Accuracy of Liver Fibrosis Degree Based on King's Score to Fibroscan in Chronic Hepatitis B

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ABSTRACT

Background: *A great interest has been dedicated to the development of non-invasive predictive models in recent years to substitute liver biopsy for fibrosis assessment and follow-up. Cross et al proposed King's score, age (years) x aspartate aminotransferase/AST (IU/L) x [international normalized ratio (INR)/platelets (10^9/L)]. This study aims to investigate the accuracy of King's score for predicting liver fibrosis in patients with chronic Hepatitis B.*

Method: *From February until July 2013, sixty two patients confirmed chronic Hepatitis B, underwent Fibroscan in Division of Gastroenterology and Hepatology at Haji Adam Malik Hospital, Medan. Serum obtained and analyzed for AST, INR, and pancreolauryl test (PLT) activity, and the King's score was computed. Liver fibrosis pathology was staged according to a defined system on a scale of F0 to F4 in Fibroscan. We used predictive values to assess the accuracy of King's score.*

Results: *King's score greater than or equal to 12,3 in predicted significant fibrosis has 48.1% sensitivity, 88.6% specificity, 76.5% positive predictive value (PPV), 68.9% negative predictive value (NPV). King's score greater than or equal to 16,7 in predicted cirrhosis has 83.3% sensitivity, 85.7% specificity, 38.5% positive predictive value (PPV), 98% negative predictive value (NPV). The validation set confirmed the utility of this index, area under receiver operating characteristic curves for each non-significant and cirrhosis was 0,684 (95% CI: 0,545-0,822; p = 0,014) and 0,845 (95% CI: 0,664-1,027; p = 0,006), respectively.*

Conclusion: *The King's score predicts cirrhosis (grade-4 fibrosis) in patients with high accuracy for significant fibrosis, this score did not show accurate result.*

Keywords: *King's score, FibroScan, liver fibrosis, chronic Hepatitis B*

ABSTRAK

Latar belakang: *Dalam beberapa tahun terakhir ini, perhatian yang besar telah didedikasikan bagi pengembangan model prediksi non-invasif dalam mengurangi tingkat kebutuhan biopsi hati untuk penilaian dan evaluasi fibrosis hati. Cross et al telah mengusulkan King's score, dengan mengukur usia (tahun) x aspartate aminotransferase/AST (IU/L) x [international normalized ratio (INR)/jumlah platelet (10^9/L)]. Penelitian ini bertujuan untuk menilai akurasi King's score dalam memprediksi derajat fibrosis hati pada pasien penyakit hepatitis B kronik.*

Metode: *Dari Februari hingga Juli 2013, 62 pasien penyakit hepatitis B kronik menjalani fibroscan di Divisi Gastroenterologi dan Hepatologi, Rumah Sakit Umum Pusat Haji Adam Malik, Medan dan dilakukan*

pemeriksaan serum AST, INR, pancreolauryl test (PLT) serta selanjutnya mengkalkulasi King's score. Patologi fibrosis hati digradasi berdasarkan sistem penilaian fibroscan dari skala F0 sampai F4. Digunakan nilai-nilai prediktif diagnostik dalam menilai akurasi King's score.

Hasil: *King's score ≥ 12,3 memiliki sensitivitas sebesar 48,1%, spesifisitas 88,6%, nilai prediksi positif 76,5%, nilai prediksi negatif 68,9% dalam memprediksi signifikan fibrosis. Untuk memprediksi sirosis, King's score ≥ 16,7 memiliki nilai akurasi yang tinggi dengan sensitivitas sebesar 83,3%, spesifisitas 85,7%, nilai prediksi positif 38,5%, nilai prediksi negatif 98%. Nilai area under receiver operating characteristic (AUROC) untuk masing-masing non-signifikan dan sirosis adalah 0,684 (95% CI: 0,545-0,822; p = 0,014) dan 0,845 (95% CI: 0,664-1,027; p = 0,006).*

Simpulan: *King's Score memiliki kemampuan memprediksi sirosis (fibrosis grade 4) pada pasien penyakit hepatitis B kronik dengan tingkat akurasi yang tinggi, sehingga pasien dengan nilai King's score ≥ 16,7 tidak membutuhkan biopsi hati lagi.*

Kata kunci: *King's score, fibroscan, fibrosis hati, penyakit hepatitis B kronik*

INTRODUCTION

Chronic liver disease was involving a progressive destructive and regenerative process that begins with liver fibrosis, mostly progress to liver cirrhosis and hepatocellular carcinoma. Liver fibrosis was caused by chronic damage in liver tissue, related to abundant accumulation of extracellular matrix (ECM) protein.[1,2] The main cause of liver fibrosis was chronic infection of Hepatitis B and C virus, alcoholism, autoimmune disease, cholestatic disease, and non-alcoholic steatohepatitis (NASH). Accumulation of ECM protein will damage liver architecture by forming fibrous connective tissue and development of liver nodule. A well-formed nodule stage was also known as liver cirrhosis.[2] Liver fibrosis was a healing process in response to chronic liver tissue injury. Liver cirrhosis detection and staging were important in chronic hepatitis patient management.[2] Chronic Hepatitis B was the most common infection in chronic hepatitis worldwide. A predictive model was designed specifically for chronic Hepatitis B patients by Shanghai Liver Fibrosis Group (SLFG), Hui et al, and Mohamadnejad et al.[3,4] However, only several of models above that have been validated and implemented in clinical situation.[3,4]

Since it has been known that fibrosis was the main problem that lead to high morbidity and mortality in chronic hepatitis, liver fibrosis degree assessment was needed to determine the suitable early treatment.[5] Liver biopsy as an invasive method was still become the gold standard in diagnosing liver fibrosis. The main problem was that clinical presentation of the disease was vary among patients and not always similar to its degree, besides that several patients also refused biopsy procedure.[5] Limitation in biopsy procedure was variation among biopsy result of both intra and interobserver, and also a sampling error. There were also difficulties to get similar quantity in each liver fibrosis degree groups.[6,7] Because of its difficulties during this invasive method, several studies was aimed to find a non-invasive diagnostic instrument for liver fibrosis.[5]

There were a lot of research to develop any non-invasive predictive model that strongly correlate to liver fibrosis stages in recent years. Nowadays, an instrument was found to assess liver fibrosis non-invasively.[4,5,8] This technique was known as ultrasound elastography, commercially known as Fibroscan. This new imaging technique has been proven to assess liver fibrosis degree with high accuracy.[4,8] But, its cost was high and also difficult to become a routine test in clinical practice. This instrument was more sensitive to determine liver fibrosis stages, by calculating liver stiffness to its fibrosis scale in kilopascal unit (kPa).[4,8] Liver fibrosis determined by FibroScan was significantly similar to its real fibrosis stages. This diagnostic accuracy of FibroScan was also higher compared to several biochemistry markers examination. The advantage of FibroScan was that it is done in a short time periode, without any pain, and less misinterpretation risk compared to liver biopsy.[4,7,8,9] There has been previous study to investigate the correlation of liver fibrosis degree with King's score in compared to Fibroscan in chronic Hepatitis C patients.[10] Therefore, we aimed to investigate the correlation between liver fibrosis degree with simple non-invasive method to predict liver fibrosis in chronic Hepatitis B infection based on King's score compared to FibroScan, as a daily clinical reference for chronic Hepatitis B patients.

METHOD

This study was a cross sectional study conducted from February to July 2013 located in Internal Medicine Department Ward and Polyclinic Haji Adam Malik Hospital, Medan, and several gastroenterology clinics in Medan. This study has been approved by North Sumatra Health Research Ethical Committee. Population was all chronic Hepatitis B patients, while sample was chronic Hepatitis B patients in ward and polyclinic Haji Adam Malik Hospital, Medan, and several gastroenterology clinics in Medan. With known proportion of chronic Hepatitis B patients in Indonesia was 0,36 while in this study was approximately 0,11, the sample size of this study was 39 patients. Inclusion criteria was: (1) Male or female aged ≥ 18 years; (2) Chronic Hepatitis B patients with positive viral marker; and (3) Willing to participate by signing informed concent letter. Exclusion criteria was: (1) Human immunodeficiency virus (HIV) or Hepatitis C virus (HCV) coinfection, alcohol consumption of > 30 g/day; and (2) Other cause of chronic Hepatitis, decompensated liver cirrhosis, and chronic kidney failure patients.

Laboratory examination was done in Clinical Pathology Laboratorium in Haji Adam Malik Hospital, Medan. King's score was a non-invasive examination using variable: age, platelet count, aspartate aminotransferase (AST) level, and international normalized ratio (INR). The formula of this score is:

King's Score = Age (years) x AST (U/L) x [INR / Platelet count (10^9/L)]

King's Score ≥ 16,7 : cirrhosis
12,3 – 16,6 : significant fibrosis
King's Score ≤12,2 : insignificant fibrosis

To measure its diagnostic value, receiving operating characteristic (ROC) curve was used to assess its sensitivity (Se), specificity (Spe), positive predictive value (PPV), negative predictive value (NPV), diagnostic accuracy (DA), positive likelihood ratio (LR+), and negative likelihood ratio (LR-) based on cut off value in its original journal. Analysis was done using SPSS ver 15 software.

RESULTS

Overall, a total of 62 chronic Hepatitis B patients was involved in this study. Clinical characteristic, biochemistry, and liver fibrosis degree is shown in Table 1. Mean patient age was 46 years, consist of 39 male patients (62,9%) and 23 female patients (37,1%). All patients was not in decompensated liver cirrhosis condition. Table 1 showed a lowest and highest level of platelet count (58.000/mm^3 and 417.000/mm^3, respectively), AST level (14 and 124, respectively), and INR (0,64 and 2,62 IU/L, respectively). The FibroScan result showed a lowest and highest score of 3,8 kPa and 67,8 kPa, while King's score showed 0,7 and 88,2, respectively. Liver fibrosis degree based on FibroScan result classified into fibrosis 4 (F4) of 9,7%, absent and mild fibrosis (F0-F1) of 56,5% F3 of 16,1%, and F2 of 17,7% from all patients.

Table 1. Subject characteristic of the study

Variable	n (%)	Chronis Hepatitis B patients
Patient	62 (100)	
Gender		
Male	39 (62,9)	
Female	23 (37,1)	
Age (year)		45,92 (SD 12,60)
Platelet (10^9/L)		230 (SD 85,82)
AST (g/L)		30 (14-124)
INR (IU/L)		1,07 (0,64-2,62)
FibroScan (kPa)		6,1 (3,8-67,8)
King's Score (score)		6,5 (0,7-88,2)
Fibrosis (FibroScan)		
F0-1	35 (56.5)	
F2	11 (17.7)	
F3	10 (16.1)	
F4	6 (9.7)	

AST: aspartate aminotransferase; INR: international normalized ratio

Based on Kolmogorov-Smirnov normality test, age and platelet count were normally distributed (mean, SD), while other data was nor normally distributed (median, min-max measurement). Liver fibrosis degree was based on Fibroscan, presented as number and percentage.

Cut off value of King's score and its formula was based on its original investigation (Cross et al).[10] Cut off value that confirmed cirrhosis was ≥ 16,7 and cut off value to confirm significant fibrosis was ≥ 12,2. Predictive value of this model in identifying significant fibrosis and cirrhosis in chronic Hepatitis B patients was shown in Table 2. Among 27 patients that diagnosed significant fibrosis by FibroScan, 13 patients (48,1%) showed a King's score higher than 12,2. With that score, 68,9% patients could be classified to not develop significant fibrosis.

Cirrhosis cut off value was ≥ 16,7. Five patients (83,3%) that have King's score more than 16,7 from total of six patients was diagnosed to have liver cirrhosis using FibroScan. With King's score more than 16,7, about 98% of patients could be classified to not develop liver cirrhosis. King's score diagnostic value

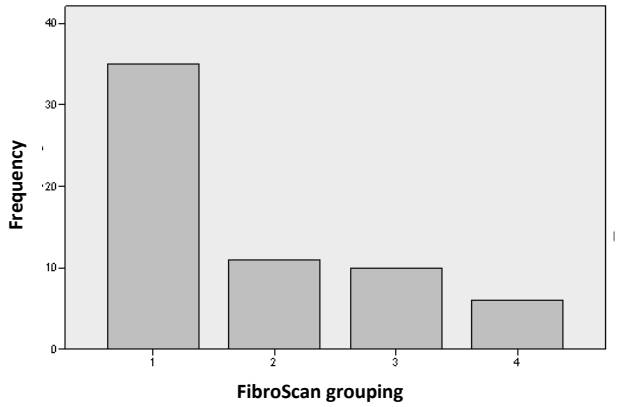

Figure 1. Liver fibrosis degree based on FibroScan

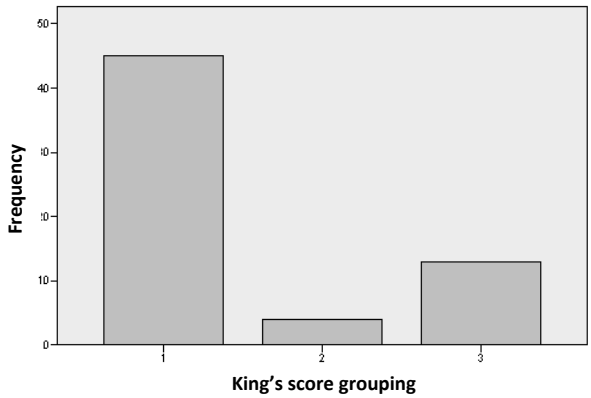

Figure 2. Liver fibrosis degree based on King's score grouping

was further evaluated using area under ROC curve (AUROC), LR (+), LR (-), and diagnostic accuracy. In predicting fibrosis, AUROC was 0,684 for King's score (Figure 3). Otherwise, in predicting significant liver fibrosis, AUROC for King's score was 0,845 (Figure 4). Form this result, although only consist of routine laboratory examination, King's score was accurate and well-predictive in cirrhosis prediction.

Sensitivity, specificity, PPV, NPV, LR (+), LR (-), and accuracy value of this predictive model was shown in Table 2. In Table 2, King's score showed a high predictive value to predict liver cirrhosis, and also a high sensitivity, high NPV, and low LR (-) so that it has lower false negative incidence. Result in King's score showed a 48,1% sensitivity, 88,6% specificity, 76,5% PPV, 68,9% NPV, 0,54 LR (+), 0,53 LR (-), and 70,96% accuracy to identify significant fibrosis in chronic Hepatitis B patients. King's score also showed a 83,3% sensitivity, 85,7% specificity, 38,5% PPV, 98% NPV, 0,98 LR (+), 0,96 LR (-), and 85,48% accuracy to identify cirrhosis in chronic Hepatitis B patients.

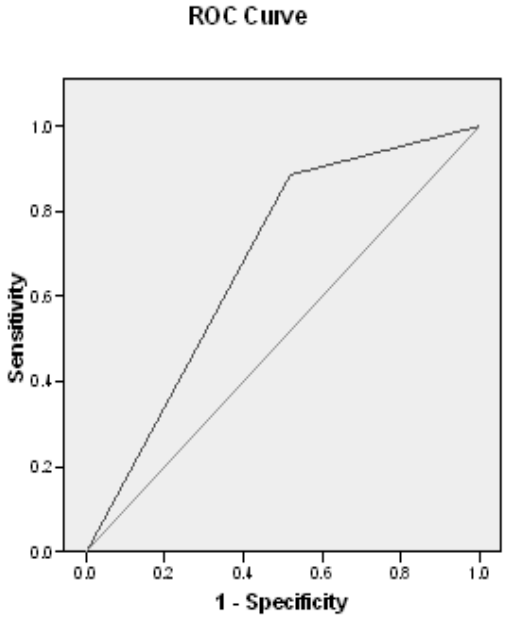

Figure 3. ROC curve of King's score in predicting significant fibrosis in chronic Hepatitis B patients

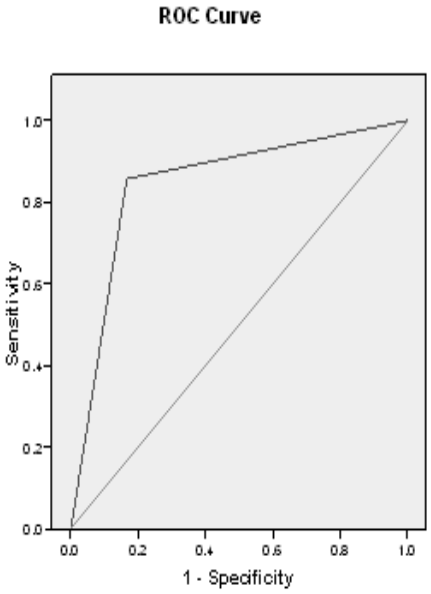

Figure 4. ROC curve of King's score in predicting liver cirrhosis in chronic Hepatitis B patients

Table 2. Predictive value of King's score model as predictive model of significant fibrosis in chronic Hepatitis B patients.

Model	Cut-off (significant fibrosis)	Significant Fibrosis FibroScan		Sen (%)	Spe (%)	PPV (%)	NPV (%)	AUROC	LR +	LR -	Accuracy (%)
		F2-4 n = 27	F0-1 n = 35								
King's Score	≥ 12,2	13	4	48,1	88,6	76,5	68,9	0,684	0,54	0,53	70,96

Sen: sensitivity; Spe: specificity; PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio; AUROC: area under the ROC curves.

Table 3. Predictive value of King's score model as predictive model of liver cirrhosis in chronic Hepatitis B patients.

Model	Cut-off (cirrhosis)	Sirosis FibroScan		Sen (%)	Spe(%)	PPV (%)	NPV (%)	AUROC	LR +	LR -	Accuracy (%)
		F4 n = 6	F0-3 n = 56								
King's Score	≥ 16,7	5	8	83,3	85,7	38,5	98	0,845	0,98	0,96	85,48

Sen: sensitivity; Spe: specificity; PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio; AUROC: area under the ROC curves.

DISCUSSION

There were several previous non-invasive diagnostic model in chronic Hepatitis that have been published. Most of those diagnostic model was used in chronic Hepatitis C patients and only a few in chronic Hepatitis B patients.[11] Although two last study of FibroTest in chronic Hepatitis B patients showed a 0,77 and 0,78 in AUROC value, those model was using unroutine laboratory examination, such as haptoglobin, A2M, and apolipoprotein A1. Its complexity and cost reduce its utility in daily practice.[12]

Several predictive model that design for chronic Hepatitis B patients was already proposed, but this study was still have several unique factors. First, SLFG model was designed and validate only for HBeAg positive patients with ALT between 2 and 10 times from upper limit of normal (ULN), while Mohamadnejad et al proposed a formula that only suitable for HBeAg negative patients.[11] Hui et al only recruited patients with HBV DNA > 10^5 copy/mL and ALT between 1,5 and 10 from upper limit of normal. In current study, patients recruited was all patients with chronic Hepatitis B without considering its treatment, HBeAg level, ALT, and HBV DNA level. Therefore, this study result was more applicable for chronic Hepatitis B patients with wider coverage.[10,12,13]

Second, this predictive model of King's score was based in routine laboratory examination. Platelet count, AST, and INR was a routine test that available widely in clinical settings, so there were no need of extra laboratory examination.[10,11,12,13] Previous study by Kun Zhou et al showed that accuracy of diagnostic model that consist of routine test compared to specific test such as HA and A2M showed that SLFG model and Hepascore was better in identify significant fibrosis than Forns score and APRI, but the result was insignificant for advanced fibrosis and liver cirrhosis.[12,14,15,16,17] This result showed that specific test could increase its sensitivity to predict early fibrosis process. Otherwise, unroutine test in daily practice was reduce its utility for standardization, validation, and routinely difficult.[14]

Third, King's score was easy to calculate. Several previous model, except APRI, consist of complex formula that need a calculator in algoritm calculation.[9,12] This simplicity of King's score and APRI showed that it is clinically easier to be applied. But, APRI that previously investigated in chronic Hepatitis C patients having one of its indicator, AST, to be proven insignificant for fibrosis incidence in chronic Hepatitis B patients, according to Kun Zhou et al.[12] This was the explanation why APRI has a lower AUROC compared to King's score.[9,12]

On the other hand, there were several limitations in this study. In this study, not all patients was undergo liver biopsy, and liver fibrosis degree was only based on FibroScan (transient elastography), although, not shown in this report, ten patients was undergo liver biopsy with similar result to FibroScan result.[8] In Kun Zhou et al, liver biopsy is one of their limitation too by explaining that liver biopsy was not the gold standard because of the possibility in sampling error and observer variability. A prospective analysis result was also claimed that the risk of liver biopsy failure was > 7 times higher than any diagnostic marker.[8,12,18] To reduce variability and subjectivity, the use of laparoscopic biopsy, FibroScan, or validating non-invasive test could help the reliability of liver biopsy as gold standard. Other limitation is that this study result was validate in the same population and in small coverage population.

In Asia countries, chronic Hepatitis B was the majority of all chronic liver disease. The main purpose of identifying fibrosis degree in those patients was to identify eligble patients for antiviral therapy.[19] Based on Asian-Pacific Guideline in Chronic Hepatitis B Management, liver biopsy was indicated for patients aged > 40 years with ALT < 2x ULN and HBV DNA > 20.000 IU/mL (HBeAg-positive) or > 2000 IU/mL (HBeAg-negative). Patients with significant fibrosis was the main candidate for antiviral therapy. Based on that guideline, if a candidate have been undergo FibroScan, liver biopsy could be skipped. In patients with normal ALT and FibroScan result < 6,0 kPa, no therapy was indicated, < 7,5 kPa was observed, and > 12 kPa should be considered to received therapy.[4,15,19]

Although most of non-invasive predictive model could not accurately assess liver fibrosis degree

because of different fibrosis stages among patients, those predictive model was having a good accurate value in predict significant fibrosis. The main role of predictive model was to reduce liver biopsy procedure for significant fibrosis and liver cirrhosis identification, but not for totally replace liver biopsy.[11,12,13,14] Using optimized cut-off core form King's score, it is expected that further livver biopsy needs wa reduced. Furthermore, a combination of several predictive model and invasive diagnostic technique could bring this diagnostic tools into higher level.[10] Combination of both FibroScan and King's score was an intersting method in chronic Hepatitis B patients management. But it has been known that, in daily clinical practice, priority should be given into model that have been validate in large scale study, because of its accuracy could be interfered by different etiologies, populations, and methods.[10,12]

CONCLUSION

King's score has the ability to predict cirrhosis (fibrosis grade 4) in chronic Hepatitis B patients with high accuracy, so that patients with King's score ≥ 16,7 did not need to undergo liver biopsy. Otherwise, for significant fibrosis, this model did not show an accurate result. King's score as non-invasive predictive model for liver cirrhosis in chronic Hepatitis B patients have a high accuracy. A further study was needed to validate this result in a larger scale with different population.

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