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Research Article

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A Pilot Scoring Model of Hepatocellular Carcinoma Screening in Liver Cirrhosis Based on Clinical Symptom and Daily Laboratory Parameter

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Abstract

Background: *Hepatocellular carcinoma is persistent in developing countries. However, it remains difficult to diagnose due to lack of access to radiological and specific tumours marker examination.*

Aim: *To build a simple scoring model for hepatocellular carcinoma screening in liver cirrhosis patients by using clinical and standard laboratory examinations in the rural areas.*

Methods: *A cross-sectional, analytical observational study was done to collect data of liver cirrhosis and hepatocellular carcinoma patient. A total of 96 hospitalized patients with liver cirrhosis were included in the study. Multivariate regression analysis was conducted to determine independent factors related to hepatocellular carcinoma. The score of each variable was calculated using the (B/SE)/lowest B/SE formula with strong discrimination power. A scoring model was developed and assessed in terms of sensitivity and specificity. The probability of the total score was calculated using the formula 1/1+exp(-y).*

Results: *Fourteen (14.6%) patients were hospitalized with hepatocellular carcinoma. The model constructed from the ten potential variables. Three variables were included in the model; high platelet-to-lymphocyte ratio (PLR) ≥150 (p<0.001), high AST-to-ALT ratio (de Ritis ratio) ≥2 (p= 0.020), and presence of hematemesis/melena (p=0.011). Based on the formula, each variable scored 1. The sensitivity and specificity of the model for diagnosis of HCC in liver cirrhosis at a cut-off point ≥1.5 was 85,7% and 79,3%, respectively (AUC=88,4%). The probability was 0.3%, 4.0%, 36.1%, and 88.4%, following the total score of 0, 1, 2, and 3, respectively.*

Conclusion: *The existence of hepatocellular carcinoma in liver cirrhosis patients can be detected based on this pilot scoring system for rural areas.*

Keyword: Hepatocellular Carcinoma, Cirrhosis, De Ritis Ratio, Scoring Models

1. Introduction

Liver cancer is the sixth most common cancer diagnosis and the second leading cause of cancer-related death in the world. Ninety percent of all liver tumours are hepatocellular carcinoma (HCC). Hepatocellular carcinoma is highly prevalence in Asia and sub-Saharan Africa [1]. In 2020, Asia reported 72.5% of the world's cases of HCC, although hepatitis C and hepatitis B infections slightly declined by eradication and prevention programs. The prevalence of non-hepatitis-related HCC is rapidly increasing in Asia, making overall HCC still high [2]. In Indonesia, HCC is the fourth most common malignancy in males, with an age-standardized incidence rate of 13.4 per 100.000. Data from National Hospital Dr. Cipto Mangunkusumo Jakarta reported 29,4% of HCC patients have a meager survival rate (138 days) [3].

The prognosis of HCC is highly linked to the tumour stage. The best patient survival is seen in patient diagnoses at an early stage. The curative treatment of early-stage HCC yields more than 70% of 5-year survival rates. In contrast, there is no option for curative treatment in advanced HCC [4].

Since cirrhosis is present in up to 90% of HCC, the global guideline recommends HCC screening for these at-risk patients [1]. The surveillance recommendation by American Association for the Study of Liver Disease HCC uses ultrasonography scanning

with or without alpha-fetoprotein (AFP). However, the screening program for HCC is limited by low utilization rates. HCC screening to date is a sub-specialist scope, the inherent limitation of ultrasound scanning base surveillance [5]. On the other hand, most of the cirrhosis patient stays outside tertiary centers. They are generally followed up by primary care physicians [4].

To date, the GALAD score (gender, age, AFP-L3, AFP, and des-gamma carboxyprothrombin [DCP]) for HCC detection seen resolved the ultrasound scanning-based limitation. Compared to ultrasound scanning, GALAD model was superior in detecting early HCC [6]. However, laboratory examinations of AFP, AFP-L3, and DCP were not widely available, mainly in rural areas. Asia Pacific Association for Study of Liver (APASL) recommends using another PIVKA-II along with AFP, but in Indonesia, the test is unavailable [7]. A simple, affordable method for developing countries is a key to achieving early diagnosis and treatment of HCC, thus improving the survival rate. We aimed to develop a simple screening model based on clinical symptoms and routine laboratory examination for HCC detection.

2. Method

2.1. Ethical Clearance

This study is part of the study with ethical clearance no: 997/UN14.2.2.VII.14/LT/2021 approved by Research Committee of Faculty of Medicine of Udayana University/Sanglah General Hospital.

2.2. Population and Study Design

This cross-sectional study involved 96 patients with liver cirrhosis: 14 with hepatocellular carcinoma and 72 without hepatocellular carcinoma. We identified adult patients with liver cirrhosis through a computerized database from November 2021 until January 2022. To determine eligibility, we manually review their medical record. Inclusion criteria were age >18 years and the presence of cirrhosis. Cirrhosis was either clinically or radiological diagnosed. Clinical diagnosis based on ascites, jaundice, encephalopathy, variceal bleeding, splenomegaly, and spider angioma. Radiological diagnosis based on inhomogeneity of liver tissue, liver parenchymal nodule, ascites, splenomegaly in ultrasonography examination or patient with METAVIR F4 [8].

Hepatocellular carcinoma was diagnosed based on the presence of underlying chronic disease (hepatitis B or C related liver disease, liver cirrhosis), tumour marker (AFP ≥200 ng/mL and tendency to increase, or PIVKA-II ≥ 40mAU/mL), and radiological examination (hyper vascular in arterial phase and washout in portal vein phase, or delayed phase of CT-scan or MRI three phase). We excluded patients with other malignancies.

2.3. Demographic, Clinical, and Laboratory Parameter of the Study

Demographic characteristics included age, gender, and body mass index. Age is classified into two categories, ≥65 years and <65 years. The clinical symptom was the presence of ascites, hematemesis/melena, or oesophageal varices at admission. The ethology of liver cirrhosis was determined by serology examination. The presence of HBsAg was defined as hepatitis B infection, anti-HCV reactive was defined as hepatitis C, and otherwise defined as non-hepatitis. A routine laboratory examination was extracted from the medical record. Leucocytosis was defined as leukocyte count ≥11 x 10^3/µL, anemia if the patient has a hemoglobin level <10 g/dL, and thrombocytopenia if a platelet count <150 x 10^3/µL. Serum AST and ALT were classified as normal and abnormal (>2 times the upper limit). Abnormal bilirubin level was defined as >1.2 for total bilirubin and >0.5 for direct bilirubin. Abnormal INR if >1.1, abnormal PPT if >12.7 seconds, and abnormal aPTT if >34.7 seconds. Hypoalbuminemia was defined as albumin level <3.5 g/dL. High BUN level is defined as >23 mg/dL. Normal natrium serum was 136-145 mmol/L.

2.4. Liver Cirrhosis-Related Indicator and Laboratory Ratio

We identify five laboratory ratios associated with cirrhosis and hepatocellular carcinoma; we compute the ratio according to the original formula using Ms. Excel. The ratio included was platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte ratio (NLR), AST/ALT ratio (de Ritis ratio), AST to platelet ratio index (APRI), and the sum of neutrophil and basophil count (N-B sum). The abnormal laboratory ratio cut-off was determined based on the literature. High PLR if ≥150 high NLR if ≥4, and abnormal N-B sum if >4.6 10^6/µL [9,10]. De Ritis ratio ≥2 reflected other causes of liver disease or alcoholic hepatitis [11].

The liver function indicator included in this study was Model for End-stage Liver Disease (MELD), Child-Turcotte-Pugh (CTP), and Fibrosis-4 (FIB-4). MELD is divided into two categories, ≥12.5 and <12.5. CTP score was classified into CTP-C and non-CTP-C. Meanwhile, FIB-4 was not categorized. Overall, we try to identify potential indicators applicable in rural areas.

2.5. Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences ver.21.0. Continuous measurements are presented as mean ± standard deviation in normal distribution data, otherwise are presented as median (minimum-maximum value). Comparative analysis was done with either an independent T-test or Mann-Whitney U-test as appropriate. The categorical measurement is presented as frequencies. Bivariate analysis was conducted by using Chi-square or Fisher's exact test. The variable with p-value <0.1 was considered for entering the multivariate analysis.

Logistic regression for multivariate analysis was used backward LR method. Odd ratios (OR) are calculated to assess the strength of association with hepatocellular carcinoma. All significant variables ($p<0.05$) of the final model were included in the final scoring system. The quality of the formula was evaluated by Hosmer and Lemeshow test for calibration and the area under the curve (AUC) for discrimination. The scores were calculated using B/SE/lowest B/SE formula. The following formula 1/1+exp(-y) was used to obtain the probability of the total score. To determine the optimal cut-off of the scoring system, analysis with receiver operating characteristic (ROC) was obtained.

3. Result

Of the 96 patients with liver cirrhosis in Prof. Dr. I.G.N.G Ngoerah General Hospital were included. Fourteen patients (14.5%)

were diagnosed with hepatocellular carcinoma. The mean age of the patients was 53.06 ± 11.0. The characteristics of the patients are shown in Table 1. The 76 patients (79.2%) had evidence of hepatitis infection based on serology examination (21.9% had positive anti-HCV and 57.3% had positive HBsAg), and the rest 20.8% had negative serology results.

Characteristics	HCC (n=14)	Non-HCC (n=82)	p-value
Demographic			
Age (years)	58.79 ±12.867	52.72 ±10.492	0.056
Gender (M: F)	9:5	57:25	0.758
Body mass index (kg/m^2)	21.0 (10.5-27.0)	22.2 (10.5-28.0)	0.613
Ethology			
Hepatitis C	2 (21.4%)	18 (22.0%)	0.787
Hepatitis B	9 (64.3%)	46 (56.1%)	
Non-Hepatitis	2 (14.3%)	18 (22.0%)	
Clinical symptoms n (%)			
Ascites	10 (71.4%)	29 (35.8%)	0.012†
Hematemesis/Melena	10 (71.4%)	31 (35.8%)	0.019†
Esophageal varices	3 (42.9%)	47 (61.0%)	0.433
Blood examination result			
Leukocytes, 10^3/µL	9.38 (5.01-23.51)	6.71 (1.59-34.37)	0.019**
Haemoglobin, g/dL	9.72 ±2.664	10.36 ±3.371	0.505
Haematocrit, %	29.45 (13.40-40.90)	30-50 (6.80-48.10)	0.648
RDW, %	19.04 ±3.60	16.04 ±2.84	0.001*
Platelet, 10^3/µL	233.0 (106.0-551.0)	110.5 (1.0-463.0)	0.001**
AST, U/L	103.1 (12.1-723.5)	47.5 (13.3-520.0)	0.003**
ALT, U/L	45.1 (6.9-155.1)	31.4 (8.8-467.8)	0.233
Total bilirubin, mg/dL	2.1 (0.8-27.9)	1.9 (0.17-36.3)	0.593
Direct bilirubin, mg/dL	1.3 (0.41-20.3)	1.1 (0.09-23.7)	0.304
Indirect bilirubin, mg/dL	0.8 (0.20-7.56)	0.9 (0.08-15.3)	0.848
aPTT, second	31.0 (23.0-56.8)	33.5 (23.3-81.2)	0.625
PPT, second	14.4 (10.7-34.5)	15.8 (9.8-57.9)	0.347
INR	1.2 (0.94-2.49)	1.2 (0.85-4.26)	0.651
Albumin, g/dL	2.6 (1.86-3.68)	2.9 (1.23-5.00)	0.461
BUN, mg/dL	24.8 (13.6-85.5)	16.9 (3.00-57.9)	0.010**
Natrium, mmol/L	129.0 (123.0-144.0)	135.0 (103.0-146.0)	0.179
Laboratory ratio			
Platelet-to-lymphocyte (PLR)	163.7 (38.5-697.92)	86.89 (0.69-712.3)	0.000**
Neutrophil-to-lymphocyte (NLR)	6.24 (2.44-13.56)	3.52 (0.55-301.0)	0.005**
AST/ALT	2.38 (0.44-11.71)	1.44 (0.47-268.0)	0.001**
APRI	1.67 (0.28-9.05)	1.35 (0.96-200.3)	0.626
Neutrophil-Basophil Sum	7.61 (3.67-19.55)	4.12 (3.67-19.5)	0.004**
Liver Function Indicator			
MELD	18.0 (6.0-32.0)	18.0 (7.0-37.0)	0.680
CTP Score	8.50 (7.0-14.0)	8.0 (5.0-14.0)	0.147
FIB-4	5.49 (0.64-18.4)	4.43 (0.49-226.0)	0.406

*independent samples t-test, **Mann-Whitney U-test, †Chi-square

Table 1: Patient Characteristics

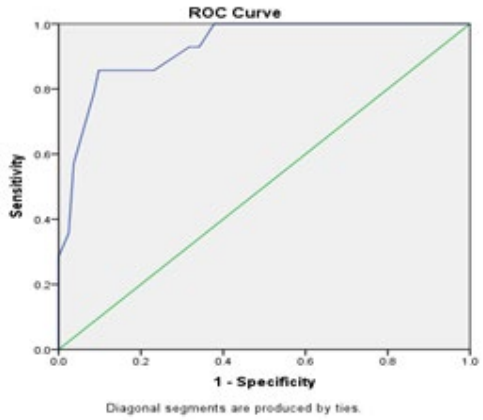
We collected the variable potentially as an indicator of HCC in liver cirrhosis patients. The variables included were demographic data, evidence of hepatitis infection, clinical symptoms at admission, and routine laboratory examination. We identify a laboratory ratio and liver function score related to HCC or liver cirrhosis. A total of 12 variables were included in the bivariate analysis (Table 2). Among all data considered for statistical model analysis, the data completeness was 100%.

Characteristics	HCC (n=14)	Non-HCC (n=48)	p-value
Age, n (%)			
≥65 years	5(35.7%)	9(64.3%)	0.030**
<65 years	9(11.0%)	73(89.0%)	
Ascites			
Yes	10(25.6%)	29(74.4%)	0.012*
No	4(7.1%)	52(92.9%)	
Hematemesis/melena			
Yes	10(24.4%)	31(75.6%)	0.019*
No	4(7.3%)	51(92.7%)	
Leukocytes count			
≥11 x10^3/µL	6(25.0%)	18(75.0%)	0.107
<11 x10^3/µL	8(11.1%)	64(88.9%)	
RDW			
≥14.8	14(21.5%)	51(78.5%)	0.004**
<14.8	0(0.0%)	31(100.0%)	
Platelet count			
≤150 x10^3/µL	4(7.1%)	52(92.9%)	0.015*
>150 x10^3/µL	10(25.0%)	30(75.0%)	
AST			
≥68 mg/dL	9(25.7%)	26(74.3%)	0.019*
<68 mg/dL	5(8.2%)	56(91.8%)	
BUN			
≥23 mg/dL	7(21.9%)	25(78.1%)	0.219
<23 mg/dL	7(10.9%)	57(89.1%)	
PLR			
≥150	10(43.5%)	13(56.5%)	0.000**
<150	4(5.5%)	69(94.5%)	
NLR			
≥ 4	12(26.1%)	34(73.9%)	0.003*
<4	2(4.0%)	48(96.0%)	
AST/ALT			
≥2	10(32.3%)	21(67.7%)	0.001**
<2	4(6.2%)	61(93.8%)	
N-B sum			
≥4.6 x10^6/µL	12(24.0%)	38(76.0%)	0.006*
<4.6 x10^6/µL	2(4.3%)	44(95.7%)	

*Chi-square, **Fisher-exact

Table 2: Bivariate analysis of all potential variables in predicting HCC

In the final model built on the discovery data set, it was found three variables were significant; the presence of hematemesis/melena (p=0.011), AST/AST ≥2 (p=0.020), and PLR ≥150 (p<0.001). Table 3 shows the estimated coefficients (SE) and OR (95% confidence interval, CI) from multivariate analysis. To determine the quality of analysis, the Hosmer and Lemeshow test was performed with a p-value>0.05. The area under the ROC curve (AUC) of the final model showed a total of 92.8% with a p-value <0.001 (Figure 1). Scoring system build including only the significant variable. Following the formula of (B/SE)/lowest B/SE, each variable was scored as 1 (Table 3).



ROC: Receiver operating characteristic; AUC: Area under curve

Figure 1: The ROC Curve of the Final Model of Multivariate Analysis. (AUC: 0.92; p<0.001)

Following the formula of 1/1+exp (-y), the probability of HCC in liver cirrhosis patients was 0.3%, 4.0%, 36.1%, and 88.4% for the total score of 0,1,2, and 3 (respectively). The sensitivity and specificity of the pilot scoring for diagnosis of HCC in liver cirrhosis at a cut-off point ≥1.5 was 85,7% and 79,3%, respectively (AUC: 0.884; SE:0.042; p <0.001; 95%CI:0.801-0.967) (Figure 2).

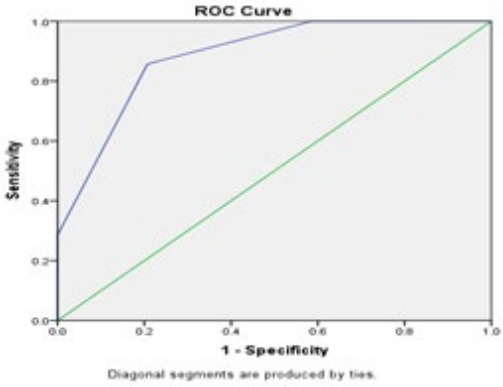


Figure 2: The ROC curve to determine the optimal cut-off for the scoring system. The cut-off score ≥1.5 provided the best accuracy with sensitivity of 85,7% and specificity of 79,3% (AUC: 0.884; SE:0.042; p <0.001; 95%CI:0.801-0.967). ROC: Receiver operating characteristic; AUC: Area under the curve

Variables	B	SE	Exp (B)	95% CI		Score
				Upper	Lower	
H-M	2.609	1.029	13.585	1.809	102.029	1
AST/ALT ≥2	2.009	0.889	8.161	1.402	47.514	1
PLR ≥150	3.536	1.014	34.319	4.704	250.407	1
AST ≥68	1.571	0.835	4.813	0.938	24.708	-

Table 3: The Final Model of Multivariate Analysis with Logistic Regression, from total of 10 Variables, along with its Scoring Points

Scoring model of HCC screening for liver cirrhosis patients			
Patient's name			
No	Yes	No	Patient's score
1.	Does the patient have coffee-ground vomiting and/or black watery stool	1	0
2.	Serum aspartate aminotransferase (AST) per alanine aminotransferase (ALT) equal or more than 2	1	0

3.	Platelet to lymphocyte ration (PLR) equal or more than 150	1	0
Total			
Interpretation	Total Score	Probability having HCC	
Unlikely	0	0.3%	
	1	4.0%	
Probable	2	36.1%	
Possible	3	88.4%	

Table 4: The Final Model of the New Scoring System for Screening Hepatocellular Carcinoma in Liver Cirrhosis Patient

4. Discussion

Hepatocellular carcinoma arises in the context of liver cirrhosis. The risk HCC in cirrhosis patients is not uniform and related to the etiologic of cirrhosis. The prognosis of liver cancer is poor, and the mortality rate of HCC increase continuously [12]. Especially in advanced stage HCC who are only eligible for palliative treatment have survival rates less than one year [5]. In early-stage HCC (Barcelona Clinic Liver Cancel [BLCC] stage 0-A) have a 69.0-86.2% overall survival rate following radical treatment [13]. Early detection in high-risk patients is the key to improving survival rates.

This study showed several variables ranging from demographic characteristic, underlying etiologies, clinical symptom, and routine laboratory parameters, which can be used as a simple scoring system to detect HCC in cirrhosis patients. The presence of hematemesis melena, de Ritis ratio dan platelet to lymphocyte ratio were significantly related to HCC. We develop a screening card that applicable in primary health care, hence improving the detection of HCC in rural areas.

Most HCC arises on the background of chronic inflammation. The inflammatory cell has been reported to be associate with tumour initiation, progression, and clinical treatment response. The recent evidence shows that neutrophils play an essential role in HCC pathogenesis, including tumorigenesis, local tumour progression, and metastasis. Elevated neutrophil count relates to advanced disease, poor prognosis, and poor response to therapy in HCC [9]. Neutrophilia leads to increase production of neutrophil-derived cytokines, including vascular endothelial growth factor (VEGF), which promotes angiogenesis [14]. Lymphocytes are recruited to engage in cell-mediated tumour response. Peripheral lymphopenia impairs the host's anti-tumour response and conducts tumour progression and metastasis. In HCC, low lymphocyte count and high monocyte were associated with a lower survival rate [9].

This study found that a high platelet-to-lymphocyte ratio significantly indicated HCC in liver cirrhosis. Platelets have contributed to tumour angiogenesis. Activation of platelet induces secretion of platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and platelet-derived microparticles (PMPs) that promotes angiogenesis. Activated platelets react with endothelial cells to promote coagulation and enhance tumour and endothelial cell adhesion. As mentioned above, lymphocyte also has a significant role in an anti-tumour activity, and its depletion reflects the impairment of anti-tumour response. Natural killer and cytotoxic T cells are the critical mediators of anti-tumour response. At the same time, B cell activation results tumour-infiltrating lymphocytes for anti-tumour activity [10]. Therefore, the platelet-to-lymphocyte ratio (PLR) has risen in active tumour cells.

AST and ALT are essential liver enzymes widely used to assess liver function. AST is primarily found in the mitochondria of liver cells. Meanwhile, ALT is mainly found outside of the mitochondrial cell. AST and ALT alone can impact by many non-tumour-related factors, including coronary heart disease, drugs, and chronic hepatitis. The combination of AST and ALT as AST/ALT ratio is more valid than used as a single predictor. AST plays an essential role in aerobic glycolysis due to its ability to move nicotinamide adenine dinucleotide hydrogen into mitochondria through malate-aspartate shuffling. Cancer cells have a high proliferative status than normal cells, thus, they have a higher rate of aerobic glycolysis. ALT also plays an important role in glutaminolysis and pyruvate production in tumour cells. Therefore, more serum AST than ALT detects in high proliferative cells (cancer cells). Accordingly, the AST/ALT ratio could reflect the metabolic state of cancers cell, possibly indicating the progression and growth of the tumour [12]. This current study showed the role of AST/ALT in detecting HCC. The previous study reports an unusually elevated AST/ALT ratio (greater than 5) in hepatic neoplasia [15].

Many patients with HCC have portal hypertension due to tumour thrombus in the portal vein or liver cirrhosis related. GI bleeding in patients with HCC is mainly caused by variceal rupture, rarely by the invasion of tumour cells into the duodenum or gaster [16,17]. The risk of GI bleeding in patients with liver cancer was two-hundredfold compared to the remaining population (15.2% vs. 0.69%) [18]. The recent meta-analysis reports an increasing rate of gastrointestinal invasion by HCC cells. It is due to GI tract segment, and the liver are anatomically related. HCC in the right lobe typically invade the duodenum, while those in the left lobe usually invade the stomach. There was a higher prevalence of gastrointestinal bleeding (49.74%) than any other presentation, such as abdominal pain (26.9%) and abdominal mass (3.55%) [19]. Our study found that 43.4% of patients with HCC had hematemesis/melena at admission. This symptom was significantly related to HCC in cirrhosis patients.

Patients from rural regions and lower-income households has

more advanced tumor stages at diagnosis and significantly higher HCC mortality. These disparities likely reflect suboptimal access to consistent, high-quality liver disease care, including HCC surveillance [7]. The current study could address the barrier of HCC surveillance. This simple model screening provides a new comprehension of using routine laboratory data and clinical symptoms to detect HCC in liver cirrhosis. The screening card is easy for primary care physicians and uses a parameter available widely in rural areas with reasonable specificity.

Nevertheless, this study has several limitations need to be highlighted. Firstly, a small sample size study and conducted in a single center. Secondly, the model is not able to determine the severity of HCC. Thirdly, we did not provide complete physical examination data on this model. Therefore, a multicentre study with well-defined HCC severity and examination results should be conducted to validate this pilot model.

5. Conclusion

A number of clinical symptoms and routine laboratory examinations available in primary health care may provide information about HCC development in liver cirrhosis patients. This novel scoring system may benefit the surveillance program of HCC and primary care physicians to detect HCC in liver cirrhosis patients.

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