Clinical Usefulness of Platelet Count in Management of Liver Disease

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Agenda

The role of platelets in liver disease

1. Pathophysiology of alteration of platelet count in chronic liver disease

2. Diagnostic and prognostic usefulness of platelet count in patients with chronic liver disease

3. Platelet count as an epidemiological marker

4. Conclusions
Platelets and Liver Disease

- Haemostasis
- Diagnostic parameter
- Prognostic indicator
- Epidemiological marker
- Liver damage
- Liver regeneration
Pathophysiology of Alteration of Platelet Count in Chronic Liver Disease
Correlation Between HVPG and Platelet Count in Cirrhosis

213 patients with compensated cirrhosis and PHT, without varices

Not influenced by aetiology of cirrhosis
Consistent up to 5-year follow-up

\[ r_s = -0.44; P < .0001 \]
Mechanism of TPO Feedback

TPO serum levels depend upon hepatic synthesis and binding to platelet and megakaryocyte receptors

Correlation Between Serum TPO Levels and Fibrosis Stage

TPO levels and liver fibrosis in patients without splenomegaly

\[ P = .0001 \]
\[ P = .0001 \]

TPO Serum Levels Decrease as Liver Function Worsens


R = 0.489, P = .002
Pathophysiologic Basis

Antibody production

Decreased TPO production

Portal hypertension

Bone marrow suppression

Thrombocytopenia

Giannini EG. Aliment Pharmacol Ther 2006; 23: 1055–1065
Diagnostic Use of Platelet Count in Chronic Liver Disease
Diagnostic Use of Platelet Count in CLD

- Advanced fibrosis
- Cirrhosis
- Response to antiviral therapy
- Presence and degree of PHT
Correlation Between Liver Disease Severity and Platelet Counts

Platelet count and Severity of Fibrosis in Chronic Hepatitis C

Platelet count and significant fibrosis: transportability of results

US series (n=90)

Italian series (n=309)

$r_s = -0.377; P <.001$

$r_s = -0.498; P <.001$

Diagnostic Accuracy of Platelet Count in Chronic Hepatitis C

Italian and US cohorts = 409 patients

- Significant fibrosis = 42.8%
- Cirrhosis = 19.1%

AUC = 0.733
+LR = 3.21
-LR = 0.47

Cut-off = 163,000/mm³

AUC = 0.900
+LR = 6.17
-LR = 0.21

Cut-off = 141,000/mm³

### Performance of Non-invasive Methods to Assess Fibrosis in Chronic Viral Hepatitis

<table>
<thead>
<tr>
<th>Score</th>
<th>Serum markers</th>
<th>Etiology</th>
<th>n</th>
<th>≥F2 (%)</th>
<th>AUC≥F2</th>
<th>F4 (%)</th>
<th>AUCF4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrotest</td>
<td>GGT, haptoglobin, bilirubin, apoA1, alpha2-macroglobulin</td>
<td>HCV</td>
<td>2,342</td>
<td>33-74</td>
<td>0.74-0.89</td>
<td>3-25</td>
<td>0.82-0.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HBV</td>
<td>218</td>
<td>56-68</td>
<td>0.77-0.85</td>
<td>15-20</td>
<td>0.76-0.87</td>
</tr>
<tr>
<td>Forns</td>
<td>Age, GGT, cholesterol, platelets</td>
<td>HCV</td>
<td>1,982</td>
<td>32-59</td>
<td>0.75-0.91</td>
<td>3-20</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HBV</td>
<td>456</td>
<td>56-74</td>
<td>0.63-0.72</td>
<td>15-26</td>
<td>0.81</td>
</tr>
<tr>
<td>APRI</td>
<td>AST, platelets</td>
<td>HCV</td>
<td>3,160</td>
<td>27-74</td>
<td>0.69-0.88</td>
<td>3-25</td>
<td>0.61-0.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HBV</td>
<td>886</td>
<td>56-79</td>
<td>0.72</td>
<td>15-20</td>
<td>0.64-0.76</td>
</tr>
<tr>
<td>FIB-4</td>
<td>Age, ALT, AST, platelets</td>
<td>HCV/HIV</td>
<td>1,778</td>
<td>21-36</td>
<td>0.74-0.85</td>
<td>7</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HBV</td>
<td>776</td>
<td>65-79</td>
<td>0.74-0.86</td>
<td>15-34</td>
<td>0.80-0.93</td>
</tr>
<tr>
<td>Fibrometer</td>
<td>Platelets, PT, macroglobulin, AST, hyaluronate, age, urea</td>
<td>HCV</td>
<td>1,039</td>
<td>41-56</td>
<td>0.78-0.89</td>
<td>4-15</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HBV</td>
<td>108</td>
<td>56</td>
<td>0.74</td>
<td>15</td>
<td>0.89</td>
</tr>
<tr>
<td>Hepascore</td>
<td>Age, sex, alpha2-macroglobulin, hyaluronate, bilirubin, GGT</td>
<td>HCV</td>
<td>1,660</td>
<td>39-79</td>
<td>0.74-0.86</td>
<td>6-34</td>
<td>0.80-0.94</td>
</tr>
<tr>
<td>ELF</td>
<td>NT-PIIIP, hyaluronate, TIMP-1, age</td>
<td>HCV/HBV</td>
<td>1,346</td>
<td>27-64</td>
<td>0.77-0.87</td>
<td>12-16</td>
<td>0.87-0.90</td>
</tr>
</tbody>
</table>

Thrombocytopenia and Degree of Portal Hypertension

213 patients with compensated cirrhosis and PHT, without varices

![Bar chart showing HVPG (mmHg) vs % of patients with HVPG >10mmHg.](chart1.png)

- Normal platelet count: 0% patients with HVPG >10mmHg
- Thrombocytopenia: 61% patients with HVPG >10mmHg

![Bar chart showing % of patients with <150,000/mm³ vs >150,000/mm³ platelet count.](chart2.png)

- <150,000/mm³: 32% patients with HVPG >10mmHg
- >150,000/mm³: 61% patients with HVPG >10mmHg

Platelet Count for the Noninvasive Diagnosis of Oesophageal Varices

LOV: Platelet count < 160,000

Pilette et al. J Hepatol 1999; 31: 867-873

LOV: Platelet count < 88,000; splenomegaly (by CT or palpatory)

Chalasani et al. Am J Gastroenterol 1999; 94: 3285-3291

LOV: Platelet count < 88,000

Zaman et al. Am J Gastroenterol 1999; 94: 3292-3296

OV: Platelet count < 150,000 (spleen size); ascites

Ng et al. J Gastroentrol Hepatol 1999; 14: 785-790

OV: Platelet count < 100,000; PA <70%; Portal vein diameter >13mm

Schepis et al. Hepatology 2001; 33; 333-338

OV: Platelet count < 90,000; Child-Pugh’s class (B+C versus A)

LOV: Platelet count < 80,000; Child-Pugh’s class (B+C versus A)

Zaman et al. Arch Inten Med 2001; 161: 2564-2570

OV: Platelet count < 68,000; splenomegaly; ascites


LOV: Platelet count < 68,000; splenomegaly

OV: Platelet count < 140,000; Mayo risk score

Platelet Count for the Noninvasive Diagnosis of Oesophageal Varices

Median platelet count at time of varices development = 91,000/mm³

(IQR = 65,000 – 123,000/mm³)

AUC = 0.630
(95% CI, 0.554 – 0.706)

Platelet Count During Antiviral Therapy in HCV

Haematopoiesis evaluated in 4 treatment groups from 6 prospective trials (n = 133)

# Platelet Count and Null Response to Antiviral Therapy

Multivariate analysis of baseline and week-20 factors associated with null *versus* full or partial response (HALT-C Trial)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (<em>per</em> 5 y)</td>
<td>0.95 (0.92-0.98)</td>
<td>.005</td>
</tr>
<tr>
<td>African American</td>
<td>2.75 (1.55-4.87)</td>
<td>.0005</td>
</tr>
<tr>
<td>Previous combination therapy</td>
<td>1.78 (1.04-3.07)</td>
<td>.04</td>
</tr>
<tr>
<td>Genotype 1</td>
<td>5.19 (1.97-13.67)</td>
<td>.0009</td>
</tr>
<tr>
<td>Albumin (<em>per</em> 0.5 g/dL)</td>
<td>0.35 (0.19-0.63)</td>
<td>.0005</td>
</tr>
<tr>
<td>Weight loss to week 20 (<em>per</em> 3 kg)</td>
<td>0.90 (0.84-0.95)</td>
<td>.0003</td>
</tr>
<tr>
<td>ALT (<em>xULN</em>) decrease to week 20</td>
<td>0.83 (0.72-0.96)</td>
<td>.01</td>
</tr>
<tr>
<td>White blood cell decrease to week 20 (<em>per</em> 1,000/mm³)</td>
<td>0.76 (0.64-0.90)</td>
<td>.002</td>
</tr>
<tr>
<td>*<em>Platelet level decrease to week 20 (<em><em>per</em> 40,000/mm³)</em></em></td>
<td>0.99 (0.98-0.995)</td>
<td>.0002</td>
</tr>
</tbody>
</table>

Prognostic Use of Platelet Count in Chronic Liver Disease
Prognostic Use of Platelet Count in CLD

- Variceal bleeding
- SBP

- Non-hepatic surgery
- Liver transplantation

- Compensated disease
- Advanced disease
Thrombocytopenia and Platelet Count Cut-off

Liver cirrhosis

- \(<150 \times 10^9/l\)
- \(<50 \times 10^9/l\)
- \(<20 \times 10^9/l\)

Prevalence (%)

<table>
<thead>
<tr>
<th>Liver Cirrhosis</th>
<th>Child-Pugh A</th>
<th>Child-Pugh B</th>
<th>Child-Pugh C</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150 x 10^9/l</td>
<td>9</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>&lt;50 x 10^9/l</td>
<td>61</td>
<td>83</td>
<td>90</td>
</tr>
<tr>
<td>&lt;20 x 10^9/l</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

### Prognostic Indicators in Cirrhosis of the Liver

Variables that were most commonly found to be significant predictors of death assessed in 31 ‘good’ studies

<table>
<thead>
<tr>
<th>Variable</th>
<th>Good studies in which variable was among first 5 significant ones (n)</th>
<th>Good studies evaluating variable (n)</th>
<th>Good studies in which variable was among first 5/respectively total of studies (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child-Pugh score/class</td>
<td>13</td>
<td>20</td>
<td>65</td>
</tr>
<tr>
<td>Bilirubin*</td>
<td>11</td>
<td>23</td>
<td>48</td>
</tr>
<tr>
<td>Albumin*</td>
<td>11</td>
<td>23</td>
<td>48</td>
</tr>
<tr>
<td>Age</td>
<td>11</td>
<td>28</td>
<td>39</td>
</tr>
<tr>
<td>Prothrombin time*</td>
<td>8</td>
<td>21</td>
<td>38</td>
</tr>
<tr>
<td>Encephalopathy*</td>
<td>7</td>
<td>14</td>
<td>50</td>
</tr>
<tr>
<td>Ascites*</td>
<td>4</td>
<td>14</td>
<td>29</td>
</tr>
<tr>
<td>Gender</td>
<td>5</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>BUN</td>
<td>3</td>
<td>4</td>
<td>75</td>
</tr>
<tr>
<td><strong>Platelets</strong></td>
<td><strong>3</strong></td>
<td><strong>10</strong></td>
<td><strong>30</strong></td>
</tr>
</tbody>
</table>

Hypersplenism and Incidence of Oesophageal Varices Bleeding

Incidence of variceal bleeding:

19% versus 5% ($P = .0001$)

HR = 4.1 (1.7-10.0, 95%CI), $P = .002$

Severe hypersplenism defined as platelet count <75,000/mm³ and/or WBC count <2,000/mm³
Hypersplenism and Incidence of Spontaneous Bacterial Peritonitis

Severe hypersplenism defined as platelet count <75,000/mm³ and/or WBC count <2,000/mm³

Incidence of SPB:

16% versus 3% ($P = .003$)

HR = 8.0 (3.1-20.5, 95%CI), $P = .0001$

Prognostic Meaning of Platelet Count in Compensated Viral Cirrhosis

Child-Pugh class A (n=297). Follow-up 79 months (6 – 191 months)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Variable</th>
<th>Regression coefficient</th>
<th>SE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC</td>
<td>Age</td>
<td>0.061</td>
<td>0.017</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Bilirubin</td>
<td>1.899</td>
<td>0.715</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>Albumin</td>
<td>-0.064</td>
<td>0.030</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td>Viral status</td>
<td>0.425</td>
<td>0.324</td>
<td>NS</td>
</tr>
<tr>
<td>Decompensation</td>
<td>Platelets</td>
<td>-0.005</td>
<td>0.002</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td>Albumin</td>
<td>-0.083</td>
<td>0.023</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Gammaglobulin</td>
<td>0.043</td>
<td>0.018</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>AST/ALT ratio</td>
<td>1.525</td>
<td>0.486</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Viral status</td>
<td>-0.523</td>
<td>0.234</td>
<td>0.026</td>
</tr>
<tr>
<td>Survival</td>
<td>Age</td>
<td>0.061</td>
<td>0.014</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>0.627</td>
<td>0.303</td>
<td>0.038</td>
</tr>
<tr>
<td></td>
<td>Platelets</td>
<td>-0.006</td>
<td>0.003</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>Albumin</td>
<td>-0.110</td>
<td>0.024</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Viral status</td>
<td>0.367</td>
<td>0.271</td>
<td>NS</td>
</tr>
</tbody>
</table>
Thrombocytopenia and Prognosis of Compensated Cirrhosis

Risk factors for death or OLT  | Hazard ratio (95% CI)  | P value
--- | --- | ---
Thrombocytopenia at baseline | 4.4 (1.3 – 13.6) | .0191
Leukopenia at baseline | 1.8 (1.0 – 3.3) | .083
Baseline HVPG | 1.1 (1.0 – 1.2) | .0132
Child-Pugh score at baseline | 1.6 (1.1 – 2.2) | .0105


![Survival curve showing the impact of thrombocytopenia on survival](image)
Hypersplenism and Overall Survival in Advanced Liver Disease

Severe hypersplenism defined as platelet count <75,000/mm³ and/or WBC count <2,000/mm³

Median survival:

32 versus 47 months \((P = .03)\)

HR = 2.0 (1.2-3.4, 95\%CI), \(P = .008\)

Prognostic Meaning of Platelet Count in Cirrhotic Patients Undergoing Surgery

Patients undergoing cholecystectomy: predictors of 90-day morbidity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>International normalized ratio &gt;1.2</td>
<td>16.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bilirubin level &gt; 1.0 mg/dL</td>
<td>7.1</td>
<td>.01</td>
</tr>
<tr>
<td>Creatinine level &gt; 1.4 mg/dL</td>
<td>11.8</td>
<td>.04</td>
</tr>
<tr>
<td><strong>Platelet count &lt; 150 (\times 10^3/mm^3)</strong></td>
<td>8.3</td>
<td>.04</td>
</tr>
<tr>
<td>ALT level &gt; 40 or AST level &gt; 30 U/L</td>
<td>4.5</td>
<td>NS</td>
</tr>
<tr>
<td>Albumin level &lt; 3.4 g/dL</td>
<td>3.9</td>
<td>NS</td>
</tr>
<tr>
<td>Hematocrit level &lt; 37%</td>
<td>2.2</td>
<td>NS</td>
</tr>
<tr>
<td>White blood cell count &gt; 10.8 (\times 10^3/mm^3)</td>
<td>1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Alkaline phosphatase &gt; 10^5 U/L</td>
<td>1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Hemoglobin &lt; 12 g/dL</td>
<td>1.2</td>
<td>NS</td>
</tr>
</tbody>
</table>
Platelets and Liver Transplantation

Platelets Count Dynamics During and After Liver Transplantation

FFP Transfusion-related

Graft-related

Platelet activation & consumption

Prognostic Meaning of Platelet Count After Liver Transplantation

90-days survival, n = 449

- Platelet consumption/chronic DIC
- Poor liver function/low TPO
- Small-for-size/portal hypertension

$P = .01$

Platelet Count

as an

Epidemiological Marker
## Risk Factors for Thrombocytopenia in Community Surveys

Analysis of risk factors for thrombocytopenia (<100,000/mm³) in a community of hyperendemic HBV and HCV infection

1,690 subjects. Prevalence of HCV = 17.4%. Prevalence of HBV = 9.2%

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HCV positivity</td>
<td>6.0</td>
<td>(3.2 – 11.2)</td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td>4.3</td>
<td>(2.0 – 9.5)</td>
</tr>
<tr>
<td>ALT level ≥ 40 or AST level &gt; 30 U/L</td>
<td>2.1</td>
<td>(1.1 – 3.9)</td>
</tr>
<tr>
<td>HBsAg positivity</td>
<td>0.9</td>
<td>(0.4 – 2.1)</td>
</tr>
</tbody>
</table>

Prevalence of Anti-HCV Positivity by Platelet Count

National Health and Nutrition Examination Survey III (n = 16,196)

Overall HCV prevalence = 2.4%

Platelet Count as a Tool for Hepatocellular Carcinoma Screening

High anti-HCV prevalence, elderly residents, low resources (n = 1,002)

Screening strategies

- HBsAg, anti-HCV, AFP (>20ng/mL), AST (>40U/L), ALT (>40U/L), and platelet count (<150,000/mm³)
  - Any positive → Liver US (n = 527)
  - 16 HCC cases

- AFP (>20ng/mL) and platelet count (<150,000/mm³)
  - Any positive → Liver US (n = 215)
  - 14/16 HCC cases (88%)

Cost = 44,816 USD

Cost = 18,044 USD (- 60%)


Summary and Conclusions
Increase in portal pressure and decrease in liver function are the main pathophysiological mechanisms responsible for decreased platelet counts in CLD patients.

In these patients, platelet count can be used as a diagnostic parameter, a prognostic indicator, and an epidemiological marker.

From the clinical standpoint, platelet count – alone or in composite scores – represents an aid to identify advanced fibrosis and cirrhosis, to foresee the occurrence of complications of cirrhosis and establish patients prognosis, and may help targeting screening programs for hepatocellular carcinoma.
PLATELETS AGGREGATE

THEN A MIRACLE OCCURS

A CLOT

The Hepatologist’s View of Coagulation