COMPARATIVE DIAGNOSTIC PERFORMANCE OF SERUM PIIINP AND COLLAGEN TYPE IV AS NON-INVASIVE BIOMARKERS FOR LIVER FIBROSIS STAGING

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Background: Liver fibrosis is a progressive consequence of chronic liver diseases and may lead to cirrhosis and hepatocellular carcinoma. Non-invasive biomarkers are increasingly used to reduce reliance on liver biopsy. Procollagen type III N-terminal propeptide (PIIINP) and collagen type IV are extracellular matrix components associated with fibrogenesis. To compare the diagnostic performance of serum PIIINP and collagen type IV in staging liver fibrosis. A prospective analytical study included 120 participants: chronic HBV (n=40), chronic HCV (n=40), and healthy controls (n=40). Serum PIIINP and collagen IV levels were measured using ELISA. Fibrosis stage was assessed by transient elastography (FibroScan). Correlation analyses and ROC curve analyses were performed to evaluate diagnostic performance. Both biomarkers were significantly elevated in HBV and HCV groups compared with controls (p<0.01). PIIINP showed strong correlation with elastography (r=0.71, p<0.001), while collagen IV demonstrated slightly stronger correlation (r=0.74, p<0.001). ROC analysis revealed good discrimination for advanced fibrosis (≥F3), with AUC values of 0.87 for PIIINP and 0.90 for collagen IV. Combined biomarker analysis improved AUC to 0.93. Both PIIINP and collagen IV are valuable non-invasive markers of liver fibrosis. Collagen IV demonstrated marginally superior diagnostic performance, while combined assessment provided the highest accuracy.

Keywords: *liver fibrosis; PIIINP; collagen type IV; biomarker; extracellular matrix; ROC analysis; elastography.*

INTRODUCTION

Liver fibrosis represents a common pathological outcome of chronic liver injury and is characterized by excessive deposition of extracellular matrix (ECM) components, including collagens types I, III, and IV [1,2]. Progressive fibrosis may culminate in cirrhosis, portal hypertension, and hepatocellular carcinoma [1].

Although liver biopsy remains the reference standard for fibrosis staging, it is limited by invasiveness, sampling variability, and inter-observer differences [3]. Consequently, non-invasive approaches such as serum biomarkers and transient elastography have gained increasing clinical importance [4]. PIIINP is released during the synthesis of type III collagen and reflects active fibrogenesis [5]. Collagen type IV, a major component of basement membranes, is associated with sinusoidal capillarization and structural remodeling in advanced fibrosis [6]. Despite individual studies evaluating these markers separately, direct comparative analyses remain

limited. This study aimed to compare the diagnostic performance of PIIINP and collagen type IV in staging liver fibrosis and to determine whether their combined use enhances diagnostic accuracy.

2. Materials and Methods

2.1 Study Design and Population

This prospective study included 120 participants:

- Chronic HBV (n=40)
- Chronic HCV (n=40)
- Healthy controls (n=40)

Inclusion criteria: confirmed chronic viral hepatitis; age 20–65 years. Exclusion criteria: decompensated cirrhosis, malignancy, pregnancy, systemic fibrotic diseases.

2.2 Laboratory Assessment

Serum PIIINP and collagen IV levels were measured using commercially available ELISA kits. Liver function tests (ALT, AST) and FIB-4 index were calculated.

2.3 Fibrosis Staging

Transient elastography (FibroScan) was used to classify fibrosis stages (F0–F4).

2.4 Statistical Analysis

Continuous variables were expressed as mean ± SD. Pearson correlation analysis assessed associations between biomarkers and elastography values. ROC curves were constructed to evaluate diagnostic performance for significant fibrosis (≥F2) and advanced fibrosis (≥F3). AUC values were compared using DeLong's test. $p<0.05$ was considered statistically significant.

3. Results

3.1 Biomarker Levels

Mean serum levels:

Group	PIIINP (ng/mL)	Collagen IV (ng/mL)
Controls	4.2 ± 1.1	95 ± 18
HBV	8.7 ± 2.3*	168 ± 35*
HCV	9.4 ± 2.8*	182 ± 41*

*$p<0.01$ vs controls.

3.2 Correlation with Fibrosis Stage

- PIIINP vs elastography: $r=0.71$ ($p<0.001$)
- Collagen IV vs elastography: $r=0.74$ ($p<0.001$)

3.3 ROC Analysis

For advanced fibrosis (≥F3):

Biomarker	AUC (95% CI)	Sensitivity (%)	Specificity (%)
PIIINP	0.87	82	78
Collagen IV	0.90	85	81
Combined model	0.93	88	85

Collagen IV showed slightly higher discriminative ability. The combined biomarker model demonstrated superior diagnostic performance.

4. Discussion

This comparative analysis demonstrated that both PIIINP and collagen IV are significantly associated with fibrosis severity. PIIINP reflects active type III collagen synthesis, which predominates in early fibrogenesis [5]. In contrast, collagen IV reflects basement membrane remodeling and sinusoidal capillarization, processes more prominent in advanced fibrosis [6].

The slightly higher AUC for collagen IV suggests superior discrimination for advanced fibrosis. However, the combined model yielded the highest AUC, supporting the concept that multi-marker strategies improve diagnostic accuracy [4].

These findings align with previous studies highlighting the importance of ECM-related biomarkers in fibrosis assessment [1,6].

Limitations include single-center design and reliance on elastography rather than histological confirmation.

5. Conclusion

Both PIIINP and collagen type IV are reliable non-invasive biomarkers for liver fibrosis assessment. Collagen IV demonstrated marginally superior diagnostic accuracy, particularly for advanced fibrosis. Combined biomarker analysis further enhances diagnostic performance and may represent a practical strategy for non-invasive fibrosis staging.

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