간암 환자의 기저 간기능 평가 방법: Old & New

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허내윤
목차

• 간암 환자에서 기저 간기능 평가의 필요성
• 개별 간기능 평가 지표
• 통합 간기능 평가 지표
• 새로운 통합 간기능 평가 지표
• 요약 및 결론
Importance of Liver Function Evaluation in HCC patients

• Resectability/Operability to operation

• Tolerability to medical treatment

• Competing risk (HCC vs. liver failure)
Post-TACE liver failure

- 53/M
- HBV LC
- s/p TIPS & episode of HEP
- Hepatic mass in S5 (5 cm) → Liver bx: HCC
- Child B (CTP score 7)
- TACE was done

TACE induced hepatic infarction:

POD0

- AST/ALT 33/21 IU/L
- T-bil 1.2 mg/dL
- PT 58%

POD3

- AST/ALT 1450/1073 IU/L
- T-bil 3.0 mg/dL
- PT 47%
Post-TACE Liver Failure in HCC & Ascites

A retrospective cohort study

- 100 of 614 HCC patients with TACE had ascites
- Liver failure: bilirubin ≥ 2.0 mg/dL, increasing or newly developed ascites, or
  HE within 2 weeks of TACE
- Post-TACE liver failure occurred in 17% of only patients with HCC & ascites
- GI bleeding & Child B were independent risk factors associated with post-
  TACE liver failure in patients with HCC & ascites

- Independent Predictors of Poor Prognosis

<table>
<thead>
<tr>
<th>Variables</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP &gt;39 ng/mL</td>
<td>1.72 (1.35-2.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin ≤3.3 g/dL</td>
<td>1.70 (1.28-2.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ascites</td>
<td>1.75 (1.20-2.57)</td>
<td>0.004</td>
</tr>
<tr>
<td>Performance status ≥2</td>
<td>1.84 (1.33-2.56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelet count ≤118,000/mm³</td>
<td>1.46 (1.13-1.87)</td>
<td>0.003</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>2.08 (1.53-2.83)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

2012 유럽간학회 가이드라인

• The benefits of chemoembolization should not be offset by treatment-induced liver failure

• Liver functional reserve is also a critical component for a careful selection. Patients should present relatively well-preserved liver function (mostly Child–Pugh A or B7 without ascites), while those with liver decompensation or more advanced liver failure should be excluded since the ischemic insult can lead to severe adverse events
Liver Decompensation after Resection

A retrospective cohort study

- 543 HCC patients
- Child A (94%) Child B (6%)
- MELD score [median, (IQR)] 8 (7-10)
- Portal HTN (E varix, F≥1; PLT <100,000/mm³; splenomegaly >12 cm)
- Liver Decompensation (LD): defined by ascites, bilirubin, INR, creatinine

- Host factor
- Surgical factor ~ Functional liver remnant

2014 대한간암학회 가이드라인

• 문맥압항진증과 고빌리루빈혈증이 모두 없는 Child-Pugh 등급 A 환자에서 간에 국한된 단일 간세포암종은 간절제술이 일차 치료법이다.

• 경미한 문맥압항진증 또는 경미한 고빌리루빈혈증을 동반한 Child-Pugh 등급 A 및 상위 B등급의 간세포암종은 제한적 간절제술을 선택적으로 시행할 수 있다.
Eligible criteria for Sorafenib in Advanced HCC

A multicenter, phase 3, RCT
- 602 patients with advanced HCC
- Placebo vs. Treatment group (sorafenib)

Eligible criteria included
- Performance status score ≤2
- Child-Pugh class A
- A life expectancy ≥ 12 weeks
- PT INR ≤2.3
- Albumin ≥2.8 g/dL
- Total bilirubin ≤3 mg/dL
- ALT, AST ≤ 5 ULN
- etc.

2014 대한간암학회 가이드라인

• Child-Pugh 등급 A의 간기능과 양호한 전신상태를 가진 간세포암종 환자에서 국소 림프절, 폐 등의 간외 전이가 있는 경우, 또는 다른 치료법들에 반응하지 않고 암이 진행하는 경우 소라페닙 치료를 시행할 수 있다.

• Child-Pugh 등급 A의 간기능과 양호한 전신상태를 가진 간세포암종 환자에서 간혈관침범이 있는 경우 소라페닙 치료를 시행할 수 있다.

• Child-Pugh 등급 상위 B의 간기능과 양호한 전신상태를 가진 1항 및 2항 중앙 조건의 간세포암종 환자에서 소라페닙 치료를 시행할 수 있다.
2012 EASL Clinical Practice Guidelines

BCLC staging

Performance status & Liver function
Liver Function Test

• Hepatocellular damage (AST, ALT)
• Abnormal cholestasis (ALP, GGT)
• Liver excretion (Bilirubin)
• Protein synthesis (Albumin, Prothrombin time)
Portal Hypertension

- Clinical: varix, ascites, splenomegaly, encephalopathy
- Laboratory: PLT count
- Fibrosis work-up
  - Invasive: liver bx
  - Non-invasive: Fibroscan, MR elastography, APRI, Fibrotest
Composite Liver Function Indices

- Child-Pugh classification
- Model of End-stage Liver Disease (MELD) score
- Indocyanine green (ICG) test
Clinical and Laboratory Classification of Patients with Cirrhosis in Terms of Hepatic Functional Reserve

<table>
<thead>
<tr>
<th>Group Designation</th>
<th>“A” Minimal</th>
<th>“B” Moderate</th>
<th>“C” Advanced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>&lt;2.0</td>
<td>2.0-3.0</td>
<td>&gt;3.0</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>&gt;3.5</td>
<td>3.0-3.5</td>
<td>&lt;3.0</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Easily controlled</td>
<td>Poorly controlled</td>
</tr>
<tr>
<td>Neurologic disorder</td>
<td>None</td>
<td>Minimal</td>
<td>Advanced, “coma”</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Excellent</td>
<td>Good</td>
<td>Poor, “wasting”</td>
</tr>
</tbody>
</table>
# Child-Pugh Classification

## Grading of Severity of Liver Disease

<table>
<thead>
<tr>
<th></th>
<th>Points scored for increasing abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy (grade)*</td>
<td>None</td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>1-2</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt;3.5</td>
</tr>
<tr>
<td>Prolonged PT (s)</td>
<td>1-4</td>
</tr>
</tbody>
</table>

*According to grading of Trey, Burns, and Saunders (1966)

- Total score 5~6 : Grade A, 7~9 : Grade B, ≥10 : Grade C
Preoperative Assessment (1)

- 38 patients with esophageal variceal bleeding
- Transection operation via transthoracic approach
- To assess postoperative mortality

<table>
<thead>
<tr>
<th>Grade</th>
<th>In hospital mortality</th>
<th>Mortality within 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade A (n=7)</td>
<td>2/7 (29%)</td>
<td>2/7 (29%)</td>
</tr>
<tr>
<td>Grade B (n=13)</td>
<td>5/13 (38%)</td>
<td>7/13 (54%)</td>
</tr>
<tr>
<td>Grade C (n=18)</td>
<td>14/18 (78%)</td>
<td>17/18 (94%)</td>
</tr>
</tbody>
</table>

Preoperative Assessment (2)

- 92 cirrhotic patients
- **Abdominal operations** including cholecystectomy (n=17), hernia (n=9), GI tract (n=54), and other procedures (n=12)
- To assess postoperative mortality

<table>
<thead>
<tr>
<th>Child</th>
<th>Postoperative mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child A</td>
<td>10%</td>
</tr>
<tr>
<td>Child B</td>
<td>30%</td>
</tr>
<tr>
<td>Child C</td>
<td>82%</td>
</tr>
</tbody>
</table>

Preoperative Assessment (3)

- 216 cirrhotic patients
- Hepatic resection for HCC
- To assess postoperative mortality

- In-hospital mortality

- Postop morbidity

Natural History & Survival in Cirrhosis

- 1,236 Korean cirrhotic patients
- Cirrhosis defined by histological or clinical findings
Progression of Liver Fibrosis

- **Compensated cirrhosis**
  - No varix
  - Varix without bleeding

- **Decompensated cirrhosis**
  - Ascites
  - Variceal bleeding
  - Encephalopathy

- Child A
- Child B
- Child C
Limitations of Child-Pugh Classification

• Empirically selected variables
  – Not statistical base

• Arbitrary use of cut-off values
  – Ceiling effect ($T$-bil 5 mg/dL & 15 mg/dL → same score)

• Same weight to difference variables
  – Over- or under-estimating the real impact

• Important other prognostic factors are not considered
  – ex. renal function

Risk Score of Poor Survival after TIPS

- To predict patient survival and identify those patients whose liver-related mortality post-TIPS would be 3 months or less
- 231 patients with refractory ascites (25%), and variceal bleeding (75%)

- Univariate Cox Regression Analysis
  - Demographic
    - Age, center, cause of cirrhosis, reason of TIPS
  - Clinical
    - Ascites, encephalopathy
  - Child-Pugh score
  - Biochemical
    - Albumin, bilirubin, creatinine, INR
  - Hepatic hemodynamics
    - Pre-TIPS gradients etc.

- Multivariable Cox Regression Analysis
  \[ R = 0.957 \log_e (\text{creatinine [mg/dL]}) + 0.378 \log_e (\text{bilirubin [mg/dL]}) + 1.120 \log_e (\text{INR}) + 0.643 \text{ (cause of cirrhosis)} \]

Malinchoc, M et al. Hepatology 2000;31:864-871
Risk Score of Poor Survival after TIPS

- **Observed survival**
- **Mayo model**

**Low risk, R <1.8, n=65**

P=0.88

**High risk, R >1.8, n=6**

P=0.41

Malinchoc, M et al. Hepatology 2000;31:864-871
The Principles of Organ Allocation

• Allocated in order of medical urgency

• The role of waiting times minimized

• To avoid futile transplants and to promote efficient use of scarce donor organs
Limitations of the UNOS Liver Allocation Policy by CTP classification

- Only 3 categories of disease severity for patients with end-stage liver disease
  - Status 3 (CTP score ≥7)
  - Status 2B (CTP score ≥10)
  - Status 2A (CTP score ≥10, in ICU and less than 7 days to live)

- **Waiting time** is tiebreaker in the same category
MELD model validated for several cohorts

• MELD score
  – 10 × the original TIPS model
  – Rounded to the nearest integer

• MELD score = 9.6 \log_e (\text{creatinine [mg/dL]}) + 3.8 \log_e (\text{bilirubin [mg/dL]}) + 11.2 \log_e (\text{INR}) + 6.4 (\text{cause of cirrhosis})
MELD model validated for several cohorts

- Validation to predict 3-month mortality
  - Patients undergoing TIPS (original)
  - Hospitalized patients with advanced end-stage liver disease
  - Ambulatory patients with non-cholestatic cirrhosis & PBC
  - Unselected historical cohort of heterogeneous cirrhotic patients

MELD model validated for several cohorts

- ROC curve for the MELD score in hospitalized cirrhotic patients predicting 3-month mortality

<table>
<thead>
<tr>
<th>C-statistic</th>
<th>Diagnostic accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.8~0.9</td>
<td>Excellent</td>
</tr>
<tr>
<td>≥0.7</td>
<td>Useful</td>
</tr>
</tbody>
</table>

Area under curve (c-statistic) = 0.87
N=283
Death=59

cf. c-statistic of CTP score = 0.84

MELD model validated for several cohorts

- Concordance in predicting 3-month mortality

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
<th>No. of Deaths Within 3 Mo</th>
<th>3-Month Mortality (concordance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized cirrhotics (group A)</td>
<td>282</td>
<td>59</td>
<td>0.87 (0.82-0.92)</td>
</tr>
<tr>
<td>Outpatient cirrhotics (group B)</td>
<td>491</td>
<td>34</td>
<td>0.80 (0.69-0.90)</td>
</tr>
<tr>
<td>PBC outpatients (group C)</td>
<td>326</td>
<td>5</td>
<td>0.87 (0.71-1.00)</td>
</tr>
<tr>
<td>Historical cirrhotics (group D)</td>
<td>1,179</td>
<td>220</td>
<td>0.78 (0.74-0.81)</td>
</tr>
</tbody>
</table>

✓ MELD score could be generalizable!

- Impact of exclusion of the etiology of liver disease

<table>
<thead>
<tr>
<th></th>
<th>Hospitalized N = 282</th>
<th>Ambulatory Noncholestatic N = 491</th>
<th>Ambulatory PBC N = 326*</th>
<th>Historical N = 1,179</th>
</tr>
</thead>
<tbody>
<tr>
<td>With etiology in the model</td>
<td>0.87 (0.82-0.92)</td>
<td>0.80 (0.69-0.90)</td>
<td>0.87 (0.71-1.00)</td>
<td>0.78 (0.74-0.81)</td>
</tr>
<tr>
<td>Without etiology in the model</td>
<td>0.86 (0.81-0.92)</td>
<td>0.82 (0.73-0.91)</td>
<td>0.87 (0.71-1.00)</td>
<td>0.78 (0.74-0.81)</td>
</tr>
</tbody>
</table>

✓ Etiology of liver disease could be omitted!

Application of MELD score to Organ Allocation

- In 2002, UNOS/OPTN adopted the MELD scoring system in organ allocation
  - Exclusion of the cause of liver disease
  - Minimal score of 6
  - Upper limit of the MELD score of 40
- In Post MELD era, ↓3.5% reduction in waiting list death, ↑10.2% in cadaveric transplants

- Previous allocation system
  - Status 3 (Child B)
  - Status 2B (Child C)
  - Status 2A (Child C + ICU care)
  - Status 1 (ALF)

- Updated allocation system
  - MELD 6 7 8 9 ..............................................................40

국내 간장 응급도 기준

• 2016년 6월 1일부터 Child 점수를 근간으로 한 등급기준에서 MELD 시스템으로 전환하여 운영

• 간세포암 동반 대기자의 예외적인 MELD 점수 부여
  - Milan 척도를 만족시키는 간세포암 환자의 경우, 간 이식 후 예후가 다른 간질환으로 간 이식을 받는 환자와 대등하다.
  - 하지만, 간세포암 환자가 계산된 MELD 점수만을 바탕으로 이식을 기다릴 경우 암이 진행하여 이식 대기자에서 탈락하거나, 사망이 증가할 수 있다.

국내 간장 응급도 기준

대기자 생존율

간세포암을 동반한 MELD 0~13점수대의 대기자는 추가 점수 4점
간세포암을 동반한 MELD 14~20점수대의 대기자는 추가 점수 5점

Indocyanine Green Test

- ICG: a water-soluble, inert anionic compound
- After injection, taken by hepatocytes, then excreted into bile
- ICG-R15 : % of retained in the blood at 15 min after bolus injection
- ICG-R 15>15% is a high risk factor for serious post-hepatectomy complications

New Composite Indices

- MELD-Na score
- Albumin-Bilirubin (ALBI) grade
- Albumin-Indocyanine Green Evaluation (ALICE) grade
- Zhong system
MELD-Na score

- Serum Na and the relative risk of death after adjustment for the MELD score

✓ HypoNa is associated with death within 90 days on the waiting list

MELD-Na score

- MELD-Na = MELD + 1.59 (135-Na)

- MELD-Na scores of 20, 30, and 40 were associated with 6%, 16%, and 37% of risk of death within 6 months of listing, respectively.

- If this new score were used to allocate grafts, it would be 27% of the transplant recipient.
ALBI Grade

• **Albumin-Bilirubin score**: a new mathematical model for evaluation of liver function

• Derived from a training cohort of 1,313 Japanese patients with HCC by multivariable Cox regression

• Linear predictor = $-0.085 \times (\text{albumin g/l}) + 0.66 \times \log (\text{bilirubin µmol/l})$

• Categorized into THREE grades
  – **ALBI-1** ($\leq -2.60$)
  – **ALBI-2** ($>2.60$ to $-1.39$)
  – **ALBI-3** ($>-1.39$)
ALBI Grade

- Survival curve according to ALBI grade
- Survival curve according to Child class
ALBI Grade

- Sub-classification of Child A HCC patients

✓ **ALBI grade 1** patients are appropriately treated with surgical resection
✓ **ALBI grade 2** patients may be more suitable for LT or less invasive curative ablative therapy

ALBI Grade

- Integration of ALBI score into BCLC system for HCC

<table>
<thead>
<tr>
<th>BCLC stage</th>
<th>0</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1–2</td>
<td>3–4</td>
</tr>
<tr>
<td>Tumor stage</td>
<td>Single &lt;2 cm</td>
<td>Single or three nodules &lt;3 cm</td>
<td>Multinodular</td>
<td>Vascular invasion or extrahepatic spread</td>
<td>Any</td>
</tr>
<tr>
<td>Child–Pugh grade</td>
<td>A</td>
<td>A–B</td>
<td>A–B</td>
<td>A–B</td>
<td>C</td>
</tr>
<tr>
<td>ALBI grade</td>
<td>1</td>
<td>1–2</td>
<td>1–2</td>
<td>1–2</td>
<td>3</td>
</tr>
</tbody>
</table>

*Modification of BCLC system by direct substitution of Child–Pugh grade by ALBI grade.*

2012 EASL Clinical Practice Guidelines
BCLC staging

HCC

Stage 0
- PST 0, ALBI-1a
  - Very early stage (0)
    - Single <2 cm
    - Carcinoma in situ
      - Single
        - Portal pressure/bilirubin
          - Increased
            - Associated diseases
              - No
              - Yes
                - Resection
                - Liver transplantation (CLT/LDLT)
                - RF/PEI

      - 3 nodules ≤3 cm

Stage A-C
- PST 1-2, ALBI-1,2
  - Early stage (A)
    - Single or 3 nodules ≤3 cm
      - PS 0
        - Multinodular
          - PS 0
            - TACE
            - Target: 20%
              - OS: 20 mo (45-14)

Stage D
- PST 3-4 ALBI-3
  - Intermediate stage (B)
    - Multinodular
      - Portal invasion, N1, M1, PS 1-2
        - Sorafenib
        - Target: 40%
          - OS: 11 mo (6-14)

  - Terminal stage (D)
    - Best supportive care
    - Target: 10%
      - OS: <3 mo

ALBI Grade

- Stage distribution between Child-based & ALBI-based BCLC systems

- The overall prognostic performance of ALBI-based and CP-based BCLC systems was similar

ALICE grade

- **Albumin-Indocyanine Green Evaluation (ALICE) grade**
- Resection for HCC is normally limited to patients with normal bilirubin level
- Another simple model to assess the preoperative liver function
- Linear predictor=$0.663 \times \log_{10} \text{ICG R15(\%)} - 0.0718 \times \text{albumin (g/L)}$
- Categorized into THREE grades
  - **Grade 1** ($\leq -2.20$)
  - **Grade 2** ($> -2.20$ to $-1.39$)
    - Grade 2a ($> -2.20$ to $-1.88$)
    - Grade 2b ($> -1.88$ to $-1.39$)
  - **Grade 3** ($> -1.39$)

ALICE grade

- Survival according to ALICE grade in Child A HCC patients

ALICE grade

- Proposed surgical treatment strategy for HCC patients according to ALICE grade

- Ascites or high serum bilirubin
  - Yes → No surgical indication
  - No
    - ALICE grade 1
      - Normal liver function
      - Up to 6 segments
    - ALICE grade 2
      - Impaired liver function
      - 2a: Up to 4 segments
      - 2b: Up to 3 segments
    - ALICE grade 3
      - Poor liver function
      - Limited resection
      - Ablation
      - Transplantation

“Zhong system”

- Preoperative liver evaluation before resection
  - ICG test: liver function
  - CT volumetry: remnant liver volume

This enables 3D-measurements of segmental liver function and liver functional volume

“Zhong system”
Summary

• Although **CP classification** has been a useful liver function evaluation since 1960’s, but, several shortcomings remain.

• **MELD model** is superior to CP classification for predicting short-term mortality in end-stage liver disease. Then, it was introduced to organ allocation system.

• **ALBI grade** is a simple predictive tool as good as CP classification. Especially, it could discriminate the survival among CP-A class HCC patients.
Conclusions

• Recently, new liver function indices has been introduced as a simple, accurate prediction model for survival of the patients with cirrhosis & HCC.

• It is required to validate in more heterogeneous population to be used in clinical practice in the future.
Thank you for your attention!

Welcome to Haeundae