients with SVR



Number At Risk (Number of Events)					
algo = LCR Low	2568 (0)	1642 (17)	766 (21)	142 (29)	0 (29)
algo = LCR High	837 (0)	365 (81)	66 (92)	5 (95)	0 (95)

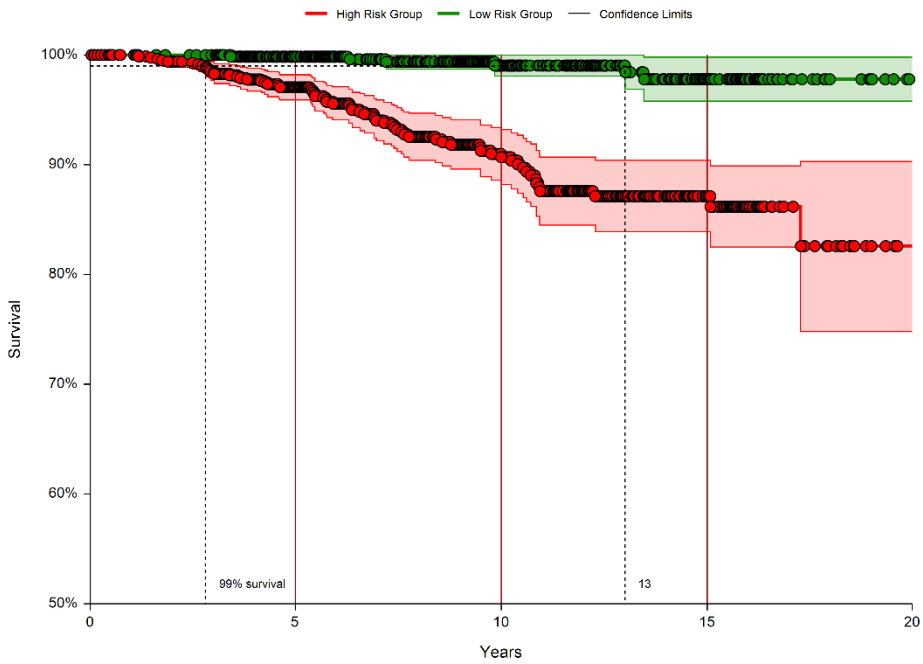
Fig. S1B. 20-year survival without HCC according to LCR1-LCR2 cut-offs, among the subset of patients without SVR



Number At Risk (Number of Events)

algo = LCR Low	851 (0)	614 (7)	442 (18)	86 (25)	0 (26)
algo = LCR High	251 (0)	162 (23)	89 (40)	10 (52)	0 (52)

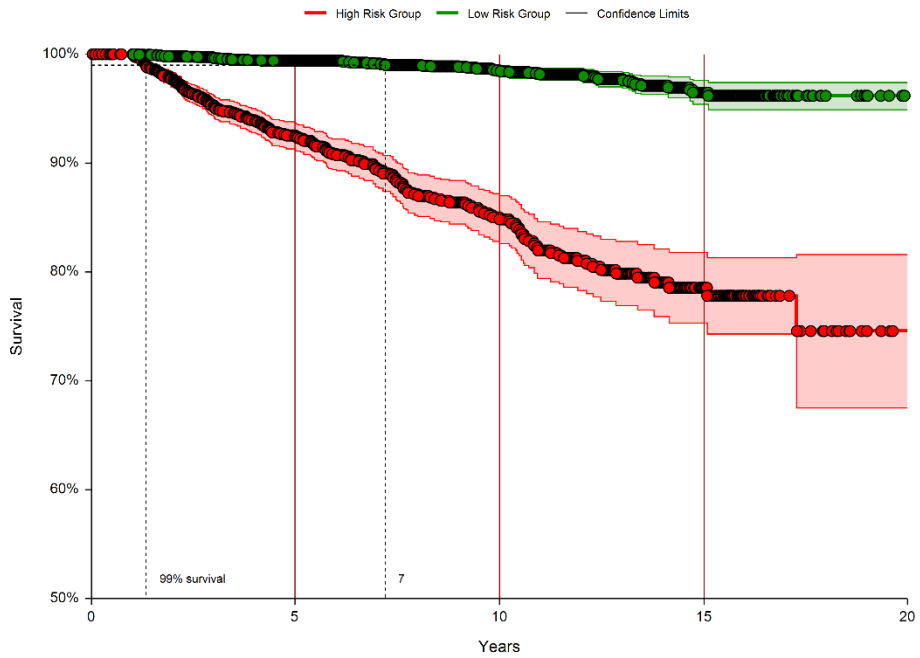
Fig. S2. Original-Study updated. Survival without HCC according to LCR1-LCR2 cut-offs.



Number At Risk (Number of Events)

algo = High Risk Group	847 (0)	636 (23)	301 (54)	98 (64)	6 (66)
algo = Low Risk Group	662 (0)	535 (1)	284 (4)	105 (6)	12 (6)

Fig. S3. 20-year survival without HCC according to LCR1-LCR2 cut-offs in the pooled data base combining the present External validation and the Original-Study.



Number At Risk (Number of Events)

algo = High Risk Group	1995 (0)	1182 (136)	462 (197)	114 (222)	6 (224)
algo = Low Risk Group	4417 (0)	3021 (25)	1604 (43)	348 (61)	12 (62)

Table S1. Comparison of Hepather patients' characteristics between the included and the non-included patients in the external validation of LCR1-LCR2 algorithm Missing data are detailed in Table 1. In case of non-normal distribution, the mean is given along with the median and IQR. Time to SVR is time between FibroTest assessment and SVR before HCC.

	Hepather cohort included	**Hepather cohort not included**	**P value**
Number of patients	4,903	5,418	
HCC	214 (4.4%)	292 (5.4%)	0.01
Follow-up time (years)	5.8 [4.2-11.4] mean 7.5	4.6 [3.0-5.9] mean 4.8	<0.001
Age at inclusion	55.6 [49.0-64.4]	56.3 [50.7-64.1]	<0.001
Age at FibroTest time	52.6 [45.1-61.1]	49.9 [41.5-58.1]	0.277
Men	2,412 (49.2%)	3,235 (59.7%)	<0.001
Body mass Index (kg/m^2)	24.4 [21.9-27.4]	24.8 [22.2-27.8]	<0.001
Geographical origin			0.11
France or Eastern Europe	3,488 (71.7%)	3,748 (70.3%)	
Asia	108 (2.2%)	117 (2.2%)	
North Africa	427 (8.8%)	543 (10.2%)	
Other (mostly Sub-Saharan)	841 (17.3%)	925 (17.3%)	
missing	39	85	
Past excessive alcohol use	1,225 (25.0%)	1,700 (31.4%)	<0.001
HCV treatment naive at inclusion at FibroTest time	 2,388 (48.8%) 2,916 (59.5%)	 2,529 (46.8%) -	
HCV genotype			0.001
1	3,300 (67.6%)	3,441 (64.5%)	
2	332 (6.8%)	353 (6.6%)	
3	547 (11.2%)	719 (13.5%)	
4	583 (11.9%)	716 (13.4%)	
5,6,7	117 (2.4%)	106 (2.0%)	
missing	24	83	
Fibrosis stage (using Hepather algorithm*) at inclusion			
F0	1,271 (27.1%)	953 (19.4%)	
F1	1,055 (22.5%)	818 (16.7%)	
F2	540 (11.5%)	445 (9.1%)	
F3	801 (17.1%)	802 (16.4%)	
F4	1,026 (21.9%)	1,884 (38.4%)	
missing	210	516	
ALT (UI/l) at inclusion	55 [36-90] mean 74.6	62 [39-104] mean 83.8	
Type-2 Diabetes	506 (10.3%)	747 (13.8%)	<0.001
Arterial hypertension	1,313 (26.8%)	1,614 (29.8%)	<0.001

AFP (ng/ml)	4.4 [3.0-7.6] mean 14.2	5.4 [3.2-10.4] mean 12.2	0.662
missing	1,182	2,011	
AFP class (ng/ml)			<0.001
< 6	2,396 (64.4%)	1,825 (53.6%)	
6 to <10	674 (18.1%)	671 (19.7%)	
10 to <20	417 (11.2%)	523 (15.4%)	
20 to <120	207 (5.6%)	345 (10.1%)	
>120	27 (0.7%)	43 (1.3%)	
missing	728	2,011	

Table S2. Characteristics of incident HCCs.

Table S2**A C**haracteristics of incident HCCs according to LCR1-LCR2 cut offs.

Characteristics	**Low LCR1-LCR2**	**High LCR1-LCR2**	**P-value**
	N=56	N= 158	
Time between last normal evaluation and first abnormal (months)	16 6.00 [5.1-16.6]	6.50 [2.6-22.8]	0.20
missing	24	40	
Time between first abnormal evaluation and diagnosis (months) (std)	1.2 [0-2.70]	0.6 [0-3.0]	0.78
missing	15	11	
Time between last normal evaluation and diagnosis (months) (std)	9.3 [6.1-18.9]	9.9 [5.3-16.5]	0.87
missing	23	33	0.88
Macroscopic pattern			
Infiltrative	4 (8.3 %)	18 (11.4%)	
Nodular	44 (91.7 %)	140 (88.6 %)	0.23
missing	8	0	
In nodular patterns:			
Number of tumors at diagnosis	1.1 (1.1)	1.54 (1.2)	0.84
Missing	13	20	
Largest nodule size (mm)	25.0 [20.0-30.0]	20.0 [15.0-30.0]	0.44
Missing	9	2	
Total nodule size	25.5 [20.0-38.0]	22.3 [15.0-40.0]	
Missing	11	4	
Alpha foetoproteine			
At entry	1.54 [1.02-2.00]	2.46 [1.87-3.14]	< 0.001
<6	34 (60.9 %)	33 (20.9 %)	< 0.001
6-10	14 (23.9 %)	32 (20.3 %)	
10-20	6 (10.9 %)	47 (30.0 %)	
20-120	2 (4.3 %)	38 (23.8 %)	
≥120	0 (0 %)	8 (5.0 %)	
At diagnosis	2.13 [1.44-5.00]	2.77 [1.74-4.53]	0.26
<6	20 (44.4 %)	41 (26.3 %)	0.04
6-10	5 (11.1 %)	18 (11.5 %)	
10-20	4 (8.9 %)	25 (16.0 %)	
20-120	4 (8.9 %)	41 (26.3 %)	
≥120	12 (26.7 %)	31 (19.9 %)	
missing	11	2	
Liver biopsy at diagnosis	22 (45.8 %)	56 (35.9 %)	0.21
Missing	8	2	
Grade WHO			
Well differentiated	10	20	
Moderately differentiated	6	20	
Poorly differentiated/undifferentiated	2	4	
Cholangiocarcinoma	1	0	
Not interpretable	1	2	
Others	0	0	
Missing	2	10	

Table S2B. Comparison of patients' characteristics between the low-risk population with HCC vs. the low-risk population without HCC and vs. the high-risk population without HCC.

	Low LCR1-LCR2 5yr HCC+	**Low LCR1-LCR2 HCC-**	**High LCR1-LCR2 HCC-**	**P value**
Number of patients	24	3,731	1,035	
F0/F1/F2/F3/F4	0/**2/6**/5/11	1605/1057/395/520/104	0/39/70/300/626	<0.0001
Follow-up time (years)	3.0 [1.7-3.3]	5.0 [4.5-5.0]	5.0 [4.0-5.0]	<0.0001
Age at FibroTest time	53.2 [48.3-58.7]	49.9 [43.0-57.2]	63.1 [54.8-71.0]	<0.0001
Men	**17 (70.8 %)**	1713 (45.9 %)	594 (57.4 %)	<0.0001
Body mass Index (kg/m^2)	24.7 [22.6-26.4]	24.1 [21.6-27.1]	25.4 [22.8-28.3]	<0.0001
Geographical origin				<0.0001
France or Eastern Europe	19 (79.2 %)	2694 (72.2 %)	693 (67.0 %)	
Asia	0 (0 %)	93 (2.5 %)	14 (1.4 %)	
North Africa	3 (12.5 %)	299 (8.0 %)	114 (11.0 %)	
Other, mostly Sub-Saharan	1 (4.2 %)	615 (16.5 %)	206 (19.9 %)	
missing	1	30	8	
Past excessive alcohol use	**8 (33.3 %)**	886 (23.8 %)	285 (27.5 %)	0.0265
HCV genotype				
1	8 (33.3 %)	2463 (66.3 %)	766 (74.4 %)	<0.0001
2	0 (0 %)	278 (7.5 %)	46 (4.5 %)	
3	**12 (50.0 %)**	423 (11.4 %)	82 (8.0 %)	
4	4 (16.7 %)	454 (12.2 %)	115 (11.2 %)	
5,6,7	0 (0 %)	95 (2.6 %)	21 (2.0 %)	
missing				
FibroTest stage				<0.0001
F0	0 (0 %)	1605 (43.2 %)	0 (0 %)	
F1	**2 (8.3 %)**	1057 (28.3 %)	39 (3.8 %)	
F2	**6 (25.0 %)**	395 (10.6 %)	70 (6.8 %)	
F3	5 (20.8 %)	520 (13.9 %)	300 (29.0 %)	
F4	11 (45.8 %)	154 (4.1 %)	626 (60.5 %)	
missing				
Type-2 Diabetes	**5 (20.8 %)**	250 (6.7 %)	222 (21.5 %)	<0.0001
Arterial hypertension	2 (8.3 %)	818 (21.9 %)	442 (42.7 %)	<0.0001
AFP (ng/ml)	**4.8 [2.7-7.6]**	3.2 [2.1-5.0]	8.2 [5.0-14.7]	<0.0001
AFP by classes				
< 6	14 (58.3 %)	2457 (81.8 %)	344 (33.2 %)	<0.0001
6 to < 10	**7 (29.2 %)**	356 (11.9 %)	269 (26.0 %)	
10 to <20	**3 (12.5 %)**	149 (5.0 %)	236 (22.8 %)	

20 to <120	0 (0 %)	40 (1.3 %)	169 (16.3 %)	
>120	0 (0 %)	1 (0 %)	17 (1.6 %)	
missing	0	708	0	

Table S3. Comparison of patients' characteristics between the low and high -risk populations according to LCR1-LCR2 algorithm (n=4,903)

	Low LCR1-LCR2	**High LCR1-LCR2**	**P value**
Number of patients	3,755 (76.6%)	1,148 (23.4%)	
HCC number by F0/F1/F2/F3/F4)	False negative	True positive	
within 5 years	24 (0/2/6/5/11)	113 (0/0/1/11/101)	<0.0001
within 10 years	39 (4/5/7/10/13)	143 (0/0/4/20/119)	<0.0001
End of follow-up	56 (5/10/8/18/15)	158 (0/1/6/24/127)	<0.0001
Follow-up time (years)	6.4 [4.5-12.1] mean 8.0	4.9 [3.6-6.4] mean 5.7	<0.001
Age at FibroTest time	49.9 [43.1-57.2]	62.8 [54.8-70.7]	<0.001
Men	1,730 (46.1%)	682 (59.4%)	<0.001
Body mass Index (kg/m^2)	24.1 [21.6-27.1]	25.4 [22.9-28.2]	<0.001
Geographical origin			0.003
France or Eastern Europe	2,713 (72.9%)	775 (68.0%)	
Asia	93 (2.5%)	15 (1.3%)	
North Africa	302 (8.1%)	125 (11%)	
Other (mostly Sub-Saharan)	616 (16.5%)	225 (19.7%)	
missing	31	8	
Past excessive alcohol use	894 (23.8%)	331 (28.8%)	
HCV genotype			<0.001
1	2,471 (66.1%)	829 (72.6%)	
2	278 (7.4%)	54 (4.7%)	
3	435 (11.6%)	112 (9.8%)	
4	458 (12.3%)	125 (10.9%)	
5,6,7	95 (2.5%)	22 (1.9%)	
missing	18	6	
FibroTest stage			<0.001
F0	1,605 (42.7%)	0 (0%)	
F1	1,059 (28.2%)	39 (3.4%)	
F2	401 (10.7%)	71 (6.2%)	
F3	525 (14.0%)	311 (27.1%)	
F4	165 (4.4%)	727 (63.3%)	
missing	0	0	
Type-2 Diabetes	255 (6.8%)	251 (21.9%)	<0.001
Arterial hypertension	820 (21.8%)	493 (42.9%)	<0.001
AFP (ng/ml)	3.2 [2.1-5.0] mean 4.5	8.4 [5.0-15.2] mean 35	0.035
AFP by classes			<0.001
< 6	2471 (81.7 %)	370 (32.2 %)	
6 to < 10	364 (12.0 %)	290 (25.3 %)	
10 to <20	152 (5.0 %)	268 (23.3 %)	
20 to <120	39 (1.3 %)	197 (17.2 %)	
>120	1 (0 %)	23 (2.0 %)	
missing	728	0	

Table S4. Fifth post-hoc analysis. **Characteristics of patients with or without SVR.**
Table S4A. Subset of patients with SVR

	Hepather cohort patients included with SVR during follow-up	**Missing data**
Number of patients	3 405	0
HCC	124 (3.6 %)	0
LCR1-LCR2 algorithm Low risk High risk	 2568 (75.4%) 837 (24.6%)	0
Follow-up time (years), median [IQR]	5.4 [4.2-9.8]	0
Age at inclusion	55.7 [49.2-64.3]	0
Age at FibroTest time	53.3 [46.1-61.7]	0
Men	1650 (48.5%)	0
Body mass Index (kg/m^2)	24.4 [21.9-27.3]	10
Smoker At inclusion In the past	 1145 (36.7%) 2062 (60.6%)	4
Geographical origin		25
France or Eastern Europe	2616 (77.4 %)	
Asia	83 (2.5%)	
North Africa	346 (10.2 %)	
Other (mostly Sub-Saharan)	335 (9.9 %)	
Past excessive alcohol use	831 (24.4 %)	0
Time since HCV infection	10.7 [3.7-17.3]	88
HCV contamination cause Drug usage Transfusion Other or unknown	 527 (24.6%) 717 (33.5%) 898 (41.9%)	1263
HCV genotype		14
1	2337 (68.9 %)	
2	204 (6.0 %)	
3	369 (10.9 %)	
4	401 (11.8%)	
5,6,7	80 (2.4%)	
Fibrosis at inclusion using Hepather criteria		129
F0	896 (27.3%)	
F1	712 (21.7%)	
F2	391 (11.9%)	
F3	585 (17.9%)	
F4	692 (21.1%)	
Fibrosis at first FibroTest assessment		0
F0 (<=0.21)	1109 (32.6%)	
F1 (>0.21)	728 (21.4%)	
F2 (0.48)	331 (9.7%)	

F3 (0.58)	591 (17.4%)	
F4 (0.74)	646 (19.0%)	
ALT (IU/l) at inclusion	55 [37-91]	36
Type-2 Diabetes	353 (10.4%)	0
Arterial hypertension	919 (27.0%)	0
AFP (ng/ml)	4.0 [2.5-7.0]	481
AFP class (ng/ml)		481
< 6	2005 (68.6%)	
6 to <10	476 (16.3%)	
10 to <20	273 (9.3%)	
20 to <120	157 (5.4%)	
>120	13 (0.4%)	

Table S4B. Subset of patients without SVR

	Hepather cohort patients included without SVR during follow up	**Missing data**
Number of patients	1102	0
HCC	78 (7.1 %)	0
LCR1-LCR2 algorithm Low risk High risk	 851 (77.2%) 251 (22.8%)	0
Follow-up time (years), median [IQR]	9.6 [4.5-13.1]	0
Age at inclusion	55.9 [49.5-64.6]	0
Age at FibroTest time	51.1 [43.8-59.3]	0
Men	595 (54.0%)	0
Body mass Index (kg/m^2)	24.6 [21.9-27.6]	4
Smoker At inclusion In the past	 384 (34.9%) 688 (62.6%)	0
Geographical origin		10
France or Eastern Europe	808 (74.0%)	
Asia	28 (2.6%)	
North Africa	128 (11.7%)	
Other (mostly Sub-Saharan)	128 (11.7%)	
Past excessive alcohol use	299 (27.1 %)	0
Time since HCV infection	8.5 [2.8-14.8]	21
HCV contamination cause Drug usage Transfusion Other or unknown	 236 (26.7%) 290 (32.8%) 358 (40.5%)	218
HCV genotype		6
1	727 (66.3%)	
2	90 (8.2%)	
3	118 (10.8%)	
4	137 (12.5%)	
5,6,7	24 (2.2%)	
Fibrosis at inclusion using Hepather criteria		58
F0	238 (22.8%)	
F1	223 (21.4%)	
F2	117 (11.2%)	
F3	185 (17.7%)	
F4	281 (26.9%)	
Fibrosis at first FibroTest assessment		0
F0 (<=0.21)	306 (27.8%)	
F1 (>0.21)	273 (24.8%)	
F2 (0.48)	117 (10.6%)	
F3 (0.58)	203 (18.4%)	

F4 (0.74)	203 (18.4%)	
ALT (IU/l) at inclusion	56.0 [36.0-93.0]	15
Type-2 Diabetes	130 (11.8%)	0
Arterial hypertension	285 (25.9%)	1
AFP (ng/ml)	4.3 [2.7-8.2]	145
AFP class (ng/ml)		145
< 6	608 (63.5%)	
6 to <10	146 (15.3%)	
10 to <20	125 (13.1%)	
20 to <120	69 (7.2%)	
>120	9 (0.9%)	

Table S4C. Performance of LCR1-LCR2 algorithm according to SVR status during using HCC Standardized Ratio Incidence (SIR)

Surveillance option			
Only patients with SVR	**Cases**	**HCC**	**Standardized Ratio Incidence**
5-years follow-up, 1-year HCC exclusion	n	n	LCR1-LCR2 Low risk/ High risk
Primary outcome	3405	98	10.0 [5.8-16.0]/ 54.4[43.2-67.6]
Secondary outcome F3F4	3405	98	10.0 [5.82-16.01]/ 54.4[43.2-67.6]
Only patients without SVR	**Cases**	**HCC**	**Standardized Ratio Incidence**
5-years follow-up, 1-year HCC exclusion	n	n	LCR1-LCR2 Low risk/ High risk
Primary outcome	1102	30	12.7 [5.1-26.2]/ 57.5[36.4-86.3]
Secondary outcome F3F4	1102	30	12.7 [5.1-26.2]/ 57.5[36.4-86.3]

Table S4D. LCR1-LCR2 predictive values, sensitivity and specificity according to SVR status

Surveillance option	**LCR1-LCR2 performances**			
	Negative Predictive Value	**Positive Predictive Value**	**Sensitivity**	**Specificity**
	% (95% CI)	%	%	%
Patients with SVR				
Primary outcome	96.7 (93.5-99.9)	15.6 (9.1-22.2)	62.5 (53.8-71.2)	75.7 (68.0-83.4)
Secondary outcome F3F4	96.7 (93.5-99.9)	15.6 (9.1-22.2)	62.5 (53.8-71.2)	75.7 (68.0-83.4)
Patients without SVR				
Primary outcome	99.2 (98.7-99.7)	9.2 (7.5-10.9)	76.7 (74.2-79.2)	78.7 (76.3-81.1)
Secondary outcome F3F4	99.2 (98.7-99.7)	9.2 (7.5-10.9)	76.7 (74.2-79.2)	78.7 (76.3-81.1)

Table S4E. Time-dependent univariate and multivariate analyses in patients with SVR.

	Time-dependent hazard ratio (HR) in SVR patients					
	Univariate			Multivariate		
	HR	95%CI	P-value	HR	95%CI	P-value
LCR1-LCR2 algorithm	**16.32**	**9.67-27.53**	**<0.001**	**12.34**	**6.74-22.59**	**<0.001**
Gender (men vs women)	4.10	2.53-6.64	<0.001	2.14	1.23-3.71	0.0070
Age (years) at FT time	1.04	1.03-1.06	<0.001			
<=50 (reference)						
<=50-60	3.84	2.11-7.02	<0.001	1.29	0.68-2.47	0.4358
>60	3.95	2.15-7.26	<0.001	1.05	0.52-2.14	0.8928
Geographical origin (European vs other)	1.44	0.84-2.46	0.1811	1.54	0.89-2.66	0.1223
Past excessive alcohol use (yes vs no)	2.22	1.48-2.32	0.0001	1.29	0.83-2.01	0.2634
Ever smoked (yes vs no)	1.57	1.02-2.42	0.0423	0.89	0.53-1.49	0.6496
Treatment-naive vs Treated	0.28	0.18-0.43	<0.001	0.52	0.33-0.81	0.0041
HCV genotype 3 (other reference)	3.79	2.46-5.82	<0.001	4.27	2.70-6.75	<0.001
Diabetes (yes vs no)	3.27	2.09-5.12	<0.001	1.42	0.89-2.27	0.1441
Arterial hypertension (yes vs no)	1.83	1.22-2.74	0.0034	1.37	0.88-2.13	0.1624

Table S5. Post-hoc analysis #6. Comparison of the HCC standardized risk ratio (SIR) in the low LCR1-LCR2 subset vs. the risk observed in the general population.

Table S5.A Standardized Incidence Ratio (SIR) by age and gender

LCR1-LCR2	Total			IC95 SIR		P value SIR=1 as reference
	Observed	Expected	SIR	low	up	
Low	24	2.45	9.80	6.27	14.58	<0.001
High	113	1.99	56.78	46.80	68.27	<0.001

Table S5.B Incidence of HCC in France adjusted on age and gender.
Defossez G, Le Guyader-Peyrou S, Uhry Z, et al. Estimations nationales de l'incidence et de la mortalite par cancer en France metropolitaine entre 1990 et 2018. Volume 1. Saint-Maurice (Fra): Sante publique France, 2019. http: //www.santepubliquefrance.fr/

Standardized incidence of HCC in France		
Age	Gender	
[years classes]	Male	Female
[0;14]	0.3	0.2
[15;19]	0.1	0.1
[20;24]	0.2	0.1
[25;29]	0.3	0.2
[30;34]	0.5	0.4
[35;39]	0.9	0.6
[40;44]	2.3	1.2
[45;49]	7.0	2.4
[50;54]	19.2	4.5
[55;59]	38.4	7.4
[60;64]	61.4	11.2
[65;69]	83.9	16.2
[70;74]	101.5	21.6
[75;79]	114.1	27.1
[80;84]	117.3	31.9
[85;89]	109.4	34.8
[90;94]	89.4	33.1
[95;+]	64.9	27.4

Table S6. Original Study. Updated characteristics for participants of the chronic hepatitis C subset, included in the first study of LCR1-LCR2 algorithm

	Original Study	**Missing data**
Number of patients	1,509	0
HCC	72 (4.8%)	0
LCR1-LCR2 algorithm Low risk High risk	 662 (43.9%) 847 (56.1%)	0
Follow-up time, median (years)	6.8 [3.0.2-10.2] mean 7.0	0
Age at inclusion (IQR)	47.0 [40.3-57.7]	0
Age at FibroTest time	47.0 [40.3-57.7]	0
Men	974 (64.6%)	0
Body mass Index (kg/m^2)	23.5 [21.1-25.6]	1070
Smoker at inclusion	250 (16.6%)	
Geographical origin		0
France or Eastern Europe	1023 (67.8%)	
Asia	84 (5.6%)	
North Africa	211 (14.0%)	
Other (mostly Sub-Saharan)	191 (12.6%)	
Excessive alcohol use at inclusion	142 (9.4 %)	0
Time since HCV infection	10.1 [3.3-16.6]	88
HCV genotype		373
1	623 (54.8%)	
2	85 (7.5%)	
3	181 (15.9%)	
4,5,6,7	247 (21.8%)	
Fibrosis at inclusion (using FibroTest cutoffs)		0
F0 (<=0.21)	482 (31.9%)	
F1 (>0.21)	301 (20.0%)	
F2 (>0.48)	148 (9.8%)	
F3 (>0.58)	230 (15.2%)	
F4 (>0.74)	348 (23.1%)	
Activity grade (ActiTest cutoff)		1
A0 (<=0.29)	556 (36.9%)	
A1 (>0.29)	402 (26.7%)	
A2 (>0.52)	151 (10.0%)	
A3 (>0.62)	399 (26.4%)	
ALT (IU/l) at inclusion	55 [36-90] mean 75	1
Type-2 Diabetes	163 (10.8%)	0
Arterial hypertension	81 (7.0%)	1
AFP (ng/ml)	4.4 [3.0-7.6] mean 14.2	0
AFP class (ng/ml)		0

< 6	1187 (78.6%)	
6 to <10	178 (11.8%)	
10 to <20	86 (5.7%)	
20 to <120	45 (3.0%)	
>120	13 (0.9%)	
HCV treatment during followup		0
Naive all followup	501 (33.2%)	
SVR	605 (40.1%)	
Non SVR	403 (26.7%)	

In case of non-normal distribution, the mean is also given along with the median and IQR

Table S7. Original-Study updated. Comparison of patients' characteristics between the Low and High -risk populations according to LCR1-LCR2 algorithm (n=1,509)

	Low Risk	**High Risk**	**P value**
Number of patients	662	847	
HCC (by F0/F1/F2/F3/F4)			
Within 5 years	**1 (1/0/0/0/0)**	**23 (1/1/4/1/16)**	**<0.001**
Within 10 years	4 (3/1/0/0/0)	54 (1/3/4/8/38)	<0.001
End of follow-up	6 (5/1/0/0/0)	66 (1/3/4/11/47)	<0.001
Follow-up years median (IQR)	9.4 (9.0-9.7)	7.8 (7.3-8.4)	<0.001
Death (not actuarial)	63 (9.5%)	224 (26.4%)	<0.001
Age at inclusion median (IQR)	41.8 (40.8-42.8)	51.5 (50.8-52.7)	<0.001
Men	335 (50.6%)	635 (75.4%)	<0.001
Body mass Index (kg/m^2)	23.5 (22.9-24.2)	24.5 (24.2-25.1)	0.002
Missing	438	564	
Geographical origin			0.78
France or Eastern Europe	448 (67.7 %)	575 (67.9%)	
Asia	41 (6.2%)	43 (5.1%)	
North Africa	89 (13.4%)	122 (14.4%)	
Other (mostly Sub-Saharan)	84 (12.7%)	107 (12.6%)	
Past excessive alcohol use	69 (10.4%)	73 (8.6%)	0.25
HIV positive	77 (11.6%)	116 (13.7%)	0.24
HCV genotype			0.07
1	264 (52.3%)	359 (56.9%)	
2	49 (9.7%)	36 (5.7%)	
3	83 (16.4%)	98 (15.5%)	
4,5,6,7	109 (21.6%)	138 (21.9%)	
Missing	157	216	
FibroTest stage			<0.001
F0	472 (71.3%)	10 (0%)	
F1	167 (25.2%)	134 (15.8%)	
F2	18 (2.7%)	130 (15.3%)	
F3	5 (0.8%)	225 (26.6%)	
F4	0 (0%)	348 (41.1%)	
Type-2 Diabetes	255 (6.8%)	251 (21.9%)	<0.001
Arterial hypertension	820 (21.8%)	493 (42.9%)	<0.001
AFP >= 20ng/ml)	7 (1.1%)	51 (6.0%)	<0.001
Treatment			<0.001
Naive	333 (50.3%)	168 (19.8%)	
Not-SVR	109 (16.5%)	296 (34.9%)	
SVR	220 (33.2%)	383 (45.2%)	

Table S8. Pooled characteristics for participants of the Hepather validation cohort and those included in the Original-Study of LCR1-LCR2 algorithm

	Pooled population	**Missing data**
Number of patients	6,412	0
HCC	286	0
LCR1-LCR2 algorithm Low risk High risk	 4417 (69.9 %) 1995 (31.1 %)	 0 0
Follow-up time, median (years)	6.2 [4.4 – 11.7]	0
Age at FibroTest time	51.3 [43.6 – 60.1]	0
Men	3376 (52.8 %)	0
Body mass Index (kg/m^2)	24.6 [22.1-27.6]	201
Smoker at inclusion	1939 (30.3 %)	7
Geographical origin		1548
France or Eastern Europe	3725 (76.5 %)	
Asia	121 (2.5 %)	
North Africa	509 (10.5 %)	
Other (mostly Sub-Saharan)	509 (10.5 %)	
Excessive alcohol use at inclusion	197 (3.9 %)	1316
Time since HCV infection		
HCV genotype		397
1	3923 (65.2 %)	
2	417 (6.9 %)	
3	728 (12.1 %)	
4,5,6,7	947 (15.8 %)	
Fibrosis at inclusion (using FibroTest cutoffs)		0
F0 (<=0.21)	2087 (32.6 %)	
F1 (>0.21)	1399 (21.8 %)	
F2 (>0.48)	620 (9.7 %)	
F3 (>0.58)	1066 (16.6 %)	
F4 (>0.74)	1240 (19.3 %)	
Activity grade (ActiTest cutoff)		2178
A0 (<=0.29)	1679 (39.7 %)	
A1 (>0.29)	1175 (27.7 %)	
A2 (>0.52)	392 (9.3 %)	
A3 (>0.62)	988 (23.3 %)	
ALT (IU/l) at inclusion	55.0 [37.0-88.0]	2173
Type-2 Diabetes	669 (10.4 %)	0
Arterial hypertension	1438 (22.4 %)	1
AFP (ng/ml)	3.9 [2.4-6.6]	728
AFP class (ng/ml)		728
< 6	4028 (70.9 %)	
6 to <10	832 (14.6 %)	

10 to <20	506 (8.9 %)	
20 to <120	281 (4.9 %)	
>120	37 (0.7 %)	
HCV treatment during follow-up		
Naive all follow-up	897 (14.0 %)	0
SVR	4008 (77.5 %)	344
Non SVR	1163 (22.5 %)	

Table S9. STROBE check list.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6-7
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	7-8 NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	10-11

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	12
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	13-14
Outcome data	15*	Report numbers of outcome events or summary measures over time	12-14

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12-14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-14
Discussion			
Key results	18	Summarise key results with reference to study objectives	16-17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2 and 12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Table S10. STARD check list.

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	3
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	3-4
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	5
	4	Study objectives and hypotheses	6
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	6-8
Participants	**6**	Eligibility criteria	6-7
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	6-7
	8	Where and when potentially eligible participants were identified (setting, location and dates)	7
	9	Whether participants formed a consecutive, random or convenience series	7-8
Test methods	**10a**	Index test, in sufficient detail to allow replication	5
	10b	Reference standard, in sufficient detail to allow replication	8-9
	11	Rationale for choosing the reference standard (if alternatives exist)	9
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	10-11
	12b	Definition of and rationale for test positivity cut-offs or result categories	10-11

		of the reference standard, distinguishing pre-specified from exploratory	
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	10-11
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	10-11
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	10-11
	15	How indeterminate index test or reference standard results were handled	10-11
	16	How missing data on the index test and reference standard were handled	10-11
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	10-11
	18	Intended sample size and how it was determined	10
RESULTS			
Participants	**19**	Flow of participants, using a diagram	12
	20	Baseline demographic and clinical characteristics of participants	12
	21a	Distribution of severity of disease in those with the target condition	12-13
	21b	Distribution of alternative diagnoses in those without the target condition	13-14
	22	Time interval and any clinical interventions between index test and reference standard	12-14
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	12-14
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	12-14
	25	Any adverse events from performing the index test or the reference standard	NA
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	17-18
	27	Implications for practice, including the intended use and clinical role of the index test	16-18
OTHER INFORMATION			
	28	Registration number and name of registry	4; 8

	29	Where the full study protocol can be accessed	7 (reference 7)
	30	Sources of funding and other support; role of funders	2; 12