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Liver Cirrhosis Investigation Using Abdominal Ultrasound as Gold Standard Test and Some Bioclinical Markers with Different Levels of Diagnostic Accuracy in Chronic Liver Disease Patients between 1990 and 2004 at Teaching Hospital of Kinshasa, Democratic Republic of the Congo

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Abstract

Liver cirrhosis (LC) is an ultimate phase of chronic liver disease. The information from the abdominal ultrasound (aUS) is one of complementary biological and clinical tests of LC assessment in the lack of liver biopsy. The aim of this study was to compare levels of diagnostic accuracy of some bio-clinical markers for LC detection using an abdominal ultrasound as a surrogate Gold standard. This was a mixed approach of consecutive patients treated for gut diseases between 1990 and 2004 at Lomo Center. LC diagnosed by aUS and confirmed by histopathology was compared to LC diagnosed by Bioclinical tests under ROC, Chi-Square, and Logistics regression (for accuracy diagnosis, Sensitivity, Specificity, AUC, and kappa) at $p < 0.05$. Out all aged 47.8 ± 14.3 years, 71% men and 29% women with sex ratio of 3M:1W were evaluated. The prevalent aUS LC cirrhosis was 43.5%. Only excessive alcohol intake

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(aOR = 3.5; 95%CI 1.4 - 8.8), leg oedema (aOR = 5.3; 95% CI 2.2 - 12.8), and icicle sign (aOR = 15.1; 95% CI 5.2 - 44) were the most important and significant independent determinants of aUS LC. For more, only ERS ≥ 60 mm/1st H (aOR = 10.5; 95% CI 1.3 - 82.4; P = 0.025), AST ≥ 60 IU/L (aOR = 10.4; 95% CI 1.3 - 84), indirect bilirubin ≥ 2 mg/dL (aOR = 6.7; 95% CI 1 - 44.7), prothrombin < 60% (aOR = 12; 95% CI 1.7 - 86.8), haemoglobin < 10 gr/dL (aOR = 17; 95% CI 1.4 - 202), and NLR ≥ 3 (aOR = 38.4; 95% CI 3.2 - 456) were the most significant and important independent determinants of aUS LC. The non-invasive aUS combined with the current clinical spectrum and biomarkers might be used as a surrogate Gold standard test for the management of chronic liver disease in poor Central Africa.

Subject Areas

Internal Medicine

Keywords

Ultrasound, Liver Cirrhosis, Haematological and Biochemical Tests, Diagnostic Performance, Central Africa

1. Introduction

The importance of liver in the metabolism and the haemostasis is very well established whereas Liver cirrhosis (LC), a public health issue worldwide, is an ultimate stage of chronic liver disease [1] [2] [3]. The burden and the underlying causes of LC were reported 4 years ago worldwide: the prevalence of LC had increased 74.53% from 1990 to 2017 with ASR increasing 0.75 per year in emerging countries (middle-high and high socio-demographic index in particular). In older publications from France, the prevalence of LC is estimated between 2000 and 3300 cases per million inhabitants, with an annual incidence of 150 to 200 cases per million, the number of deaths estimated at 1500 per year, and main causes such as excessive Alcohol intake (50% to 75%), Hepatitis virus C infection (15% to 25%), and Hepatitis B virus infection (5%) [4] [5] [6]. In developing countries in general [7] and in DR Congo (DRC) in particular [8], more particularly in Africa, this condition seems to be linked to Viral Hepatitis, chronic alcoholism and undernutrition [9]. Before 1990, the management (etiological, diagnostic, assessment report, medical decision, and monitoring) of LC in DRC was based exclusively on medical interview, physical/clinical examination and rare laboratory data (biomarkers). The introduction of abdominal ultrasound (aUS) in Kinshasa has profoundly changed the diagnostic strategies for LC.

Based on high diagnostic accuracy of aUS to detect LC in comparison with liver biopsy/Golden, [10], its information is a useful supplement to the clinical and laboratory workup in the LC first line in the poor DR Congo [11]. Indeed, pathologists and liver biopsy are not available for the diagnosis of cirrhosis [12].

Thus, this study was initiated with the aim at identifying and assessing the diagnostic performance of LC-related behaviour risks, symptoms, signs, haematological and biochemical test compared to aUS surrogate Gold standard.

2. Material and Methods

2.1. Study Setting and Design

This was a mixed (secondary analysis, cross sectional, imaging, series) approaches of consecutive patients treated for chronic liver disease according the flowchart (Figure 1). The secondary analysis retrospectively collected demographics and Bioclinical data from the medical records of patients treated between January 1, 1990 and December 31, 2004 at the gastroenterology unit of the department of internal medicine, University Clinics of Kinshasa (CUK), municipality council of Lemba, city of Kinshasa province, DRC. Were eligible (target population), the patients attending consecutive series of follow up for different liver conditions in the same period and the 3 settings of the study period.

2.2. Study Population

The study population concerned all patients Liver cirrhosis in the city of Kinshasa. The sampling was exhaustive to include all consecutive patients was logically considered (no calculated size in a huge clinical population ≥ 30 patients for epidemiological studies).The following clinical variables of interest were preceded: age, gender, abdominal pain, abdominal bloating, physical asthenia, jaundice, fever, melena, collateral circulation, clinical hepatomegaly, liver pain, firm consistency of the liver; the irregular surface of the liver, sharp edge, prehepatic dullness, declining dullness; wave sign, icicle sign, and ascites.

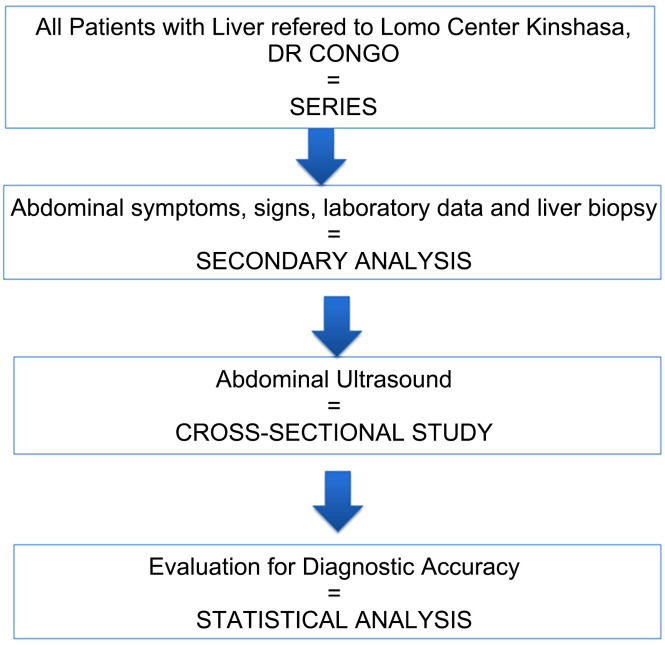


Figure 1. Flow chart of the mixed analysis.

The following blood tests from the routine laboratory methods (circulating biological/haematological and biochemical measures or biomarkers) were also considered: haemoglobin, haematocrit, white cells count, erythrocyte rate sedimentation (ERS), prothrombin, liver transaminases activities (AST and ALT), total bilirubin, direct bilirubin, indirect bilirubin, total protein, albumin, and fibrinogen.

All aUS examinations were performed within 1 week of the liver histopathology from the Service of Anatomopathology, Faculty of Medicine, University of Kinshasa, DRC, using Prosound SSD-5000SV (Aloka Co., Wisconsin, USA) equipped with a 3.5 - 5.0 MHZ convex probe at LOMO Center, Kinshasa Limete, DRC. The aUS findings made by the first author (SMM unaware of the aUS, clinical, and biomarkers diagnoses) during the cross-sectional study were reviewed by two seniors in imaging research (LMB and MLTSH, co-promotors of the first author) among 30 patients (perfect inter-observer variability, validity, and objectivity).

Using ultrasongraphy, the LC was defined by aUS score graded according to the gallbladder, the right kidney, the liver echogenicity, and the spleen (disharmonious changes in the size of the liver, finely bumpy liver contours, macronodules easier to visualize than micronodules/1 to 3 mm, hepatic parenchyma being homogeneous or heterogeneous).

2.3. Statistical Analysis

Systematic cleaning of the file data was carried out by LOMO Team throught of the completeness test and the consistency test for the harmonization and validation of the data. To assess the diagnostic accuracy of each clinical and biological parameter, Receiver-Operating characteristics (ROC) curves were obtained and the areas under the ROC curves (AUC with standard error and 95% confidence intervals/CI) were computed using the sensitivity, the specificity, and the Kappa static. The univariate analysis used a contingency table to compare the proportions by Chi-square while the Student-Test compared the means of different quantitative variables between 2 groups (group for LC as the dependent variable vs. group of clinical and biomarkers/independent variables) with Odds-ratio (OR) and 95% CI. Then, after excluding some confusion variables out the equation, the multivariate Logistics binary regression analysis was to identify the most important and significant independent determinants(adjusted OR and 95%CI) of LC. All analyses were computed by the Statistical Package for Social Sciences (SPSS) software (New York, USA), Version 25 (NEW YORK, USA). $P < 0.05$ was the difference for statistical significance.

2.4. Ethical Considerations

The data was collected anonymously and confidentially. The privacy and personality of the respondents were safeguarded. The three fundamental principles of ethics were respected at the time of the study: the principle of respect for the person, that of beneficence and that of justice.

3. Results

In total, the data of 200 patients were reviewed.

3.1. General Characteristics of Patients

Demographic data

The study population was divided into 142 men and 58 women with a sex ratio close to 3 Men: 1 Woman. The mean age was 47.8 ± 14.3 years (range 16 and 82). Out of the democraphics, risky behavior, and the clinical data, Table 1 presents some significant ($P < 0.05$) univariate associated clinical factors of aUS LC in the study population such as male sex, age ≥ 45 years, presence of abdominal bloating, leg oedema, excessive alcohol intake, resonant tympanic abdomen, wave sign and icicle sign. However, the rest of clinical variables of interest were not ($P > 0.05$) associated with aUS LC (results not presented).

Table 1. Univariate associated clinical factors of aUS LC in the study population.

Variable	aUS LC % (n)	OR (95% CI)	p
Age			
< 45 years	30.4 (24/79)	1	
≥ 45 years	52.1 (63/121)	17.0 (1.2 - 25.0)	0.002
Gender			
Female	29.3 (17/58)	1	
Male	49.3 (70/142)	2.4 (1.2 - 4.5)	0.007
Abdominal Bloating			
No	38.3 (49/128)	1	
Yes	52.8 (38/72)	1.8 (1.01 - 3.2)	0.033
Leg oedema			
No	36.1 (52/144)	1	
Yes	62.5 (35/56)	3.0 (1.6 - 5.6)	0.001
Excessive Alcohol intake			
No	36.0 (31/86)	1	
Yes	49.1 (56/114)	1.7 (1.1 - 3.0)	0.044
Resonant Tympanic Abdomen			
No	37.2 (51/137)	1	
Yes	57.1 (36/63)	2.3 (1.2 - 4.1)	0.007
Wave sign			
No	38.2 (60/157)	1	
Yes	62.8 (27/43)	2.7 (1.4 - 5.5)	0.003
Icicle sign			
Non	39.5 (70/177)	1	
Yes	73.9 (17/23)	4.3 (1.6 - 11.5)	0.002

After excluding confounders (age, sex, resonnant tympanic abdomen and wave sign) out the equation of the multivariate logistics binary regression analysis, only excessive alcohol intake (adj. OR ≈ 4; P < 0.01), leg oedema (adj. OR = 5; P < 0.0001) and icicle sign (adj. OR = 15; P < 0.0001) were the most important and significant independent determinants of aUS LC in the study population (Table 2). Thus, the prediction of aUS LC at clinics university of Kinshasa might be under the following equation Y = −2.783 + 4x Excessive alcohol intake (yes) + 5X Leg oedema (yes) + 15X Icicle sign (yes).

3.2. Independent Discriminant Clinical Spectrum

After adjustment in multivariate analysis of logistic regression, excessive alcohol intake (aOR: 3.5 95% CI: 1.4 - 8.8), leg oedema (aOR: 5.3 95% CI: 2.2 - 12.8) and the jaundice sign (aOR: 15.1 95% CI: 5.2 - 44) were independent factors predicting liver cirrhosis (Table 2).

3.3. Diagnostic Accuracy/Performance of Circulating Hematologic and Biochemical Biomarkers

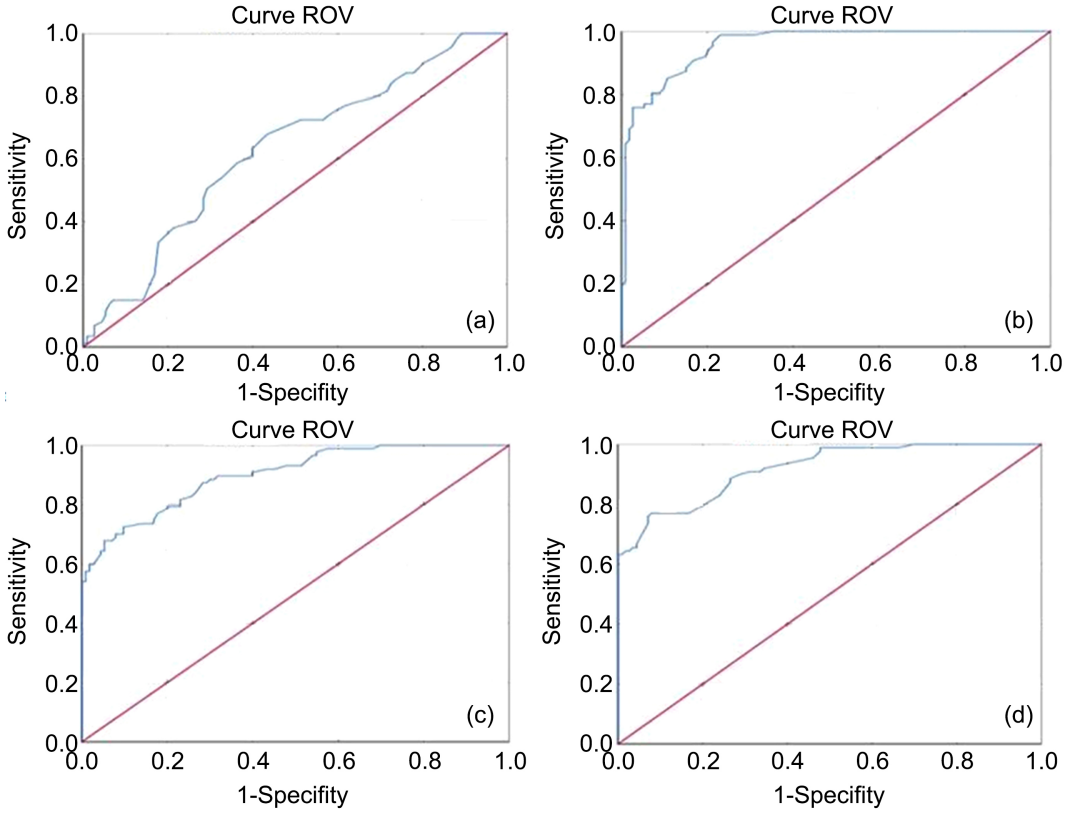
Except for hematocrit and the significant and high diagnostic accuracy detecting aUS LC were age ≥ 45 years, ERS ≥ 60 mm/1st H, indirect bilirubin ≥ 2 mg/dL, prothrobin < 60%, hemoglobin < 10 g/dL, white cells count < 4000/mm^3, lymphocyte < 20%, albumin < 30 g/L, total protein < 70 g/L, fibrinogen < 150,000 mg/dL, AST ≥ 60 IU/L, ALT ≥ 55 IU/L, GGT ≥ 45 IU/L, neutrophils ≥ 80% and NLR ≥ 3 (Table 3).

3.4. ROC Curve of Biomarkers Predicting the Diagnosis of Liver Cirrhosis

Figures 2(A)-(D) show the ROC curve of biomarkers predicting the diagnosis of Liver cirrhosis.

Table 2. Independent discriminant clinical spectrum of the presence and the absence of liver cirrhosis (LC) among all patients.

Independent variable	β	ES	aOR (95%CI)	P
Excessive alcohol Intake				
No			1	
Yes	1.261	0.464	3.5 (1.4 - 8.8)	**0.007**
Leg oedema				
No			1	
Yes	1.666	0.450	5.3 (2.2 - 12.8)	**<0.0001**
Jaundice sign				
No			1	
Yes	2.716	0.544	15.1 (5.2 - 44)	**<0.0001**
Intercept	−2.783	0.452		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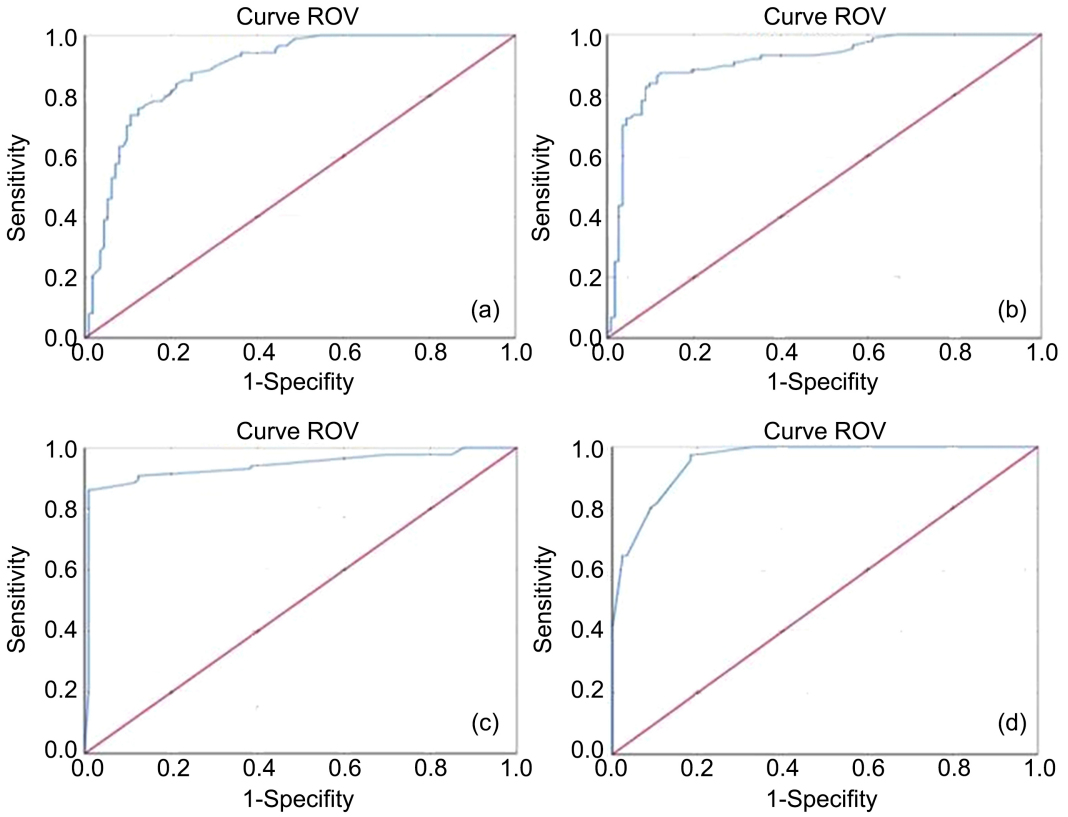
(A)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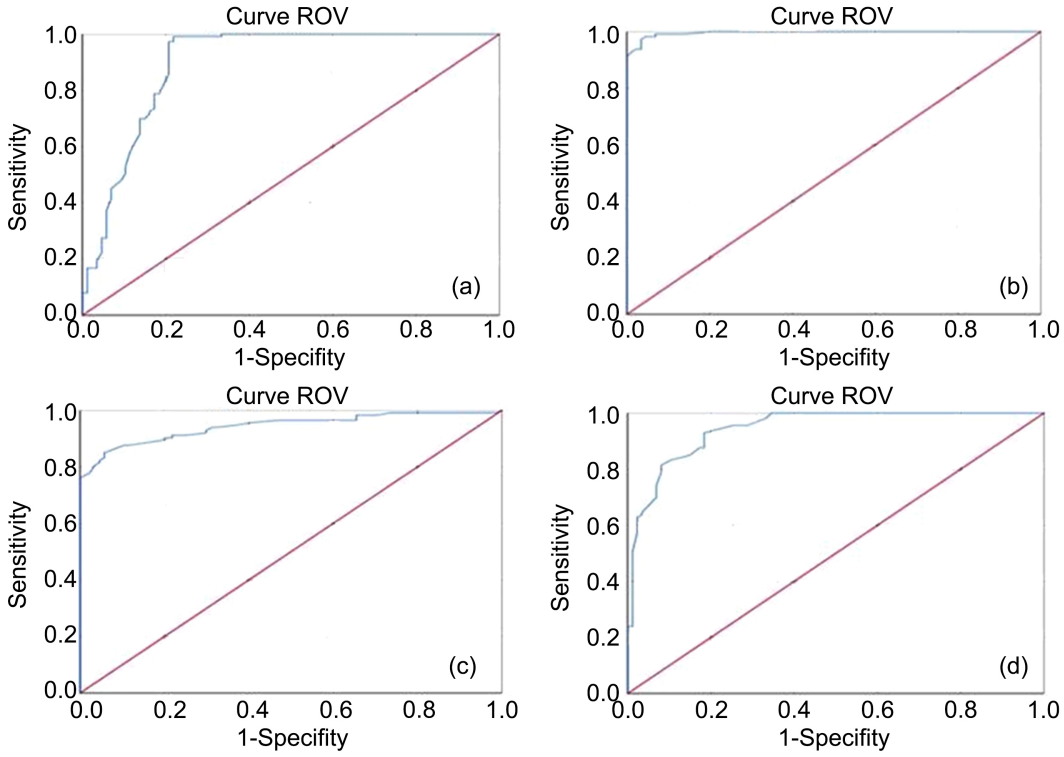

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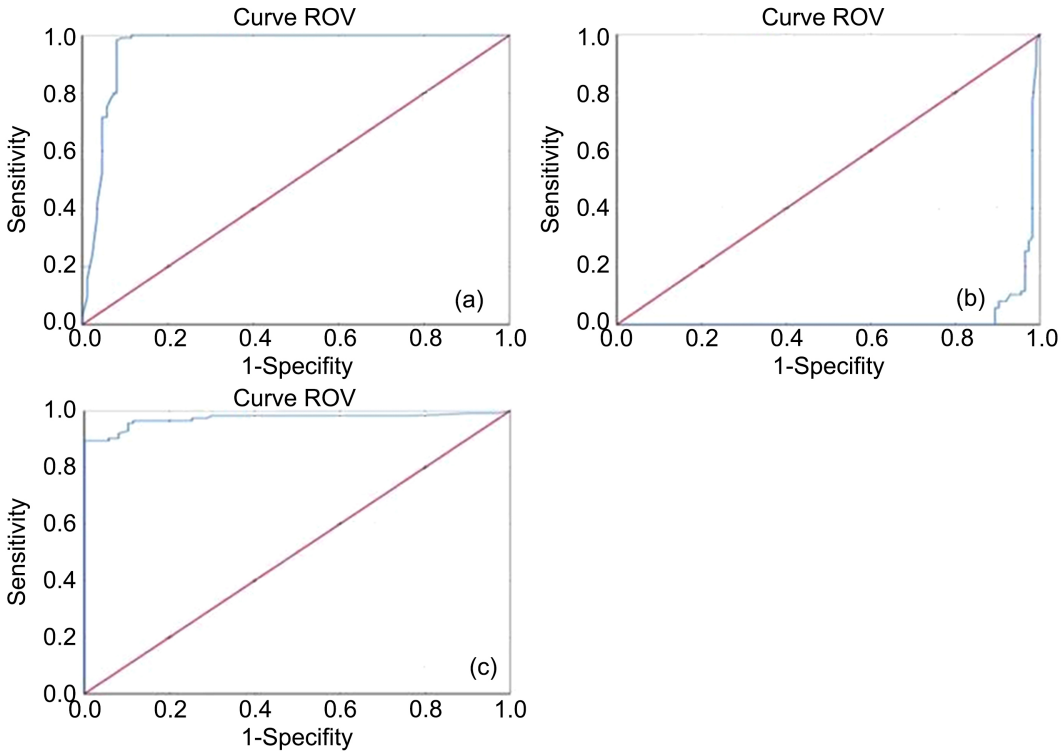

(D)

Figure 2. (A) ROC curve of biomarkers: (a) Age ≥ 45 years; (b) Neutrophile ≥ 80%; (c) ERS ≥ 60 mm/1st H; (d) GGT ≥ 45 IU/L; (B) ROC curve of biomarkers: (a) AST ≥ 60 IU/L; (b) ALAT ≥ 55 IU/L; (c) Indirect Bilirubin ≥ 2 mg/dL; (d) Hemoglobin < 10 gr/Dl; (C) ROC curve of biomarkers: (a) White Cells < 4000/mm^3; (b) Lymphocytes < 20%; (c) Prothrombine < 60%; (d) Albumine < 30 gr/L; (D) ROC curve of biomarkers: (a) Total Protein < 70 gr/L; (b) Fibrogen < 150 mg/dL; (c) NLR ≥ 3.

Table 3. Diagnostic accuracy/performance of circulating hematologic and biochemical biomarkers for Liver Cirrhosis (LC) compared to abdominal ultrasound (aUS) among all patients suffering chronic liver disease using ROC.

Variable	Sensitivity (%)	Specificity (%)	Kappa	AUC (95%CI)	P
Age ≥ 45 years	70.0	57.0	0.200	0.629 ± 0.040 (0.552 - 0.706)	0.002
Neutrophils ≥ 80%	72.4	97.0	0.718	0.957 ± 0.042 (0.933 - 0.981)	0.0001
ESR ≥ 60/mm³	88.5	70.0	0.566	0.899 ± 0.021 (0.857 - 0.941)	0.0001
GGT ≥ 45 (IU/L)	83.0	76.0	0.570	0.918 ± 0.019 (0.881 - 0.954)	0.0001
AST ≥ 60 (IU/L)	70.1	90.0	0.606	0.889 ± 0.023 (0.844 - 0.934)	0.0001
ALT ≥ 55 (IU/L)	84.0	90.0	0.745	0.912 ± 0.022 (0.889 - 0.954)	0.0001
Indirect Bilirubin ≥ 2 (mg/dL)	91.0	88.0	0.525	0.940 ± 0.020 (0.901 - 0.979)	0.0001
Hemoglobin < 10 (g/dL)	96.0	82.0	0.783	0.955 ± 0.013 (0.942 - 0.968)	0.0001

3.5. Univariate Analysis at Comparing Mean Values of Biomarkers between

Indeed, the mean levels of hemoglobin, white cells count, lymphocytes, prothrombin, fibrinogen, albumin and total protein were significantly ($P < 0.05$) lower in the presence of aUS LC than thoses in the absence of aUS LC whereas the mean levels of ERS, neutrophils, NLR, GGT, AST and ALT were significantly ($P < 0.05$) higher in the presence of aUS than those in the absence of aUS LC (Table 4).

3.6. Independent Discriminant Laboratory Data of Liver Cirrhosis

In not including neutrophils and lymphocytes within the equation. After excluding confounders (age, white cells count, total protein, albumin, fibrinogen, GGT and ALT), out the equation of the multivariate Logistic binary regression analysis only ERS ≥ 60 mm/1st H (adj. OR ≈ 11; $P < 0.055$), AST ≥ 60 IU/L (adj. OR = 10; $P < 0.059$), indirect bilirubin ≥ 2 mg/dL (adj. OR = 7; $P < 0.05$), prothrombin < 60% (adj. OR = 12; $P < 0.05$), hemoglobin < 10 g/dL (adj. OR = 17; $P < 0.05$) and NLR ≥ 3 (adj. OR = 38) were the most important and significant independent determinant of aUS LC (Table 5).

Thus, the prediction of aUS LC at Clinics University of Kinshasa might be under the following equation $Y = -6.911 + 11 \times$ ERS ≥ 60 % (yes) $+ 10 \times$ AST ≥ 60 IU/L (yes) $+ 7 \times$ indirect bilirubin ≥ 2 mg/dL (yes) $+ 12 \times$ prothrombin < 60% (yes) $+ 17 \times$ hemoglobin < 10 g/L (yes) $+ 38 \times$ NLR ≥ 3 (yes).

Table 4. Univariate analysis at comparing mean values of biomarkers between the presence (n = 27) and the absence of Liver Cirrhosis (LC).

Variables of interest	Presence of LC Mean ± SD/ESM	Absence of LC Mean ± SD/ESM	p-value
Age (years)	51.5 ± 13.2	44.9 ± 14.4	<0.001
Hemoglobin (g/dL)	7.8 ± 1.8	12.1 ± 1.6	<0.0001
White cells (/mm3)	3799 ± 2884	9747 ± 6748	<0.0001
Neutrophils (%)	83 ± 13.2	29.9 ± 23.2	<0.0001
Lymphocytes (%)	13.8 ± 5.9	73.9 ± 21.7	<0.0001
ESR(mm/1stH)	163.9 ± 83.2	40.8 ± 3.9	<0.0001
Prothrobin (%)	36 ± 16.5	76.1 ± 16.8	<0.0001
Albumin (g/L)	15.7 ± 10.4	42.9 ± 12.4	<0.0001
GGT (IU/L)	71.4 ± 22.2	31.8 ± 13.4	<0.0001
AST (IU/L)	118.3 ± 72	34.2 ± 4.8	<0.0001
ALT (IU/L)	147 ± 90.6	31 ± 4.3	<0.0001
Indirect Bilirubin (mg/dL)	6 ± 2	1.4 ± 1.1	<0.0001
Total protein (g/L)	15.5 ± 2.3	79.3 ± 15.4	<0.0001
Fibrinogen (mg/dL)	26 ± 3.3	137.5 ± 13	<0.0001
NLR	7.1 ± 3	0.6 ± 0.07	<0.0001

Table 5. Independent discriminant laboratory data of the presence and the absences of Liver Cirrhosis (LC) among all patients.

Independent Variable	β	ES	aOR (95% CI)	p
ERS				
<60 mm/1st H			1	
≥60 mm/1st H	2.354	1.050	10.5 (1.3 - 82.4)	0.025
AST				
<60 IU/L			1	
≥60 IU/L	2.338	1.068	10.4 (1.3 - 84)	0.029
Indirect Bilirubin				
<2 mg/dL			1	
≥2 mg/dL	1.898	0.970	6.7 (1 - 44.7)	0.049
Prothrombin				
≥60%			1	
<60%	2.485	1.009	12 (1.7 - 86.8)	0.014
Hemoglobin				
≥10 g/dL			1	
<10 g/dL	2.832	1.263	17 (1.4 - 202)	0.025
NLR				
<3			1	
≥3	3.648	1.263	38.4 (3.2 - 456)	0.004
Intercept	−6.911	1.482		<0.0001

4. Discussion

The present study compared the levels of diagnostic accuracy of some Bioclinical markers for Liver cirrhosis (LC) detection using a abdominal ultrasound as a surrogate Gold standard because of its very high sensitivity [13] and the increasingly rare indications for liver biopsy for histopathological study [14].

4.1. Demographic Data and Risky Behaviour

In this study population, the male vulnerability was very marked for aUS LC. The sex ratio was 3 men: 1 woman. Indeed, the male vulnerability was also reported in Italian patients from Europe [15], some sub-African countries [16], and in Pakistan from Asia [17]. Excessive alcohol consumption, one of the significant independent determinants of aUS LC in the present study, was also reported higher risk for liver cirrhosis in men than in women from Italy [18].

This study from DRC and the studies from other African countries demonstrated elsewhere in Africa [19], patients with hepatic cirrhosis and primary liver cancer are young adults [20] [21]. In Europe, on the other hand, LC patients are older around 60 years [2] [13]. However, Shaista *et al.* in Pakistan from Asia, found an average age of 39.54 ± 12.77 years [22] and younger than a mean age of 51.5 ± 13.2 years of LC patients from the DRC study and age of 45 years from Republic of Central Africa [23] where men do more drink excessive alcohol/binge than women do [24].

4.2. Bioclinical Parameters Discriminating in Hepatic Cirrhosis

There are many controversies on clinical examination of the liver and some blood liver tests related to LC with and without aUS [25] [26] [27] [28]. The researchers from the present work and those from the literature (Singini REF) do analyse age, gender, abdominal pain, abdominal bloating, physical asthenia, jaundice, fever, melena, collateral circulation, clinical hepatomegaly, liver pain, firm consistency of the liver; the irregular surface of the liver, sharp edge, prehepatic dullness, declining dullness; wave sign, icicle sign, liver surface nodularity, ascites, and blood tests such as haemoglobin, haematocrit, white cells count, erythrocyte rate sedimentation(ERS), prothrombin, liver transaminases activities (AST and ALT), total bilirubin, direct bilirubin, indirect bilirubin, total protein, albumin, and fibrinogen.

Non-disturbance of hepatic tests (AST and ALT) has already been reported in Africans with liver cirrhosis in Bangui in the Central African Republic [29]. Hung Sub Lee et al in Korea, in a study on the prediction of liver cirrhosis by ultrasound and usual blood biomarkers in 2010, also recorded non-disturbance of liver transaminases activities [30].

4.3. Diagnostic Performance of Biomarkers to Detect Liver Cirrhosis versus aUS

Thanks to the evidence from the literature [31] [32] [33] [34] and to our know-

ledge, the present study used ROC and multivariate logistics binary analysis to show high to excellent diagnostic accuracy of age ≥ 45 years, haemoglobin < 10 gr/dL, white cell count < 4000/mm^3, neutrophils ≥ 80%, lymphocytes < 20%, ERS ≥ 60 mm/1st H, albumin < 30 gr/L, GGT ≥ 45 IU/L, AST ≥ 60 IU/L, ALT ≥ 55 IU/L, indirect bilirubin ≥ 2 mg/dL, total protein < 70 gr/L, fibrinogen < 150 mg/dL, NLR ≥ 3 to detect aUS LC.

4.4. Strengths and Limitations of the Study

The present study had the following strengths: LC might be predicted by routine blood tests without special equipment, experienced physicians reviewed non-invasive and affordable cost aUS, liver biopsy obtained, findings of 30 patients to objectify the subjective sonographic images, mean measures during the cross-sectional approach, and mathematical models with DRC-specific cut-offs of analysed biomarkers.

However, the present study had limitations to some degree as follows: a retrospective secondary approach without calculated sample size/number of patients relatively small, lack of sequential measurements of representative values during a follow-up, Coupling Doppler to ultrasound, and gray-scale would have allowed the definition of portal hypertension and portal vein thrombosis [35] in hepatic cirrhosis [36].

5. Conclusions

The non-invasive aUS combined with the current clinical spectrum and biomarkers might be used as a surrogate Gold standard test for the management of chronic liver disease in poor Central Africa.

The development of the model consisting of ERS ≥ 60 mm/1st H, AST ≥ 60 IU/L, indirect bilirubin ≥ 2 mg/dL, prothrombin < 60%, haemoglobin < 10 gr/dL, and NLR ≥ 3 may be useful at identifying aUS LC with a high level of accuracy in daily practice Clinics of University of Kinshasa, DRC in combining interview, clinical examination, ultrasound and blood biomarker testing to improve LC management.

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Author's Contributions

SMM and ANN designed and analyzed the statistical data for the study. MLT, SMN, CMN, SMF, ATW, VTN, ANO, ICD, EM and LMB supervised the study. All authors have read and approved the final and revised version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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