APRI and FIB4 as effective markers for monitoring esophageal varices in HIV/HCV co-infected patients due to contaminated blood products for hemophilia

Koji Natsuda, Mitsuhisa Takatsuki,* Takayuki Tanaka, Akihiko Soyama, Tomohiko Adachi, Shinichiro Ono, Takanobu Hara, Zhassulan Baimakhanov, Hajime Imamura, Satomi Okada, Masaaki Hidaka, Susumu Eguchi

Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences

1-7-1 Sakamoto, Nagasaki 852-8501, Japan.

***Corresponding author:**

Mitsuhisa Takatsuki,

Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan.

Tel: 81-95-819-7316; Fax: 81-95-819-7319.

E-mail: takapon@nagasaki-u.ac.jp

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ABSTRACT

Aim: We examined the feasibility of the aspartate transaminase (AST)-platelet ratio index (APRI) and FIB4, which are well-established markers for liver fibrosis, as indicators for monitoring esophageal varices in patients who were co-infected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) due to contaminated blood products for hemophilia in Japan.

Patients and Methods: Forty-three HIV/HCV co-infected patients were enrolled. All were hemophilic men (median age 41, range 29–66 yrs). We analyzed the correlations between fibrosis indices (APRI, FIB4) and various liver function tests, fibrosis markers, liver stiffness measured by acoustic radiation force impulse (ARFI) elastography, and the findings of gastrointestinal endoscopy.

Results: APRI and FIB4 were well correlated with several of the factors related to liver fibrosis and the existence of esophageal varices in the patients. The cut-off values for detecting esophageal varices estimated as the area under the receiver operating characteristic curve were 0.85 for APRI and 1.85 for FIB4.

Conclusion: In patients co-infected with HIV/HCV due to contaminated blood products for hemophilia, APRI and FIB4 are effective for monitoring esophageal varices, even among patients who are apparently doing well with good liver function as Child-Pugh grade A.

Key words: HIV, HCV, co-infection, liver transplantation, APRI, FIB4, esophageal varices

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Introduction

In the 1980s in Japan, contaminated blood products intended for individuals with hemophilia caused the co-infection of human immunodeficiency virus (HIV) and hepatitis C virus (HCV). In fact, more than 90% of the hemophiliacs in Japan who are infected with HIV also have HCV (1, 2). After the introduction of antiretroviral therapy (ART) in the late 1990s, the survival of HIV-infected patients improved dramatically because the rate of opportunistic infections related to acquired immunodeficiency syndrome (AIDS) decreased; however the mortality due to HCV-related liver disease has not sufficiently declined in HIV/HCV co-infected patients, and thus liver-related disease has become the main cause of death in this population (3–7), especially in patients due to contaminated blood products (2).

It is well documented that in HIV/HCV co-infected patients, noncirrhotic portal hypertension (NCPH) is one of the specific findings that may be related to the antiviral drug didanosine. In NCPH, the portal vein is obstructed by fibrosis, and liver failure is accelerated when an episode of decompensation occurs (such as variceal bleeding or encephalopathy) even in patients who have maintained liver function as Child-Pugh grade A (8, 9). Accordingly, it is important to check the severity of liver fibrosis in NCPH patients by percutaneous biopsy and to check esophageal varices by endoscopy even if the liver function is maintained. However, especially in hemophilic patients, it is difficult to perform a liver biopsy because of the possible severe bleeding complication, and endoscopy is also an invasive modality for the monitoring of esophageal varices.

The aspartate transaminase (AST)-platelet ratio index (APRI) and FIB4 have been introduced as non-invasive monitoring modalities, as both are correlated with the severity of liver fibrosis and/or cirrhosis (10–15). We conducted the present study to analyze the efficacy of APRI and FIB4 to monitor the severity of liver fibrosis in HIV/HCV co-infected patients, and to identify a surrogate indicator for detecting esophageal varices.

Patients and Methods

Study population

The study population was patients who suffered from HIV/HCV co-infection due to contaminated blood products for hemophilia in Japan in the early 1980s. Forty-four HIV/HCV co-infected patients who belong to a social welfare corporation in Japan (i.e., the Habataki Welfare Project) underwent a comprehensive evaluation of their liver function as volunteers, as the national project named "Research of Liver Transplantation for HIV/HCV Co-infected Patients (Eguchi Project)" supported by a Health and Labour Sciences Research Grant from the Ministry of Health, Labour and Welfare, Japan.

The study was approved by the institutional review board at the Nagasaki University Graduate School of Biomedical Sciences (approval no. 09062521). The patients were all male hemophiliacs and were positive for both HIV and HCV antibodies, with the median age of 41 (range 29–66 yrs; Table 1).

Evaluation of the liver function, liver stiffness and esophageal varices

Each patient underwent an examination that including the complete blood count, general liver function tests, liver fibrosis markers, liver stiffness measured by acoustic radiation force impulse (ARFI) elastography, and gastrointestinal endoscopy. Based on the results of these tests, APRI and FIB4 were calculated according to the reported formula (14, 15). We

determined the correlations between APRI, FIB4 and the patients' total bilirubin (T.Bil), albumin (Alb), prothrombin time (PT), hyaluronic acid (HA), 7S fragment of type 4 collagen (type 4 collagen), velocity of shear wave (Vs) of ARFI elastography. We also evaluated the severity of esophageal varices as classified according to the criteria of the Japanese Society for Portal Hypertension (16). A severity grade that is ≥ grade F1: straight small-caliber varices is defined as the existence of esophageal varices.

Data analyses

The correlation between APRI, FIB4 and other liver parameters were analyzed by Spearman's rank-order correlation. All statistical analyses were performed with GraphPad Prism 6 for Windows (GraphPad, San Diego, CA). Receiver operating characteristic (ROC) curves were constructed for APRI and FIB4 to establish the cut-off values necessary to monitor the patients' esophageal varices. To evaluate the diagnostic accuracies of the detection for esophageal varices, we calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the area under the receiver operating characteristic curve (AUROC).

Results

Patient characteristics

The clinical characteristics and standard laboratory tests of the forty-three patients (except for the single patient who did not undergo gastrointestinal endoscopy) are summarized in Table 1. Thirty-seven patients (84.1%) were classified as Child-Pugh class A at the examination.

Correlations between APRI, FIB4 and the liver function tests

Generally, both APRI and FIB4 were significantly correlated with the synthetic liver function and fibrosis markers except for the total bilirubin level. APRI and FIB4 were also well correlated with the Vs of the ARFI elastography (Fig. 1). APRI and FIB4 were also significantly correlated each other ($P < 0.01$, r = 0.76) (Fig. 2). This tendency did not change in twenty-nine cases without any varices ($P < 0.01$, r = 0.67). Both indices in patients with varices (n=14) tended to be correlated each other although there was no statistical significance ($P = 0.06$).

Correlations between APRI and FIB4 and the existence of esophageal varices

Fourteen of the 43 patients (32.6%) had esophageal varices, with various grades of severity (F1 in 11 patients, F2 in the other three patients), and the red color sign was positive in three patients. We constructed ROC curves to evaluate the diagnostic accuracy of APRI and that of FIB4 to detect esophageal varices that are more severe than grade F1 (Fig. 3). The comparison of AUROCs for the fibrosis indices showed superior diagnostic accuracy of APRI (AUROC = 0.729) and FIB4 (AUROC = 0.778) to detect esophageal varices.

According to the estimated optimal cut-off of APRI, a value of 0.85 correctly classified 30 patients (69.8%), with 71.4% sensitivity and 70.0% specificity; the number of patients correctly classified as having esophageal varices was 30 (69.8%) when considering the cut-off of FIB4 (equal to 1.85; sensitivity 71.4%, specificity 70.0%). The majority of misclassified patients were false-positive cases (nine [20.9%] and nine [20.9%] patients for APRI and FIB4, respectively) rather than false-negative cases (four [9.3%] and four [9.3%] patients for APRI and FIB4, respectively) (Table 2).

The risk factors of esophageal varices

APRI and FIB4 were both significant factors related to esophageal varices, with the odds ratio of 5.56 for APRI and 5.56 for FIB4, whereas neither viral positivity nor liver fibrosis markers were related to esophageal varices (Table 3).

Discussion

Various non-invasive modalities have been introduced to monitor liver fibrosis and cirrhosis, including transient elastography or ARFI (17,18). Although these modalities are fairly effective and reliable, the device-dependent techniques are mainly limited to larger centers, and sometimes the modalities cannot be applied in obese patients or people with narrow intercostal spaces (19). APRI and FIB4 are well recognized as non-invasive markers that can be used to monitor the severity of liver fibrosis and cirrhosis in various liver diseases, including HIV/HCV co-infection (20, 21). The use of such non-invasive and simple markers to check liver fibrosis is especially important in hemophilic patients, in whom liver biopsies should be avoided because of the possible hemorrhagic complication. Although the liver biopsy is the gold standard and has been reported to be safely performed in this population (22), it should be avoided when a simpler and safer approach is available. APRI and FIB4 are easily accessible, and the calculations for these indices are relatively easy.

Our present findings indicate that not only are APRI and FIB4 effective markers for determining the severity of liver fibrosis; they are also feasible surrogate markers for monitoring esophageal varices. For their use as a marker of liver fibrosis/cirrhosis, several cut-off values have been identified. Schmid et al. showed that the APRI cut-off values for significant fibrosis (≥ F2) and cirrhosis (F4) were 1.5 and 2.0, respectively (23). Our present study's identification of the cut-off value necessary to monitor esophageal varices is lower

than that for detecting fibrosis/cirrhosis; that is, the APRI cut-off value for monitoring esophageal varices is 0.85. The reason for this result might be because esophageal varices develop during an early stage of liver fibrosis, so that it is very important to rule out esophageal varices in HIV/HCV co-infected patients because many of them may have varices even though they are apparently doing well without any liver dysfunction.

Several studies proposed that in HIV/HCV co-infected patients, portal hypertension is not correlated with the severity of liver function test even in Child-Pugh grade A cases, and liver decompensation can occur suddenly after an acute episode of variceal bleeding or encephalopathy (8, 9). Accordingly, we strongly recommend that even for patients who are apparently doing well with good liver function, physicians should perform endoscopy to check for esophageal varices when the patients show APRI or FIB4 values over the cut-off value. Although endoscopy is an invasive procedure, not only for diagnosis, a physician can then treat varices when they are identified as being at high risk of bleeding, with the red color sign. However, many hemophiliacs infected with HIV/HCV are generally followed by not hepatologist, but hematologists or infectious disease physician, so that most of them might miss the chance to undergo endoscopy opportunely. The actual purpose of this study was not to detect the varices with high risk of rupture, but to inform the physician the timing to consult the gastroenterologist or hepatologist. Actually the most cases in this study (11/14, 78.6%) were classified to F1 with no need for endoscopic therapy, but it can develop as high risk of bleeding during subsequent follow-up.

NCPH is well known as a specific finding in HIV/HCV co-infected patients (24, 25). The reverse transcriptase inhibitor didanosine had been one of the key ART drugs, its use was eventually abolished because it was identified as the cause of NCPH (26). It was not very clear about the patients' treatment history in the present study because they were volunteers who belonged to the social welfare corporation and treated by different institutes, respectively.

However, majority of the patients were expected to have didanosine because it used to be recommended by guidelines to use antiretroviral agents for HIV-infected patients not only in Japan but also in Western countries (27). As a result, majority of them had esophageal varices with varying degrees of severity although they were doing well with good liver function as Child-Pugh grade A cases.

In conclusion, many HIV/HCV co-infected patients have asymptomatic esophageal varices even they are doing well with good liver function as Child-Pugh grade A cases. APRI and FIB4 appear to be good indicators for monitoring not only liver fibrosis but also esophageal varices, and we therefore strongly recommend that endoscopy be performed when patients show an APRI or FIB4 value over cut-off value described in this study.

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Fig. 1

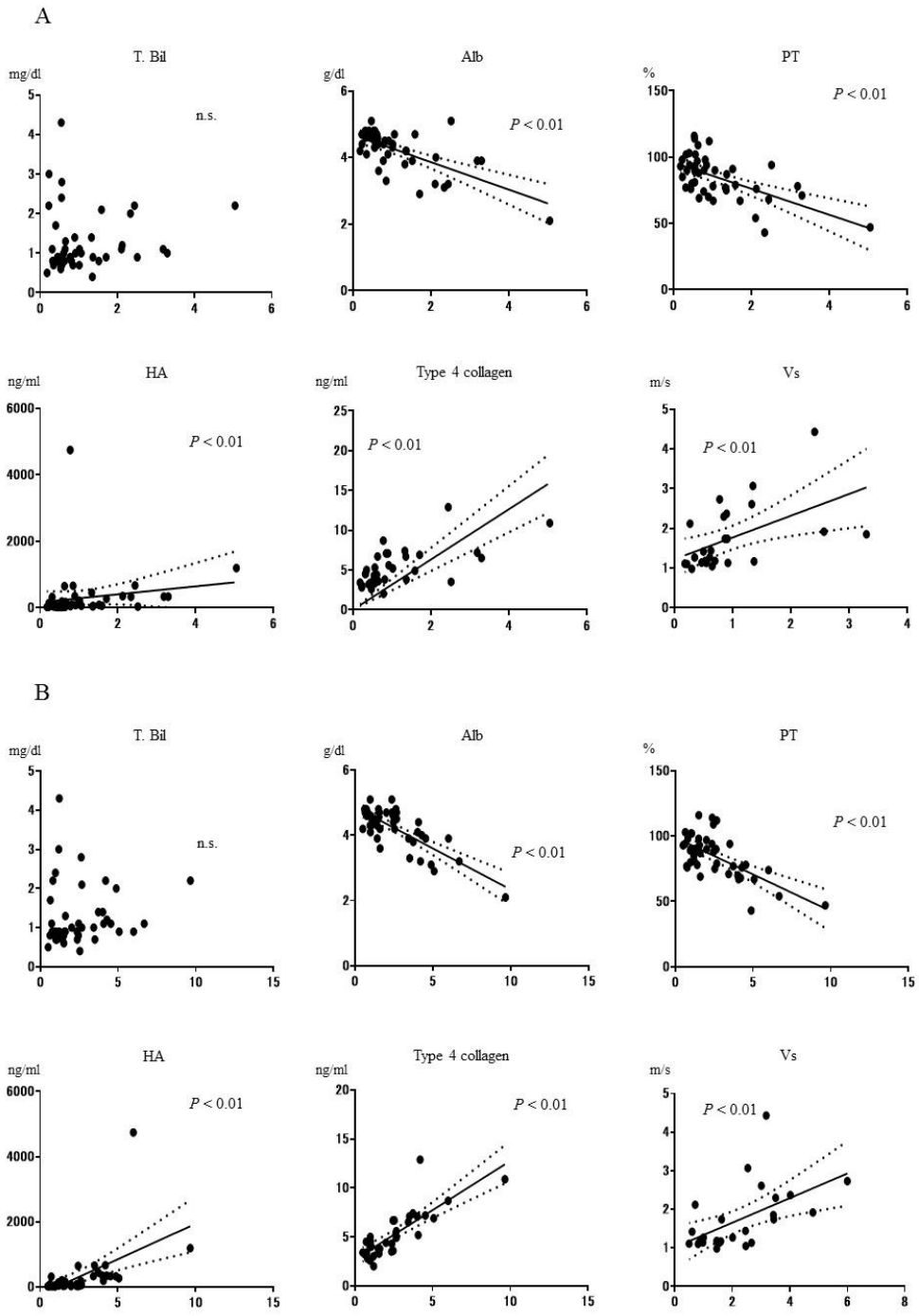

Fig. 1. The correlations between APRI (A), FIB4 (B) and the liver function tests, liver fibrosis markers, and the velocity of the shear wave (Vs) of ARFI. Both APRI and FIB4 were significantly correlated with all of these markers except total bilirubin (T. Bil). Alb, albumin; PT, prothrombin time; HA, hyaluronic acid.

Fig. 2

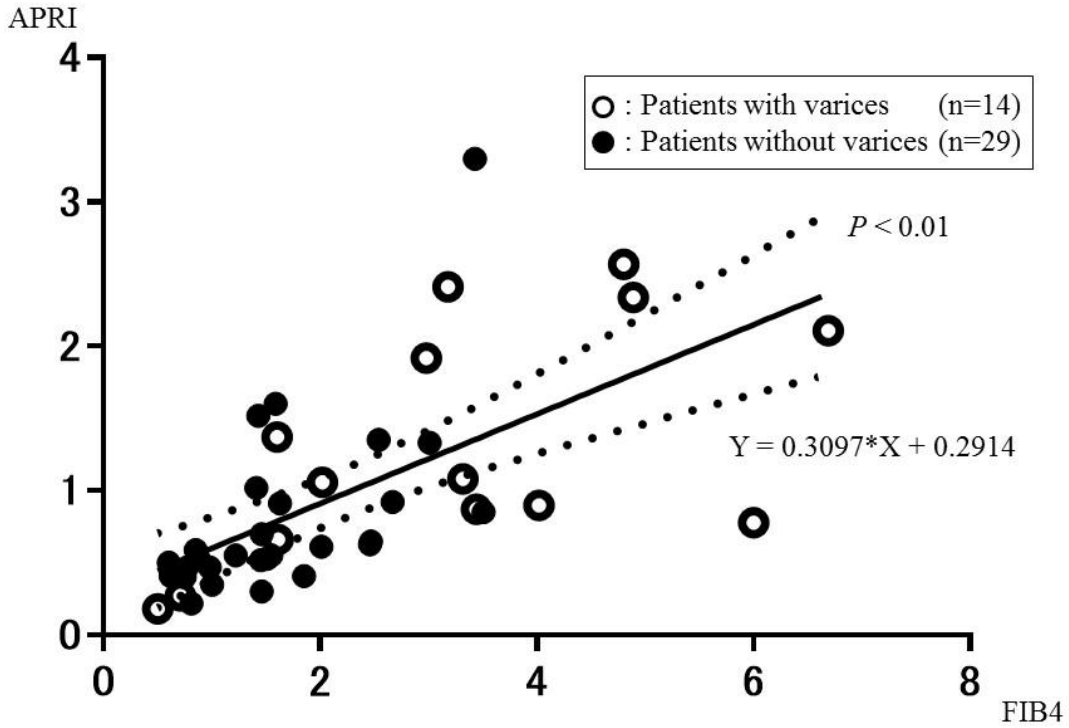

Fig. 2. The correlations between APRI and FIB4. Patients with varices (n=14) were marked with open circle, and without varices (n=29) were marked with close circle.

Fig. 3

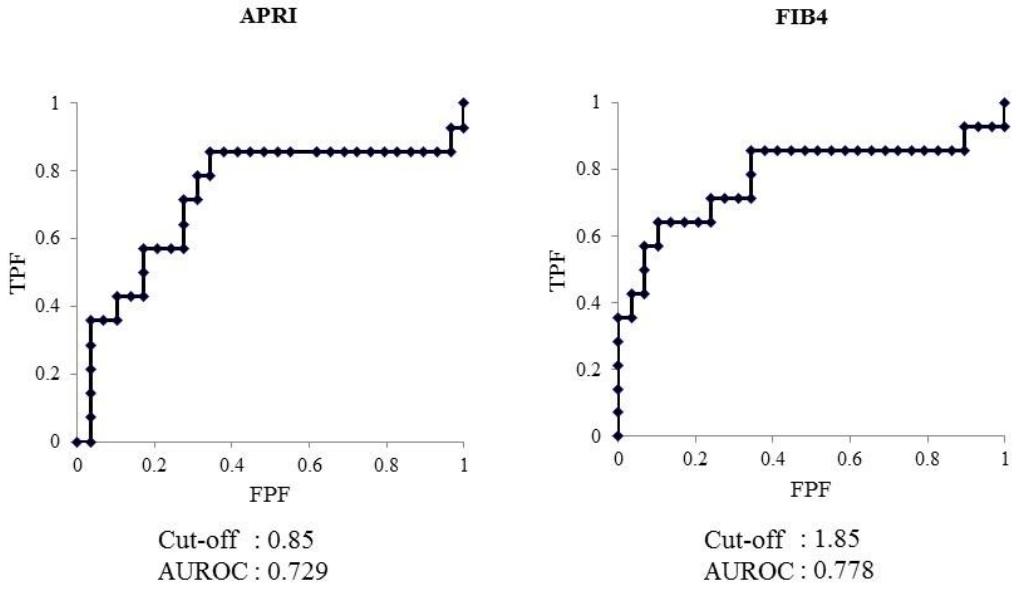

Fig. 3. ROC curves evaluating the diagnostic accuracy of APRI and that of FIB4 to detect esophageal varices that are more severe than grade F1. TPF, true positive fraction; FPF, false positive fraction; AUROC, area under the ROC.

	Median	range
Total number	43	
Gender Male/Female	43/0	
Age	41	(29 - 66)
Child-Pugh score	5	(5 - 9)
Grade A	37	
Grade B	6	
Grade C	0	
MELD	8	(6 - 22)
HCV-RNA +	23	
HCV-RNA load	4.6	(N.D. - 7.3)
HIV-RNA +	8	
HIV-RNA load	0	(N.D. - 1600)
Esophageal varices +	14	
F1	11	
F2	3	
F3	0	
RC +	3	
APRI	0.66	(0.18 - 3.30)
FIB4	1.6	(0.50 - 6.69)
Platelet ($x10^4/\mu l$)	16.1	(4.4 - 34.9)
PT (%)	89	(43 - 116)
albumin (g/dl)	4.5	(3.1 - 5.5)
T.Bil (mg/dl)	0.9	(0.4 - 4.3)
AST (IU/L)	34	(17 - 173)
ALT (IU/L)	34	(8 - 183)
type 4 collagen (ng/ml)	4.4	(2.6 - 119)
HA (ng/ml)	79	(18 - 4740)
Vs (m/s)	1.42	(0.98 - 4.43)
AFP (ng/ml)	3.3	(1.5 - 654.4)
PIVKA II (mAU/ml)	21	(8 - 223)
CD4 count (/μl)	445	(143 - 1081)
CD4/8 ratio	0.7	(0.3 - 1.7)

MELD, model for end stage liver disease; HCV, hepatitis C virus;
HIV, human immunodeficiency virus; RC, red color sign;
APRI, aspartate transaminase-platelet ratio index;T.Bil, total bilirubin;
AST, aspartate transaminase; ALT, alanine transaminase;
HA, hyaluronic acid, Vs, velocity of shear wave;
AFP, alfa fetoprotein; PIVKA II, protein induced by vitamin K absence or antagonist-II
N.D., not detected

Table 2. Diagnostic accuracy and optimal cut off values of APRI/FIB4 for the detection of esophageal varices.

	APRI	FIB4	APRI or FIB4
AUROC	0.729	0.778	-
Optimal cut-off	0.85	1.85	-
Total accuracy	69.8	69.8	62.8
Sensitivity %	71.4	71.4	78.6
Specificity %	70	70	55.2
PPV %	52.6	52.6	45.8
NPV %	83.3	83.3	84.2
Correctly classified patients n (%)	30 (69.8)	30 (69.8)	27 (62.8)
False positive cases n (%)	9 (20.9)	9 (20.9)	13 (30.2)
False negative cases n (%)	4 (9.3)	4 (9.3)	3 (7.0)

AUC, area under the receiver operating characteristic curve; PPV, positive predictive value; NPV, nagative predictive value

Table 3. Risk factors of esophageal varices.

Category		n	OR	p value	95% CI
APRI	<0.85	24	5.56	0.02	1.37 – 22.56
	≧0.85	19			
FIB4	<1.85	24	5.56	0.02	1.37 – 22.56
	≧1.85	19			
Child Pugh score	≦6	37	2.36	0.34	0.41 – 13.58
	≧7	6			
HCV-RNA	-	20	3.08	0.11	0.78 – 12.12
	+	23			
HIV-RNA	-	35	0.64	0.62	0.11 – 3.66
	+	8			
type 4 collagen	<6	18	2.8	0.24	0.5 – 15.66
	≧6	9			
HA	<50	15	4.06	0.1	0.75 – 21.92
	≧50	26			