Clinical Staging for Hepatocellular Carcinoma: Eastern Perspectives

Osamu Yokosuka, M.D.

Graduate School of Medicine, Chiba University, Chiba, Japan

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Why is staging system important?

- Cancer stage can be used in estimating a patient's prognosis.
- Staging helps the doctor plan the appropriate treatment.
- Staging is important in identifying clinical trials that may be a suitable treatment option for a patient.
- Staging helps health care providers and researchers share information about patients.
- Staging also gives them a common terminology for evaluating the results of clinical trials and comparing the results of different trials.

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Variety of staging system of HCC

Classification	Type	Stages	year
Okuda stage	System 3	Stage I, II, III	1985
CLIP	Score 7	Score 0 – 6	1998
French	Score 3	A: 0 points; B: 1–5 points; C: ≥6 point	1999
BCLC staging	Staging 5	0: Very early A: Early B: Intermediate C: Advanced D: End-stage	1999
CUPI	Score 3	Low risk: score ≤1 Intermediate: score 2–7 High: score ≥8	2000
TNM staging	System 3	Group T1, T2, T3	2002
JIS	Score 4	Stage I, II, III,IV	2003
Tokyo score	Score 7	Score 0 - 6	2005
BALAD score	Score 6	Score 0 – 5	2006
TIS	Score 7	Score 0 - 6	2010

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Okuda Staging

Criteria	Positive	Negative
Tumor size	>50 percent	<50 percent
Ascites	Clinically detectable	Clinically absent
Albumin	<3 mg/dL	>3 mg/dL
Bilirubin	>3 mg/dL	<3 mg/dL
	Stage	
I	No positive	
II	One or two positives	
III	Three or four positives	

The Okuda system is commonly used for staging hepatocellular carcinoma.
Survival correlates with the Okuda stage in untreated patients
(8.3, 2.0, and 0.7 months for stages I, II, and III, respectively).

The first systematic staging system including both tumor factor and liver function !

Okuda K, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Cancer 1985;56: 918–28.

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What are the common elements of staging systems of HCC?

- Tumor factor
  - Size, number, volume, vascular (portal) invasion, metastasis, tumor maker (AFP etc.)
- Underlying liver function
  - Albumin, bilirubin, alkaline phosphatase, ascites, fibrosis, Child-Turcotte-Pugh class, MELD score
- General Status
  - ECOG PS, Karnofsky PS scale

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The Cancer of the Liver Italian Program (CLIP) score

Variable		Score
Child-Pugh stage	A	0
	B	1
	C	2
Tumor morphology	Uninodular and extension ≤50 percent	0
	Multinodular and extension ≤50 percent	1
	Massive or extension ≥50 percent	2
Alpha-fetoprotein	<400	0
	≥400	1
Portal vein thrombosis	No	0
	Yes	1

The total score is derived by adding each of the subscores.
In one study, median survival was 36, 22, 9, 7, and 3 months for patients in CLIP categories 0, 1, 2, 3, and 4 to 6, respectively.

A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. Hepatology. 1998 Sep;28(3):751-5.

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BCLC staging system

Stage	PST	Tumor status		Liver function status
		Tumor stage	Okuda stage	
Stage A: early				
A1	0	Single	I	No portal hypertension and normal bilirubin
A2	0	Single	I	Portal hypertension and normal bilirubin
A3	0	Single	I	Portal hypertension and abnormal bilirubin
A4	0	Three tumors < 3cm	I - II	Child-Pugh A-B
Stage B: intermediate	0	Large multinodular	I - II	Child-Pugh A-B
Stage C: advanced	1-2	Vascular invasion or extrahepatic spread	I - II	Child-Pugh A-B
Stage D: endstage	3-4	Any	III	Child-Pugh C

Stages A and B, All criteria should be fulfilled
Stage C, at least one criterion: PST 1–2 or vascular invasion/extrahepatic spread
Stage D, at least one criterion: PST 3–4 or Okuda stage III/Child-Pugh C

Llove JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19:329–37.

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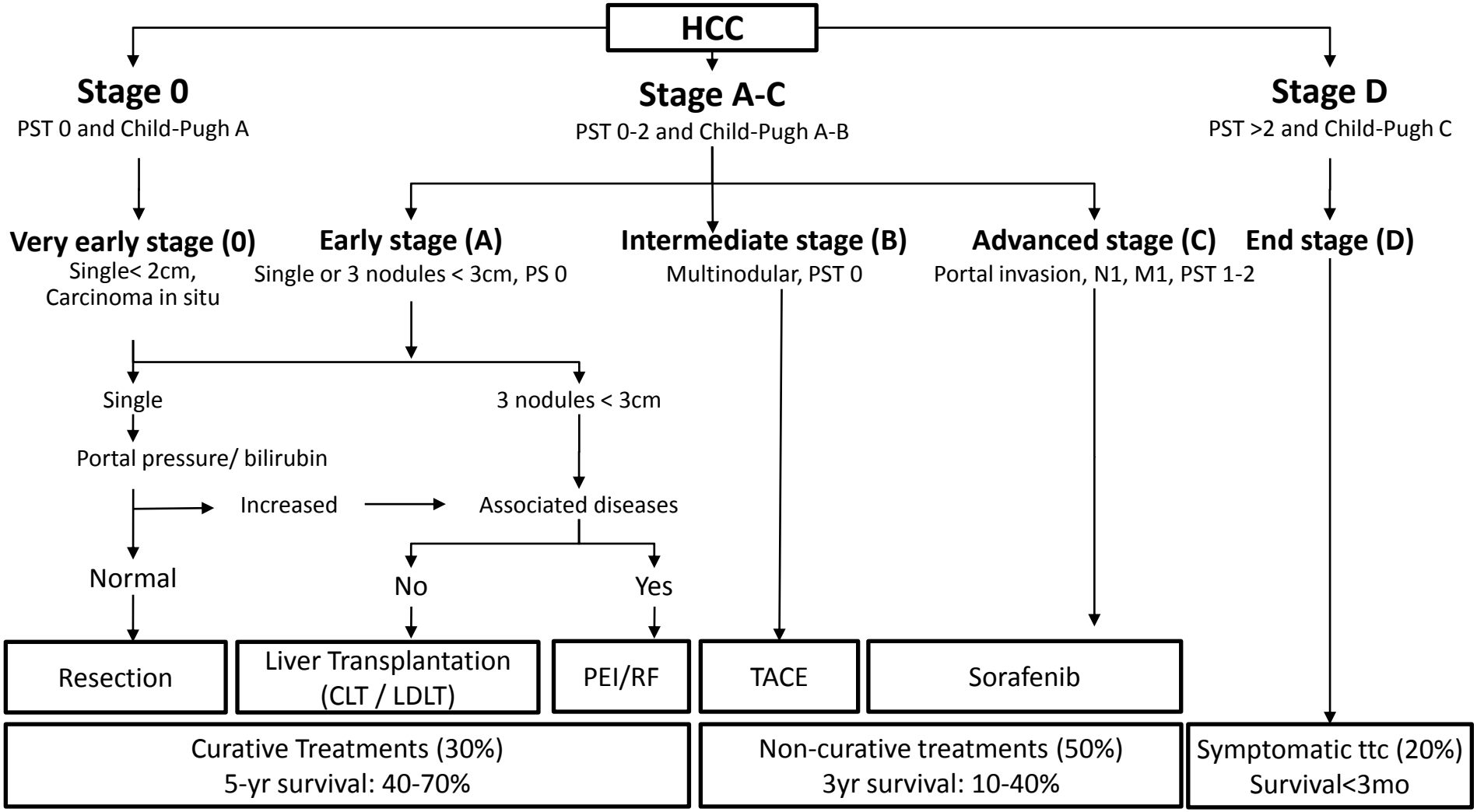
BCLC staging system



BCLC staging system is used as treatment algorithm!

Llovet JM et al. *J Natl Cancer Inst. 2008;100(10):698-711.*

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TNM staging for HCC

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor without vascular invasion
T2	Solitary tumor with vascular invasion or multiple tumors none more than 5 cm
T3a	Multiple tumors more than 5 cm
T3b	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein
T4	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum
Regional lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Fibrosis score (F)	
F0	Fibrosis score 0-4 (none to moderate fibrosis)
F1	Fibrosis score 5-6 (severe fibrosis or cirrhosis)

The AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer New York, Inc.

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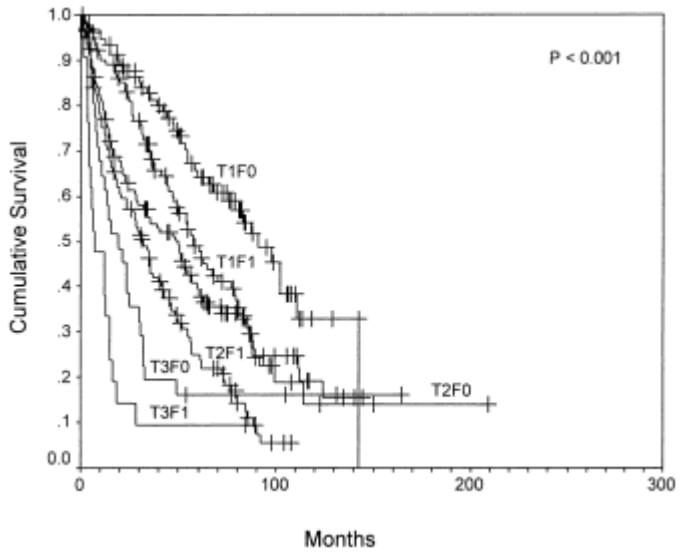
TNM staging for HCC

Anatomic stage/prognostic groups	Tumor	Lymph node	Metastasis
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T4	N0	M0
Stage IVA	Any T	N1	M0
Stage IVB	Any T	Any N	M1



TNM staging is used for various tumors, however, characteristic in using fibrosis scores for HCC.

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Chinese University Prognostic Index (CUPI)

Variable		Weight (CUPI score)
TNM stage	I and II	-3
	III and IIIb	-1
	Iva and IVb	0
Asymptomatic disease on presentation		-4
Ascites		3
AFP ≥ 500 ng/ml		2
Total bilirubin (µmol/L)	< 34	0
	34 - 51	3
	≥ 52	4
Alkaline phosphatase ≥ 200 IU/L		3

Score	group	Median survival
-7 to 1	Low risk	10.1 months
2 to 8	Intermediate risk	3.7 months
8 to 12	High risk	1.4 months

Constructed in patients including many HBV-related HCC and many advanced HCC

Leung TW, et alConstruction of the Chinese University Prognostic Index for Hepatocellular Carcinoma and Comparison with the TNM Staging System, the Okuda Staging System, and the Cancer of the Liver Italian Program Staging System. Cancer. 2002 Mar 15;94(6):1760-9.

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Japan Integrated Score (JIS)

	Scores			
Variables	0	1	2	3
Child-Pugh grade	A	B	C	
TNM stage by LCSGJ	I	II	III	IV

TNM stage by Liver Cancer Study Group of Japan (LCSGJ) criteria			
Factors	I. Single	II. Size < 2cm	III. No vessel invasion
T1	Fulfilling three factors		
T2	Fulfilling two factors		
T3	Fulfilling one factors		
T4	Fulfilling zero factors		
Stage I	T1 N0 M0		
Stage II	T2 N0 M0		
Stage III	T3 N0 M0		
Stage IV A	T4 N0 M0 or Any T N1 M0		
Stage IV B	Any T, Any N, M1		

Kudo M, et al. Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the Japan Integrated Staging Score (JIS score) J Gastroenterol 2003; 38:207–215

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Tokyo score

Tokyo score		Scores	
Variables	0	1	2
Albumin (g/dl)	>3.5	2.8-3.5	<2.8
Bilirubin (mg/dl)	<1	1-2	>2
Tumor size (cm)	<2	2-5	>5
Tumor No	<3	1	>3

Constructed and validated in patients who underwent local ablation therapy and hepatectomy.

Tateishi R, et al. Proposal of a new prognostic model for hepatocellular carcinoma: an analysis of 403 patients. Gut. 2005 Mar;54(3):419-25.

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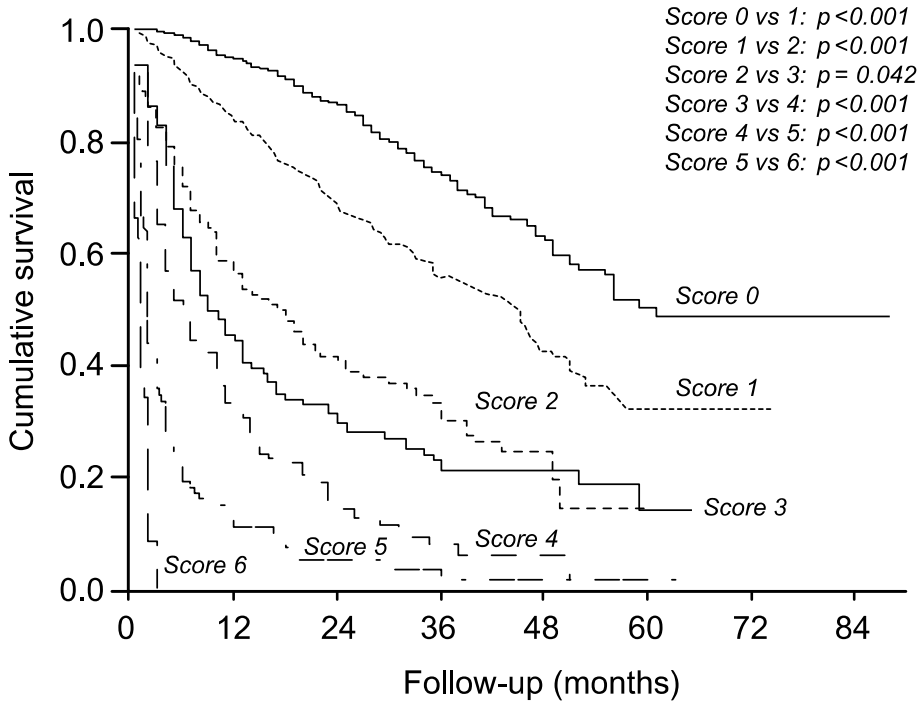
Taipei Integrated Scoring (TIS) system

	Scores			
Variables	0	1	2	3
Total Tumor Volume (cm^3)	<50	50-250	250-500	>500
Child-Turcotte-Pugh grade	A	B	C	
AFP (ng/ml)	<400	≥400		



Hsu CY, et al. A new prognostic model for hepatocellular carcinoma based on total tumor volume: The Taipei Integrated Scoring system. J Hepatol. 2010 Jul;53(1):108-17.

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Bilirubin, Albumin, *Lens culinaris* agglutinin A–reactive fraction of alfa-fetoprotein, Alfa-fetoprotein, and Des-gamma-carboxy prothrombin (BALAD) score

BALAD score

	Scores			
Variables	0	1	2	3
Bilirubin-albumin score	A	B		
No. of elevated tumor markers	0	1	2	3

BALAD score is calculated as the sum of the bilirubin-albumin score and no. of elevated tumor makers.

Bilirubin-albumin score

	0 points	1 point	2 points
Serum bilirubin (mg/dL)	<1.0	1.0-2.0	>2.0
Serum albumin (g/dL)	>3.5	2.8-3.5	<2.8

Scores A (0-1 point), B (2-3 points) and C (4 points)

Stage can be evaluated with the use of only 1 serum sample!

Toyoda H, et al. Staging Hepatocellular Carcinoma by a Novel Scoring System (BALAD Score) Based on Serum Markers. Clin Gastroenterol Hepatol. 2006 Dec;4(12):1528-36.

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The elements in each staging system

Classification	Tumor stage	Liver function	Health status
Okuda stage	50% liver involvement	Bilirubin Albumin Ascites	-
CLIP (modified)	Portal invasion 50% liver involvement AFP	Child-Pugh (MELD score)	-
French	Portal invasion AFP	Bilirubin Alkaline phosphatase	Karnofsky
BCLC staging	Portal invasion Metastases Morphology	Child-Pugh Portal hypertension Bilirubin	PST
TNM staging	Morphology Vascular invasion Metastasis	Fibrosis	-
CUPI	TNM AFP	Ascites Bilirubin Alkaline phosphatase	Symptoms
Tokyo score	Tumor size Tumor number	Albumin Bilirubin	-
BALAD score	AFP AFP-L3 PIVKA-II	Albumin Bilirubin	-
TIS	Total tumor volume AFP	Child-Turccotte-Pugh	-

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Comparison of staging systems

Authors	Journal	Year	Country	Comparison System number	Best	Conclusion
Ueno et al.	**Hepatology**	**2002**	**Japan**	**3**	**CLIP**	**Validation CLIP**
Leung et al.	**Cancer**	**2002**	**China**	**4**	**CUPI**	**Proposal CUPI**
Kudo et al.	**J Gastroenterol**	**2003**	**Japan**	**2**	**JIS**	**Proposal JIS score**
Tateishi R et al.	**Gut**	**2005**	**Japan**	**3**	**Tokyo**	**Proposal Tokyo score**
Hsu CY et al.	**J Hepatol**	**2010**	**Taiwan**	**5**	**TIS**	
Farinati et al.	Cancer	2000	Italy	3	CLIP	Validation CLIP
Levy and Sherman	Gut	2002	Canada	3	CLIP	Validation CLIP
Rabe et al.	Eur J Gastroenterol Hepatol	2003	Germany	5	None	-
Giannini et al.	J Intern Med	2004	Italy	4	None	-
Cillo et al.	J Hepatol	2004	Italy	5	BCLC	Validation BCLC
Grieco A et al.	Gut	2005	Italy	3	BCLC	Validation BCLC

The differences in East and West in HCC patients

Region	Age	Cause of Background Liver Disease	Found at:
Asia-Pacific	Young	HBV >>> Others	Late Stage
Japan	Old	HCV >> HBV > Others	Early Stage
USA	M	HCV > Alcohol > HBV	Various
Europe	M	HCV = Alcohol > HBV	Various

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The different prognosis of the East and the West HCC patients in each stage

Stage	Prognosis
Early stage	Japan >> Asia-Pacific > Europa > USA
Intermediate stage	Japan > Asia-Pacific > Europa > USA
Advanced stage	Japan > Europa = Asia-Pacific > USA
End stage	Japan > Europa = Asia-Pacific > USA

- **Prognosis in early and intermediate stage HCC patients is longer in Japan and Asia-pacific region than in Europe and USA.**

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Best staging system may vary according to patients background and treatment

- Various comparison results from various countries.
- Patients' background and prognosis are different between regions.
- The suitable staging system is different between in the treated patient group and in the untreated patient group.

  Cammà C et al. Aliment Pharmacol Ther. 2008 Jul;28(1):62-75.

- Many staging systems were proposed, but there still is no consensus what is the best one.

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Differences of patients selection and intended use in each staging

- To evaluate the prognosis
  - Untreated HCC pts (natural course)
    - Okuda staging
  - HCC pts after resection
    - TNM staging, modified JIS
  - HCC pts after curative treatment
    - Tokyo score, TIS score
  - All HCC pts
    - CLIP score, BCLC stage, JIS score, TIS score, BALAD score, etc
- To choose adequate treatment
    - BCLC stage

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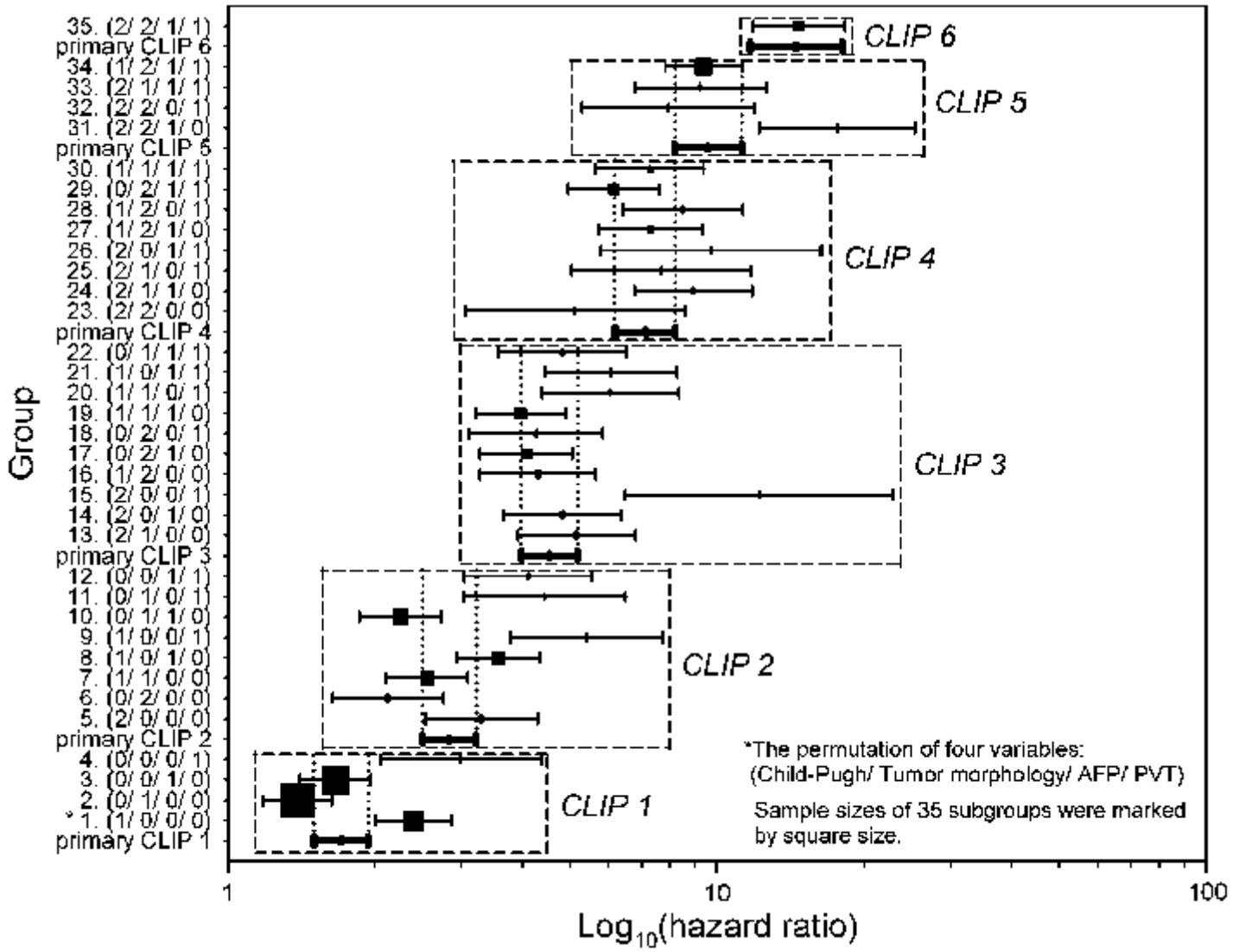
Same score, but different prognosis!



Lin CY et al. Is the Cancer of the Liver Italian Program system an adequate weighting for survival of hepatocellular carcinoma? Evaluation of intrascore prognostic value among 36 subgroups. Liver Int. 2009 Jan;29(1):74-81.

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How to use them?

- Know the characteristics of each staging system.
- Select adequate staging system which meets your purpose.
  - To choose treatment for your patients.
  - To estimate prognosis after any treatment.
  - To choose patients who meets a clinical trial.

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Future perspectives

- To Include new prognostic factors in staging system
  - New tumor maker
  - New serum maker : VEGF
    - Kaseb AO et al. V-CLIP: Integrating plasma vascular endothelial growth factor into a new scoring system to stratify patients with advanced hepatocellular carcinoma for clinical trials. Cancer. 2011 Jun 1;117(11):2478-88.
  - Gene expression
    - Chang SH et al. Predicting the prognosis of hepatocellular carcinoma using gene expression. J Surg Res. 2011 Dec;171(2):524-31.

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Conclusion

- Many HCC staging systems has been proposed.
- Most of the HCC staging systems include tumor factors and liver function.
- There are some differences of ingredients and subjects in each staging system.
- The features of each staging system should be understood and proper system should be used for adequate purpose and patients.

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