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## Prognostic Biomarkers of Mortality in Liver Cirrhosis

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### Abstract:

Liver cirrhosis is the terminal stage of most chronic liver conditions, with a high risk of mortality. Careful evaluation of the prognosis of cirrhotic patients and providing precise management are crucial to reduce the risk of mortality. Although the liver biopsy and hepatic venous pressure gradient (HVPG) can efficiently evaluate the prognosis of cirrhotic patients, their application is limited due to the invasion procedures. Child-Pugh score and the model for end-stage liver disease (MELD) score had been widely used in the assessment of cirrhotic prognosis, but the defects of subjective variable application in Child-Pugh score and unsuitability to all phases of liver cirrhosis in MELD score limit their prognostic values. In recent years, continuous efforts have been made to investigate the prognostic value of body fluid biomarkers for cirrhotic patients, and promising results have been reported. Since the collection of fluid specimens is easy, noninvasive, and repeatable, fluid biomarkers can be ideal indicators to predict the prognosis of cirrhosis. Here, we reviewed noninvasive fluid biomarkers in different prognostic functions, including the prediction of survival and complication development.

**Keywords:** Survival Rate, Mortality, Liver Cirrhosis.

**Introduction:**

Predictive models for the prognosis of cirrhosis estimate the ten-year survival in patients with compensated cirrhosis at 47%, but this drops to 16% once a decompensating event occurs. The Child-Turcotte-Pugh (CTP) scoring or classification uses serum albumin, bilirubin, PT, ascites, and hepatic encephalopathy to classify patients with cirrhosis into classes A, B, and C. One- and two-year survival rates for these classes are 100% and 85% (A), 80% and 60% (B), and 45% and 35% (C). The model for end-stage liver disease (MELD) score is another model used to predict the short-term mortality of patients with cirrhosis. It uses serum bilirubin, creatinine, and INR to predict mortality within the next three months. Based on the MELD score (more recently the MELDNa score), the priority of organ allocation for liver transplantation for patients with cirrhosis is adjudicated in the US (1).

Novel predictors of prognosis in cirrhotic patients have been emerging in recent years. Liver biopsy and hepatic venous pressure gradient (HVPG) may be used but are finite due to the invasive nature that they possess. The Child-Pugh and the model for end-stage liver disease (MELD) Scores are used to assess the prognosis of cirrhotic patients non-invasively. The former is used to grade the severity of liver disease, and the latter is employed as a verifiable system to prioritize candidates for liver transplantation. The Child-Pugh score has the inherent disadvantage of the subjective nature of the variables used to score, such as hepatic encephalopathy and ascites. On the other hand, the MELD score is more applicable for end-stage patients (2).

Several studies have attempted to compare the utility of both scores as prognostic markers for cirrhotic patients, but all were limited by the heterogeneous nature of the populations included. It is, therefore, imperative that new scores are proposed to assess the prognosis of patients with liver cirrhosis (3).

In recent years, the CLIF-COF (CLIF- consortium organ failure) score, which takes into account variables such as bilirubin, creatinine, INR, and more, has emerged as a superior predictor of prognosis in acute on chronic liver failure than the MELD score. Moreover, studies have shown that serum copeptin level is a predictor of mortality in cirrhotic patients admitted for acute decompensation, independently of MELD and CLIF-COF scores (4).

**Fluid biomarkers**

There were several fluid biomarkers and panels of biomarkers developed to predict the overall survival of cirrhosis.

Red blood cell distribution width (RDW) is a common indicator of routine blood tests and it has a certain prognostic value. **Turcato et al. (5)** carried out a retrospective study that included 542 patients with acute decompensate LC and showed that the median RDW in this patient cohort was 15.7%; the mortality rate at 1 month was significantly lower in the patients

with RDW less than 15.7% than in those with RDW more than 15.7% (8.2% vs. 21.8%). After adjusting for the age, hepatocellular carcinoma, renal function, hemoglobin value, and CLIF-C AD (Chronic Liver Failure Consortium Acute Decompensation) score, the dichotomous and continuous RDW was the independently predictive factor for predicting 1-month mortality (OR: 2.319 and 1.216, respectively). Besides, the model combined with RDW and CLIF-C AD score had a better ability of discrimination than CLIF-C AD (AUROC: 0.769 vs. 0.720;  $p=0.006$ ).

C-reactive protein (CRP) is a nonspecific biomarker of inflammation. Recently, a number of studies showed that CRP had favorable prognostic value in LC. A retrospective study in 336 cirrhotic patients with spontaneous bacterial peritonitis (SBP) showed that the patients with serum levels of CRP  $\geq 5$  mg/dL had significantly higher in-hospital mortality (45.5% vs. 28.6%) and lower rate of antibiotic responses (63.5% vs. 83.5%) than those with CRP  $< 5$  mg/dL **(6)**.

Another retrospectively observational study enrolled 202 LC patients with sepsis and 87 of them with repeated CRP measurements at day 4 and/or 5; the results showed that the ratio of the follow-up CRP level to the initial CRP level might be a useful prognostic factor to predict the mortality of LC patients (OR: 19.12), but not initial CRP level **(7)**.

Blood leukocyte and neutrophil counts are conventional inflammatory markers. Recently, it is found that neutrophil to lymphocyte ratio (NLR) is a diverse functional prognosis predictor in some diseases, such as myocardial infarction, adult polymyositis and dermatomyositis, and spontaneous intracerebral hemorrhage. NLR is related to immune dysregulation in patients with cirrhosis and is inexpensive to measure. Some studies showed that NLR is an emerging prognostic predictor in LC **(8)**.

Aspartate transaminase (AST)/PLT (APRI) is proved to be a simple noninvasive index able to predict fibrosis and cirrhosis in patients with chronic hepatitis C. Additionally, APRI is an independent prognostic index in primary biliary cirrhosis (PBC). Trivedi et al. evaluated 1015 patients with PBC and found that in both derivation and validation cohorts, the patients with higher baseline or one-year APRI values had poorer transplant-free survival **(9)**.

Serum albumin levels are able to predict the prognosis of LC. In compensated LC patients, serum albumin levels  $< 4$  g/dL indicated a worse prognosis at 5 years compared with those with serum albumin levels  $\geq 4$  g/dL. In patients with decompensated LC, albumin is changed in both quantity and quality. There are three homodimeric albumin isoforms, hdHA-DA, hdHA-L, and hdHA-native, in patients with cirrhosis and healthy controls. During 1 year follow-up, it was found that patients with a lower relative amount of the hdHA-DA or a higher relative amount of hdHA-native seemed to have a significantly longer survival ( $10.22 \pm 0.44$  vs.  $8.28 \pm 0.56$  months;  $9.94 \pm 0.42$  vs.  $8.33 \pm 0.64$  months) **(10)**.

Patients with LC are often complicated with electrolyte disorders. Hyponatremia is a common complication in LC. Several researches had proved that serum sodium levels are well prognostic in LC. Jenq et al. observed 126 patients with LC who admitted to ICU and found that the patients with lower serum sodium concentration ( $\leq 135$  mmol/L) at the first day of admission had a significantly higher in-hospital mortality (73% vs. 56%) and a poor 6-month survival rate after discharge, and the similar conclusion about 6-month survival was also achieved in the subset of patients with gastrointestinal hemorrhage (11).

Urokinase plasminogen activator receptor (uPAR) is a membrane glycoprotein. When a body suffers from a tumor, inflammation, and other pathological conditions, uPAR is upregulated and released into the blood circulation by hydrolysis of phospholipase or protease. suPAR is a soluble form of uPAR and a promising prognostic biomarker. A study indicated that suPAR could predict the hospital and long-term mortalities in patients with critical illness and sepsis (12).

Neutrophil gelatinase-associated lipocalin (NGAL) is a glycoprotein composed of a polypeptide chain with 178 amino acid residues. Due to its small molecular size, it can be filtered to the urine where it can be measured from. It shows diverse biological functions, such as embryonic development, cell differentiation, inflammation and immune response, apoptosis, signal transduction, carbohydrate lipid metabolism, tumor formation, invasion, and metastasis (4).

Recently, some studies reported that NGAL, in both blood and urine, is a novel sensitive biomarker with prognostic value for renal injury in LC patients. **Gungor et al. (13)** reported that plasma NGAL (pNGAL) had potential ability to predict the outcome of liver cirrhosis in patients with hepatorenal syndrome (HRS): the patients with pNGAL  $> 289.6$   $\mu\text{g/L}$  had a shorter survival time during 6-month follow-up, with AUROC 0.819 higher than CTP score (0.795), MELD-Na score (0.807), urine NGAL (0.686), and sensitivity 83.7% and specificity 72.2% in predicting mortality. **Ariza et al. (14)** investigated serum and urine NGAL in 716 patients in which 148 patients were with ACLF and demonstrated that urinary NGAL (uNGAL) was markedly increased in ACLF compared with non-ACLF patients and was also an independent predictive factor for 28-day transplant-free mortality when combined with MELD score and leukocyte count (AUROC: 0.880).

Patients with LC are often associated with decreased body fat mass and insulin resistance. Resistin, a secreted protein produced by adipocytes and detectable in plasma, plays an important role in insulin resistance. **Chang et al. (15)** detected resistin in 82 patients with chronic liver diseases (including 67 cirrhosis) and followed up for 6 years; they found that resistin levels were significantly elevated in cirrhosis patients compared with healthy controls and positively correlated with the stage of cirrhosis. However, **da Silva et al. (16)** did not observe a significant relationship between resistin levels and transplant-free survival: they detected plasma resistin and adiponectin levels and found that adiponectin, but not resistin, levels were associated with lower survival (HR: 1.034).

Copeptin is a fragment derived from the vasopressin precursor. Vasopressin is increased and plays a role in the development of complications in patients with cirrhosis. The measurement of vasopressin is difficult, but copeptin is more stable and easier to be detected in the blood. **Moreno et al. (17)** reported that plasma copeptin levels were increased along with the severity of liver disease in cirrhotic patients, with a 2.3-fold risk of death/liver transplantation in high-level patients compared with low-level ones, and independently predicted the 1-year mortality or liver transplantation (AUROC: 0.7). **Kerbert et al. (18)** investigated 61 LC patients at the waiting list for liver transplantation and found that patients with low levels of serum copeptin had a significantly higher transplant-free survival rate than those with high levels of copeptin. Subsequently, in 184 hospitalized cirrhotic patients, they demonstrated that patients with lower copeptin levels had a better transplant-free survival rate during 6 and 12 months of follow-up **(19)**.

M30, M65, and M65EpiDeath belong to cytokeratin 18- (CK-18-) based serum markers reflecting apoptotic or overall epithelial cell death. It was found that the increased serum levels of a fragment of CK-18 were associated with liver fibrosis and acute or chronic liver diseases **(20)**.

Insulin-like growth factor-binding protein (IGFBP) is a group of polypeptides that are homologous with insulin. IGFBP-3, the most abundant type of IGFBPs in blood circulation, is mainly synthesized in Kupffer cells of the liver. It is an indicator that can reflect the liver capacity. A study showed that serum IGFBP-3 was lower in cirrhotic patients than healthy controls, which indicated that low IGFBP-3 was associated with hepatocellular dysfunction **(4)**.

Myostatin is a cytokine able to strongly suppress skeletal muscle growth. The serum concentration of myostatin in LC patients was significantly higher than the healthy. Nishikawa et al. measured serum myostatin levels in 198 LC patients, and the results showed that the overall survival rates of patients with high myostatin were significantly lower than those with low myostatin: 1-, 3-, 5-, and 7-year cumulative survival rates were 96.0%, 77.9%, 53.0%, and 39.1%, respectively, in the high myostatin group and 96.4%, 87.6%, 77.6%, and 73.2%, respectively, in the low myostatin group after excluding hepatocellular carcinoma patients at baseline **(21)**.

The levels of Wisteria floribunda agglutinin<sup>+</sup>-colony-stimulating factor 1 receptor (WFA<sup>+</sup>-CSF1R) could reflect the progression of liver fibrosis and possibly evaluate the severity of LC. Lio et al. detected the levels of WFA<sup>+</sup>-CSF1R and total-CSF1R in 214 patients with liver diseases caused by HCV infection and found that patients with LC ( $n = 115$ ) had significantly higher plasma levels of WFA<sup>+</sup>-CSF1R and total-CSF1R than the patients ( $n = 99$ ) with chronic hepatitis (208.9 ng/ml vs. 82.3 ng/ml; 845.3 ng/ml vs. 536.4 ng/ml, respectively) and that the mortality was significantly higher in patients with WFA<sup>+</sup>-CSF1R levels  $\geq 310$  ng/ml (HR: 1.8), with an AUROC of 0.691 **(22)**.

Wisteria floribunda agglutinin positive Mac-2 binding protein (WFA<sup>+</sup>-M2BP) is a novel and noninvasive biomarker for the assessment of liver fibrosis. **Yamasaki et al. (23)** enrolled 707 hepatitis C patients including 120 cases of LC and followed up for 20 years, and the results showed that the patients with the serum levels of WFA<sup>+</sup>-M2BP 1-4 and  $\geq 4$  at admission presented higher risk to develop HCC compared with WFA<sup>+</sup>-M2BP  $< 1$  (HR = 5.115 and 8.318, respectively). In PBC patients, ones with serum WFA<sup>+</sup>-M2BP levels  $< 2.0$  had a significantly higher survival rate of 10 years compared with the patients whose WFA<sup>+</sup>-M2BP value  $\geq 2.0$  (98.8% vs. 59.1%) **(24)**.

Interleukin-22 (IL-22) is a crucial parameter of pathology in experimental liver damage and associated with the prognosis of LC. **Kronenberger et al. (25)** detected the systemic levels of IL-22 in 120 LC patients and 40 healthy donors and found that IL-22 was more detectable in LC patients compared with healthy donors (74.1% vs. 10%), and the patients with elevated IL-22 levels had a reduced survival time (321 days vs. 526 days).

Lysophosphatidic acid (LPA), a secreted glycoprotein formed from lysophosphatidylcholine by autotaxin (ATX) which possesses both phosphodiesterase and lysophospholipase D activity, activates hepatic stellate cells and inhibits their apoptosis. A prospective cohort study included 270 cirrhotic patients and found that low levels of serum autotaxin indicated a longer survival time (HR: 0.575) **(26)**.

Vitamin D is a necessary fat-soluble vitamin in the body, and its deficiency is associated with various chronic liver diseases. A study prospectively recruited 324 patients with alcoholic liver disease in which there were 254 LC patients and were followed up for one year, and the low levels of vitamin D were associated with low overall survival time (HR: 5.95) **(27)**.

Several biomarkers detected in urine also could predict the survival rate of patients with LC. Interleukin-18 (IL-18) is a proinflammatory protein able to regulate immune responses. Urinary IL-18 is associated with AKI and 90-day mortality in critically ill patients **(28)**. Recently, **Tsai et al. (29)** detected the concentration of the urinary IL-18 in 168 consecutive cirrhotic patients with severe sepsis and found that it was significantly higher in hospital survivors than in nonsurvivors and was an independent factor to predict mortality of the patients in the hospital. Monocyte chemoattractant protein-1 (MCP-1) is one of the key chemokines in regulating migration and infiltration of monocytes/macrophages and involved in various diseases.

Saliva samples can be collected easily, repetitively, and noninvasively. It is found that the saliva contains biomarkers associated with LC prognosis. Salivary caffeine clearance (CCl) could be used to evaluate the liver function and liver metabolic capacity **(4)**.

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