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Editorial board member of *World Journal of Hepatology*, Dr. Alberto Ferrarese is a Gastroenterologist devoted to the field of hepatology. He obtained his MD degree at Padua University Hospital, Italy, where his ongoing career research has focused mainly on decompensated cirrhosis and liver transplantation. His main research interests are complications of cirrhosis, bacterial infection in cirrhosis, organ allocation in liver transplantation, and adherence and quality of life after liver transplantation. He has authored 40 articles published in international peer-reviewed journals and he serves as a reviewer for several international journals in the field of hepatology. (L-Editor: Filipodia)

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“Six-and-twelve” score for outcome prediction of hepatocellular carcinoma following transarterial chemoembolization. In-depth analysis from a multicenter French cohort

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Abstract

The “six-and-twelve” (6&12) score is a new hepatocellular carcinoma (HCC) prognostic index designed for recommended transarterial chemoembolization (TACE) candidates. Quick and easy to use by the sum of tumor size (cm) and number, this model identifies three groups with different survival time (the sum is ≤ 6 ; or > 6 but ≤ 12 ; or > 12); a survival benefit with TACE can be expected for HCC patients with a score not exceeding twelve. Recently, Wang ZW *et al* showed that the “6&12” model was the best system correlated with radiological response after the first TACE. Thus, we wanted to assess its survival prediction ability as well as its prognostic value and compared it to other systems (Barcelona Clinic Liver Cancer, Hong Kong Liver Cancer (HKLC) staging, Albumin-Bilirubin grade, tumor nodularity, infiltrative nature of the tumor, alpha-fetoprotein, Child-Pugh class, and Performance Status score, Cancer of the Liver Italian Program, Model to Estimate Survival for HCC scores, up-to-seven criteria) different from Wang ZW *et al* study in a multicenter French cohort of HCC including only recommended TACE candidates retrospectively enrolled. As previously demonstrated, we show that the “6&12” score can classify survival within this French cohort, with a

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prognostic value comparable to that of other systems, except HKLC staging. More importantly, the “6&12” score simplicity and ability in patients’ stratification outperform other systems for a routine clinical practice.

Key words: Hepatocellular carcinoma; Transarterial chemoembolization; “Six-and-twelve” score; Prognosis; Albumin-Bilirubin grade; Tumor nodularity, infiltrative nature of the tumor, alpha-fetoprotein, Child-Pugh class, and performance status score

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Core tip: Not all-intermediate stage hepatocellular carcinoma (HCC) benefit from transarterial chemoembolization (TACE). The recent “six-and-twelve” (6&12) score is an easy to use prognostic model that ensure a quick and appropriate patient’ selection before the first TACE in Chinese cohorts. In this multicenter French cohort of HCC, the “6&12” score can also classify survival among recommended TACE candidates with a good prognostic performance. It may help clinicians in routine clinical practice.

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TO THE EDITOR

We have read with great interest the study by Wang *et al*^[1] who assessed and compared different prognostic models for hepatocellular carcinoma (HCC) patients undergoing transarterial chemoembolization (TACE) treatment, especially the latest “six-and-twelve” (6&12) score^[2] within a nationwide Chinese HCC cohort ($n = 1107$). Increased survival after TACE is correlated with radiological response^[3,4] and this study shows that the “6&12” index is the best system correlated with radiological response after the first TACE. The study population was more heterogeneous than the population used to develop the score, including patients with slightly altered performance status (PS) and logically a model like the 3rd version of the hepatoma arterial-embolization prognostic score^[5] (which include liver function parameters) had a higher predictive value for survival. However, simplicity (using two cut-off values for risk stratification) and presumed reliability of the “6&12” score have convinced us to assess once again^[6] the reproducibility and the predictive value of this new model in a multicenter French cohort of HCC patients including only recommended TACE candidates ($n = 324$) ie intermediate and early unresectable stages according to the treatment stage migration concept. We compared it to other systems different from Wang *et al*^[1]’s study (Barcelona Clinic Liver cancer^[7] (BCLC) staging, Child-Pugh (CP) class, Albumin-Bilirubin^[8] (ALBI) grade, NIACE^[9] [tumor nodularity, infiltrative nature of the tumor, alpha-fetoprotein (AFP), CP class, and PS] score (Table 1)) using time-dependent area under receiver operating characteristic curve (AUROC) values and C-indices.

Patients were retrospectively enrolled over a six years period in two centers (Marseille, Nancy). Demographic and clinical characteristics of HCC patients are shown in Table 2. HCC patients were mostly male (85%), with a median of age of 68 years. Cirrhosis was present in 96% of cases, CP class A (77%), CP class B7 (23%). Underlying liver disease was mostly related to alcohol abuse (38%) or viral C hepatitis (40%). Patients were BCLC stage B ($n = 179$), BCLC stage A ($n = 145$). HCC were multinodular in 71% of cases and the median tumor diameter was 35 mm (25-50). The mean session number of conventional TACE was 2.7 ± 1.8 .

After a median follow-up duration of 24.4 (15.0-36.8) mo, eighty one percent of patients died. Kaplan-Meier analyses showed significant differences in overall survival (OS) distributions across subgroups of BCLC staging, “6&12” (Figure 1) and NIACE scores within this cohort ($P < 0.05$) (Table 3). Liver function at baseline also had an impact on survival; median OS was significantly different according to the CP class

Table 1 Summary of points-based scores

CLIP (0 to 7 points)			MESH (0 to 6 points)		NIACE (0 to 7 points)	
Portal vein thrombosis	1 point		Tumor extent: Beyond Milan criteria	1 point	Tumor nodules ≥ 3	1 point
AFP ≥ 400 ng/mL	1 point		Vascular invasion and/or Extrahepatic spread	1 point	Infiltrative HCC	1.5 points
					Nodular HCC	0 point
Child-Pugh grade A	0 point		PS ≥ 2	1 point	AFP ≥ 200 ng/mL	1.5 points
B	1 point		Child-Pugh grade $\geq A6$	1 point		
C	2 points					
Tumor extent						
Unidolar and extension $\leq 50\%$	0 point		AFP ≥ 20 ng/mL	1 point	Child-Pugh grade A	0 point
Multinodular and extension $\leq 50\%$	1 point		Alkaline phosphatase ≥ 200 IU/l	1 point	Child-Pugh grade B	1.5 points
Massive or extension $> 50\%$	2 points				PS ≥ 1	1.5 points

CLIP: Cancer of the Liver Italian Program; MESH: Model to Estimate Survival for Hepatocellular carcinoma; NIACE: Tumor nodularity, infiltrative nature of the tumor, alpha-fetoprotein, Child-Pugh class, and performance status.

[CP-A, 27 (25-31) mo; CP-B7, 21 (15-24) mo ($P = 0.0003$)], or ALBI grade [grade 1, 35 (25-43) mo; grade 2, 26 (22-28) mo; grade 3, 16 (12-24) mo ($P = 0.0029$)].

Performances of the “6&12” score and other systems for survival prediction are indicated in Table 4. Time-dependent AUROC values and C-indices of the “6&12” score was not significantly different from those of other systems. We checked our results within the main cohort from Marseille ($n = 252$) (Table 2) by comparing the “6&12” score to other staging scoring systems (Hong Kong Liver Cancer^[10] (HKLC), Cancer of the Liver Italian Program^[11] (CLIP), Model to Estimate Survival for HCC^[12] (MESH), up-to-seven criteria^[13]). Significant differences in survival distributions were also found across subgroups of the “6&12” score and other systems within this single center cohort ($P < 0.05$) (Table 5). Its predictive value remained comparable to that of other systems [C-index “6&12” 0.63 (0.56-0.70) *vs* CLIP 0.70 (0.62-0.78) *vs* “up-to-seven” 0.61 (0.56-0.66) *vs* MESH 0.71 (0.63-0.78), not significant] except for HKLC staging, which provides a better prognostication ability [3-year AUROC (“6&12”) 0.56 (0.44-0.68) *vs* (HKLC) 0.69 (0.65-0.74), $P = 0.0325$] using a more complex stratification into five subgroups.

Firstly, our findings confirm previously published results^[1,2], the “6&12” score can classify survival among recommended TACE candidates. Its prognostic performance was similar within our cohort compared to Wang *et al*^[2] original study [3-year AUROC values: 0.64 (0.58-0.71) *vs* 0.65 (0.61, 0.70); C-indices: 0.66 (0.58-0.74) *vs* 0.66 (0.63, 0.69) (Table 4)], and higher than that observed in this nationwide Chinese cohort^[1] [c-index: 0.58 (0.56, 0.60)]. Moreover, HCC patients with the highest tumor burden [sum of largest tumor size (cm) and number exceeding 12] have a median survival of 15 mo similar to Wang *et al*^[1]’s manuscript. Thus, this model can also identify within our population a subgroup of patients with poor prognosis who may not achieve benefit from TACE. The “6&12” risk stratification into three subgroups is relevant. Indeed, the first one (sum of tumor size and number not exceeding six) identifies TACE candidates with long-term survival especially those who may achieve a complete necrosis after this treatment^[14,15]. Moreover, TACE is also an effective therapy for the second subgroup (sum of tumor size and number above six and not exceeding twelve), which has clear boundaries unlike intermediate stage subclassifications^[16,17] that divide tumor burden according to the up-to-seven criteria (within/out).

Secondly, in our study the “6&12” score prognostic value is comparable to that of other systems, but most of these models cannot be used to guide treatment decision directly. “6&12” simplicity outweighs other systems for a current clinical practice including models with online calculator^[5]. Indeed, therapeutic management is determined using a multidisciplinary approach and control of different published prognostic scores for TACE by clinicians (surgeons, oncologists, hepatologists and radiologists) is very unusual. By adding “the sum of largest tumor size and number”, it is true that consensus is easy to achieve among all clinicians. Moreover, other scores^[9] encompass other baseline features that are likely to impact OS such as morphology of the tumor^[18], but those parameters are not routinely recorded, which

Table 2 Baseline characteristics of hepatocellular carcinoma patients undergoing transarterial chemoembolization treatment, *n* (%)

Demographic variables	Marseille/Nancy cohort, <i>n</i> = 324	Marseille cohort ¹ , <i>n</i> = 252
Age - Median [Q1-Q3], year	68 [62-74]	68 [60-73]
Gender Male/female	276 (85)/48 (15)	214 (85)/38 (15)
Liver disease HCV/HBV/Alcoholism/MS/other	129 (40)/14 (4)/122 (38)/42 (13)/17 (5)	109 (43)/12 (5)/84 (33)/37 (15)/10 (4)
ECOG (PS-0)	324 (100)	252 (100)
Cirrhosis	311 (96)	243 (96)
Tumor variables:		
Tumor Size - mm - median [q1-q3]	35 [25-50]	32 [25-44]
Nodule (s): 1/2/3/4/≥ 5	95 (29)/72 (22)/80 (25)/38 (12)/39 (12)	83 (33)/67 (27)/34 (13)/31 (12)/37 (15)
Laboratory variables		
AFP - ng/mL, median [q1-q3]	16.3 [6.0-120.3]	11.2 [5.0-77.7]
PT (%), median [q1-q3]	76 [64-88]	78 [68-88]
Albumin (g/L), median [q1-q3]	35 [28-38]	36.6 [32.7-41.0]
Total bilirubin (mcmmol/L), median [q1-q3]	19.0 [13.7-28.7]	17 [11-27]
Child - Pugh grade A/B7	249 (77)/75 (23)	180 (71)/72 (29)
ALBI ¹ class	64 (20)/230 (71)/30 (9)	37 (15)/175 (73)/29 (12)
BCLC ¹ stage A/B	145 (45%)/179 (55%)	134 (56)/107 (44)
"6&12" ¹ score allocation <i>n</i> ≤ 6 / > 6 - ≤ 12 / > 12	154 (48)/163 (50)/7 (2)	130 (54)/106 (44)/5 (2)
NIACE score allocation ≤ 1 / 1.5 - 3 / > 3	168 (52)/134 (41)/22 (7)	
CLIP ¹ score allocation 0/1/2/≥ 3	-	55 (23)/135 (56)/45 (19)/ 6 (2)
MESH ¹ score allocation 0/1/2/3/4	-	41 (17)/77 (32)/78 (32)/37 (15)/8 (4)
Up-to-Seven model ¹ (In/Out)	-	176 (73)/65 (27)
HKLC ¹ stage 1/2a/2b/3a/3b	-	89 (37)/43 (17)/65 (27)/24 (10)/21 (9)

¹Available data for 241 patients for staging and scores calculation. The Albumin-Bilirubin (ALBI) score was calculated according to the . ALBI grades were defined as ALBI grade 1 (score ≤ -2.60), ALBI grade 2 (score > - 2.60 and ≤ - 1.39) and ALBI grade 3 (score > - 1.39). Bilirubin level in mcmmol/L and albumin level in g/L; Up-to-seven criteria: With seven as the sum of the largest tumor size (in cm) + number of tumor(s). Barcelona Clinic Liver cancer (BCLC) classification: Current (BCLC) staging considers solitary tumor > 2 cm or no more than 3 tumors not exceeding 3 cm in diameter (Performance Status-0, Child-Pugh (CP) class A or B7 grade) as stage A. No tumor was classified at the very early stage of hepatocellular carcinoma (HCC) (BCLC 0) in this multicenter French cohort. BCLC stage B HCC encompassed patients with multiple tumors beyond 3 cm, PS-0, CP A or B7 grade. Hong Kong Liver Cancer classification: Early tumor: ≤ 5 cm, ≤ 3 tumor nodules; CP grade A (stage 1), CP grade B (stage 2a), -Intermediate tumor: ≤ 5 cm and > 3 tumor nodules or > 5 cm and ≤ 3 tumor nodules, CP grade A (stage 2b), CP grade B (stage 3a), - Locally-advanced tumor: > 5 cm, > 3 tumor nodules, CP grade A or B (stage 3b). HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolization; HCV: Hepatitis C virus; HBV: Hepatitis B virus; MS: Metabolic syndrome; ECOG (PS): Eastern Cooperative Oncology Group (Performance Status); AFP: Alpha-fetoprotein; PT: Prothrombin Time; ALBI: Albumin-Bilirubin; BCLC: Barcelona Clinic Liver Cancer; "6&12": "Six-and-twelve"; NIACE: Tumor nodularity, infiltrative nature of the tumor, AFP, CP, PS; CLIP: Cancer of the Liver Italian Program; MESH: Model to Estimate Survival for Hepatocellular carcinoma; HKLC: Hong Kong Liver Cancer.

limits their use.

Thirdly, TACE should be limited to HCC patients with preserved liver function, and our results also highlight the importance of liver function in our population that included only recommended TACE candidates. Our patients are older, with more cirrhotic patients, and more alcohol-related diseases. This probably explains the differences in survival observed between this multicenter French cohort and Wang *et al*^[2] original study, with OS ranging from 31.0 to 15.0 mo compared to 43.3 to 16.8 mo (according to "6&12" score), respectively. However, OS observed in our cohort was comparable to that of this nationwide Chinese cohort^[1] including a more heterogeneous population with OS ranging from 31.3 to 18.5 mo.

Fourthly, Wang *et al*^[19] findings on ABCR score are not surprising. This model designed for further TACE combines four parameters (AFP serum level, BCLC stage, change in Child-Pugh grade, and radiological tumor Response), but unlike ART^[20,21] (assessment for re-treatment with TACE) model the highest coefficient is assigned to

Table 3 Kaplan-Meier survival analysis according to “Six-and-twelve” score and other systems in the multicenter French cohort (n = 324)

Scoring/stage systems	OS [95%CI], mo	P value (log-rank)	Sidak ¹	Hazard ratio [95%CI]	P value
“6&12” score		< 0.0001			
sum ≤ 6 (n = 154)	31 [27-35]		Ref	Ref	
sum > 6 ≤ 12 (n = 163)	20 [17-24]		0.0009	1.55 [1.21-1.99]	0.0005
sum > 12 (n = 7)	15 [5-19]		< 0.0001	3.80 [1.76-8.21]	0.0007
BCLC staging		< 0.0001			
A (n = 145)	35 [29-38]		NR	Ref	
B (n = 179)	19 [17-23]		NR	1.88 [1.47-2.41]	< 0.0001
NIACE score		< 0.0001			
≤ 1 (n = 168)	35 [28-36]		Ref	Ref	
1.5 - 3 (n = 134)	20 [16-23]		< 0.0001	1.92 [1.49-2.48]	< 0.0001
> 3 (n = 22)	11 [5-16]		< 0.0001	6.23 [3.87-10.02]	< 0.0001
Child-Pugh class		0.0003			
A (n = 249)	27 [25-31]		NR	Ref	
B (n = 75)	21 [15-24]		NR	1.66 [1.26-2.19]	0.0003
ALBI grade		0.0029			
Grade 1 (n = 64)	35 [25-43]		Ref	Ref	
Grade 2 (n = 230)	26 [22-28]		0.1228	1.50 [1.06-2.11]	0.0216
Grade 3 (n = 30)	16 [12-24]		0.0016	2.30 [1.41-3.75]	0.0009

¹Sidak test for multiple comparisons. OS: Overall Survival; CI: Confidence Interval; “6&12”: “Six-and-twelve”; Ref: Reference; BCLC: Barcelona Clinic Liver Cancer; NIACE: Tumor nodularity, infiltrative nature of the tumor, alpha-fetoprotein, child-pugh class, performance status; ALBI: Albumin-Bilirubin.

radiological tumor response.

In summary, in this multicenter French HCC cohort different staging/scoring systems classify survival among recommended TACE candidates with a similar predictive power. However, “6&12” score simplicity and ability in patients’ stratification outperform other systems for a routine clinical practice.

Table 4 Comparison of predictive accuracy for overall survival between “Six-and-Twelve” score and staging/scoring systems (multicenter French cohort $n = 324$)

Scoring/stage systems	1-yr AUROC	<i>P</i> (vs ref)	2-yr AUROC	<i>P</i> (vs ref)	3-yr AUROC	<i>P</i> (vs ref)	C-index	<i>P</i> (vs ref)
“6&12” score	0.65 [0.57-0.74]	Ref	0.65 [0.59-0.71]	Ref	0.64 [0.58-0.71]	Ref	0.66 [0.58-0.74]	
BCLC staging	0.61 [0.54-0.67]	0.1827	0.64 [0.59-0.70]	0.7079	0.61 [0.55-0.68]	0.2317	0.61 [0.54-0.68]	NS
NIACE score	0.75 [0.68-0.83]	0.0134	0.69 [0.64-0.75]	0.2368	0.69 [0.63-0.74]	0.2827	0.70 [0.64-0.77]	NS
Child-Pugh class	0.56 [0.49-0.63]	0.1057	0.56 [0.51-0.60]	0.0217	0.55 [0.50-0.59]	0.0304	0.59 [0.55-0.64]	NS
ALBI grade	0.63 [0.57-0.69]	0.6835	0.56 [0.51-0.61]	0.0479	0.55 [0.49-0.61]	0.1033	0.62 [0.55-0.68]	NS

“6&12”: “Six-and-twelve”; AUROC: Area under receiver operating characteristic curve; C-index: Concordance index; Ref: Reference; BCLC: Barcelona Clinic Liver Cancer; NS: Not significant; NIACE: Tumor nodularity, infiltrative nature of the tumor, alpha-fetoprotein, child-pugh class, performance status; ALBI: Albumin-Bilirubin.

Table 5 Kaplan-Meier survival analysis according to “Six-and-twelve” score and other systems in the main cohort from Marseille (available data for 241 hepatocellular carcinoma patients)

Scoring/stage systems	OS [95%CI], mo	<i>P</i> value (log-rank)	Sidak ¹	Hazard ratio [95%CI]	<i>P</i> value
“6&12” score		0.0004			
sum ≤ 6 ($n = 130$)	32 [28-36]		Ref	Ref	
sum > 6 ≤ 12 ($n = 106$)	20 [17-25]		0.0017	1.61 [1.21-2.14]	0.0010
sum > 12 ($n = 5$)	16 [5-34]		0.0003	3.34 [1.35-8.25]	0.0092
CLIP		< 0.0001			
0 ($n = 55$)	35 [30-68]		Ref	Ref	
1 ($n = 135$)	28 [25-32]		0.0724	1.81 [1.23-2.67]	0.0028
2 ($n = 45$)	18 [15-23]		< 0.0001	2.86 [1.81-4.54]	< 0.0001
3 ($n = 6$)	10 [1-27]		< 0.0001	8.12 [3.35-19.67]	< 0.0001
HKLC		< 0.0001			
1 ($n = 89$)	36 [30-40]		Ref	Ref	
2a ($n = 42$)	25 [19-35]		0.0024	1.79 [1.18-2.72]	0.0060
2b ($n = 65$)	26 [19-34]		0.0749	1.45 [1.01-2.10]	0.0450
3a ($n = 24$)	17 [11-23]		< 0.0001	3.30 [2.03-5.36]	< 0.0001
3b ($n = 21$)	14 [11-16]		< 0.0001	4.55 [2.73-7.58]	< 0.0001
Up-to-Seven		0.0001			
In ($n = 176$)	30 [27-35]		NA	Ref	
Out ($n = 65$)	18 [15-24]		NA	1.81 [1.34-2.46]	0.0001
MESH		< 0.0001			
0 ($n = 41$)	43 [35-70]		Ref	Ref	
1 ($n = 77$)	30 [25-35]		0.1291	2.16 [1.33-3.48]	0.0017
2 ($n = 78$)	26 [19-34]		0.0490	2.30 [1.41-3.74]	0.0008

3 (<i>n</i> = 37)	15 [10-21]	< 0.0001	6.02 [3.51-10.33]	< 0.0001
4 (<i>n</i> = 8)	13 [4-24]	< 0.0001	9.69 [3.86-24.36]	< 0.0001

¹Sidak test for multiple comparisons. "6&12": "Six-and-twelve"; OS: Overall Survival; CI: Confidence Interval; Ref: Reference; CLIP: Cancer of the Liver Italian Program; HKLC: Hong Kong Liver Cancer; MESH: Model to Estimate Survival for Hepatocellular carcinoma.

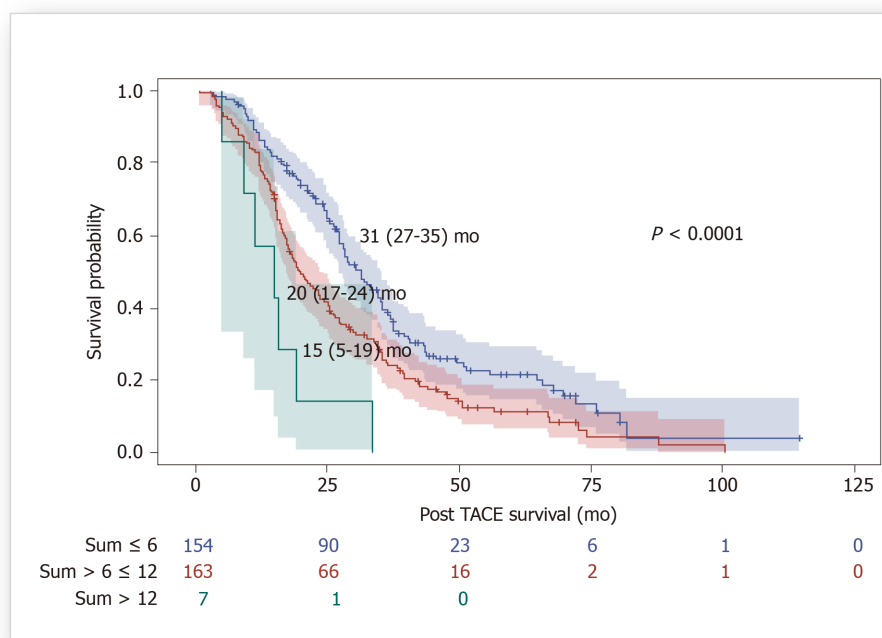


Figure 1 Kaplan-Meier analysis of overall survival according to "Six-and-twelve" criteria in the multicenter French HCC cohort (*n* = 324). TACE: Transarterial chemoembolization.

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