Historia Natural y Estadíos Evolutivos de la Cirrosis

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I have no disclosures to make relative to my presentation
The main determinant of mortality in cirrhosis is the presence of decompensation.

Cirrhosis consists of two main distinct prognostic stages:

- **Compensated cirrhosis**
  - Median survival: >12 yrs
  - Portal hypertension

- ** Decompensated cirrhosis**
  - Median survival: ~2 yrs
  - Signs of decompensation:
    - Ascites
    - Variceal hemorrhage
    - Encephalopathy
    - Jaundice

**Death**

*Source: D’Amico, Garcia-Tsao, Pagliaro. J Hepatol 2006;44:217*
In patients with compensated cirrhosis, an HVPG $\geq 10$ mmHg is the main predictor of decompensation.

Probability of decompensation (ascites, variceal hemorrhage, hepatic encephalopathy)

Log rank test: $P<0.01$

HR 3.95 (2.29–6.83)

CSPH = clinically significant portal hypertension

Also predictive of varices and HCC

HVPG= hepatic venous pressure gradient

Normal: 3–5 mmHg

The degree of liver fibrosis in a cirrhotic liver correlates with the degree of portal hypertension.

- Chronic liver disease
  - Compensated cirrhosis
    - Mild PH: 66% have thin fibrous septa on biopsy
    - CSPH: 64% have thick fibrous septa on biopsy
  - Decompensated cirrhosis
  - Death

CSPH = clinically significant portal hypertension

Patients with compensated cirrhosis and CSPH have a higher CI and lower MAP than those with mild PH

- CSPH = clinically significant portal hypertension
- MAP = mean arterial pressure
- CI = cardiac index
Varices

Increased resistance

Increased flow

Splanchnic vasodilatation

Effective hypovolemia

Activation neurohumoral systems

Mild PH (HVPG 6-10 mmHg)

CSPH (HVPG >10 mmHg)

Increased cardiac output

Sodium and water retention

Hypervolemia

Variceal hemorrhage

Ascites

CSPH is the main driver of cirrhosis decompensation

HVPG = hepatic venous pressure gradient
CSPH = clinically significant portal hypertension

Encephalopathy

Portosystemic collaterals

Cirrhosis decompensation

Varices

Increased resistance

Increased flow

Splanchnic vasodilatation

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Mild PH (HVPG 6-10 mmHg)

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Variceal hemorrhage

Ascites

Cirrhosis decompensation

HVP G = hepatic venous pressure gradient
CSPH = clinically significant portal hypertension
Patients with varices have a higher incidence of decompensation than patients without varices.

D’Amico et al. APT 2014; 39: 1180–1193
Patients with CSPH can, in turn, be sub-classified into those without and with varices.


CSPH= clinically significant portal hypertension
Patients with varices have an HVPG of at least 12 mmHg

Hepatic Venous Pressure Gradient (mmHg)

Varices Present (n=72) Varices Absent (n=15)

P<0.01

Garcia-Tsao et. al., Hepatology 1985; 5:419

HVPG= hepatic venous pressure gradient
A decrease in HVPG to levels below 12 mmHg eliminates the risk of variceal rebleeding.

Patients in whom PPG decreases to <12 mmHg do not develop ascites.

- HVPG decrease to < 12 mmHg
- HVPG decrease > 20% from baseline
- No change in HVPG

Bosch and García-Pagán, Lancet 2003; 361:952

PPG = portal pressure gradient
Serum albumin and MELD score are also independent predictors of cirrhosis decompensation

In search of a pathophysiologic classification of cirrhosis

<table>
<thead>
<tr>
<th>Histological</th>
<th>Clinical</th>
<th>Symptoms</th>
<th>Varices</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1-F3</td>
<td>Non-cirrhotic</td>
<td>None</td>
<td>No varices</td>
</tr>
<tr>
<td>F4 (Cirrhosis)</td>
<td>Compensated</td>
<td>None</td>
<td>± Varices</td>
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<td>F4 (Cirrhosis)</td>
<td>Compensated</td>
<td>None</td>
<td>Ascites, HE, Variceal bleed</td>
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<tr>
<th>HVPG</th>
<th>Hemodynamics</th>
<th>Liver Function</th>
<th>Biological</th>
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<tbody>
<tr>
<td>F1-F3</td>
<td>Fibrogenesis and neovascularization</td>
<td>Scar and X-linking</td>
<td>Thick (acellular) scar and nodules</td>
</tr>
<tr>
<td>≥ 6</td>
<td>Mild PH</td>
<td>CSPH</td>
<td>Hyperdynamic circulation</td>
</tr>
<tr>
<td>≥ 10</td>
<td></td>
<td></td>
<td>Liver insufficiency</td>
</tr>
<tr>
<td>≥ 12</td>
<td></td>
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<td>Insoluble scar</td>
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Modified from Garcia-Tsao, Friedman et al. Hepatology 2010;51:1445
Decompensated cirrhosis can be sub-staged by the type/number of decompensating events.

- Hemorrhage alone: 20%*
- First non-bleeding decompensating event (ascites): 30%*
- Second decompensating event: 88%*

*D'Amico et al. Aliment Pharmacol Ther 2014; 39: 1180-93
Decompensated cirrhosis can be sub-staged by the development of complications of the complications ("further" decompensation)

**Compensated cirrhosis** → **Decompensated cirrhosis** → **Further decompensation** → **Death**

- **Worsening vasodilatation**
  - VH
  - Ascites
  - HE

- **Further decompensation**
  - Recurrent VH/HE
  - Refractory ascites
  - Hyponatremia
  - Renal failure (HRS)
  - Coagulopathy
  - Jaundice

**VH** = variceal hemorrhage; **HE** = hepatic encephalopathy; **HRS** = hepatorenal syndrome;
Bacteria main precipitants of further decompensation

- Compensated cirrhosis → Decompensated cirrhosis
  - VH
  - Ascites
  - HE

- Bacterial translocation/Infections → Systemic Inflammation → Worsening vasodilatation → Further decompensation
  - Recurrent VH/HE
  - Refractory ascites
  - Hyponatremia
  - Renal failure (HRS)
  - Coagulopathy
  - Jaundice

- Multiorgan failure (AOCLF) → Death

VH = variceal hemorrhage; HE = hepatic encephalopathy; HRS = hepatorenal syndrome; AOCLF = acute-on-chronic liver failure
Management strategies depend on the stage of chronic liver disease.

- **Histological**
  - F1-F3: Non-cirrhotic
  - F4 (Cirrhosis)

- **Clinical Symptoms**
  - HPGV
  - HVPG

- **Compensated**
  - None (no varices)
  - None (varices present)

- ** Decomp**
  - Ascites, VH, HE
  - Rec VH, RA, HRS → MOF

- **Management strategies** depend on the stage of chronic liver disease:
  - HVPG:
    - >6
    - >10
    - >12
    - >20

- **Fibrogenesis and neovascularization**
  - Scar and X-linking
  - Thick (acellular) scar and nodules
  - Insoluble scar

- **Hyperdynamic circulation**
- Liver insufficiency
- Systemic inflammation
Management strategies depend on the stage of chronic liver disease.

**Histological**
- **F1-F3**
  - Non-cirrhotic
  - None
  - No varices

**Clinical Symptoms**
- Compensated
  - None
  - No varices

**Varices**
- Compensated
  - None
  ± Varices

**Histological**
- **F4 (Cirrhosis)**
  - None
  - Varices
  - HE VH

**HVPG**
- >6
  - Mild PH
- >10
  - CSPH
- >12
  - >20

**Further Dec ▸ AoCLF**
- RA, HRS, Recurrent VH

**[Bacterial translocation and inflammation]**

**Remove/reduce cause of damage**

**Reduce fibrosis/endothelial dysfunction**

**Reduce portal pressure**

**Inflammation, vasodilatation**
ARCHITECTURAL LIVER DISRUPTION IS THE MAIN MECHANISM THAT LEADS TO AN INCREASED INTRAHEPATIC RESISTANCE

Varices

Splanchnic vasodilatation

Sodium and water retention

Hypervolemia

Activation neurohumoral systems

Effective hypovolemia

Increased cardiac output

Increased flow

CSPH (HVPG >10 mmHg)

Mild PH (HVPG 6-10 mmHg)

Portosystemic collaterals

Variceal hemorrhage

Encephalopathy

Ascites

Will removing the cause of liver injury change natural history of cirrhosis?

HVPG = hepatic venous pressure gradient
CSPH = clinically significant portal hypertension

Elimination etiological agent
Eradication of HCV leads to lower incidence of decompensation in patients with compensated HCV cirrhosis


Van der Meer et al. JAMA 2012;308:2584-93.
Most patients with compensated cirrhosis and CSPH, remain with CSPH 6 months after SVR.

CSPH = clinically significant portal hypertension; SVR = sustained virological response; HVPG = hepatic venous pressure gradient

Calvaruso et al. AASLD 2017.
The presence or absence of varices* (prior to treatment) determines decompensation post-SVR.

DiMarco et al. Gastroenterology 2016;151:130–139

* Presence of varices indicates CSPH
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- Worsening hyperdynamic circ.
- Worsening liver function
- Insoluble scar

Modified from Garcia-Tsao, Friedman et al. Hepatology 2010;51:1445
Natural history of cirrhosis

- Cirrhosis is a heterogeneous and dynamic disease
- Cirrhosis progresses across different clinical *prognostic stages*
- The approach to each stage will be different and depend on the prevailing pathophysiological mechanism(s)
- With elimination of etiology, progression across stages can be delayed/prevented but significant portal hypertension appears to persist