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The efficacy of biomarkers in the diagnosis of acute kidney injury secondary to liver cirrhosis

Yuwei Yang, MB[a], Bin Ge, MM[b], Yan Liu, MM[b], Jiafu Feng, MD[a,*]

Abstract

This study is to investigate the role of neutrophil gelatinase-associated lipocalin (NGAL), cystatin C (CysC) and creatinine in the diagnosis of acute kidney injury (AKI) secondary to liver cirrhosis.

A total of 825 patients (including 540 liver cirrhosis patients and 285 healthy controls) were enrolled. Liver cirrhosis patients were further subdivided into AKI secondary to liver cirrhosis group (AKI group, 210 patients) and simple liver cirrhosis group (LC group, 330 patients). Serum NGAL/urine NGAL (sNGAL/uNGAL), and serum creatinine (sCr) levels as well as estimated glomerular filtration rates were measured. The diagnostic performances of these indicators in AKI secondary to liver cirrhosis were evaluated.

The levels of sNGAL, uNGAL, CysC and sCr in the AKI group were significantly higher than those of LC and healthy control groups. However, the eGFR and c-aGFR of AKI group were significantly lower. With the progression of AKI (AKI-S1→AKI-S2→AKI-S3), the levels of sNGAL, uNGAL, CysC and sCr increased gradually, while the levels of c-aGFR and eGFR decreased gradually. The sNGAL, uNGAL and CysC were positively correlated with sCr (r = 0.638, 0.635, and 0.650), but negatively correlated with c-aGFR (r = -0.617, -0.606 and -0.655). However, eGFR had a negative correlation with sCr (r = -0.711), but a positive correlation with c-aGFR (r = 0.736). ROC curve analysis showed that the area under the curve for uNGAL was the largest (0.976), followed by sNGAL (0.967). The diagnostic efficacy of uNGAL and sNGAL in AKI group were 0.907 and 0.870, and the risk degrees were OR = 54.524 and 5.115, respectively.

NGAL might perform better than sCr and CysC in the diagnosis of AKI secondary to liver cirrhosis, while uNGAL might be a better indicator than sNGAL in AKI diagnosis.

Abbreviations: AKI = acute kidney injury, AUC = area under the curve, CysC = cystatin C, KDIGO = Kidney Disease Improving Global Outcomes, NGAL = neutrophil gelatinase-associated lipocalin, sCr = serum creatinine, sNGAL = serum NGAL, uNGAL = urine NGAL.

Keywords: acute kidney injury, creatinine, cystatin C, Liver cirrhosis, neutrophil gelatinase-associated lipocalin

1. Introduction

Liver cirrhosis is an advanced outcome of various chronic liver diseases. Due to impaired immune function and/or altered hemodynamics, liver cirrhosis is often accompanied by functional kidney injury.[1] This injury may be reversed if early treatment is promptly administered.[2] On the contrary, the progression of kidney impairment and altered hemodynamics may significantly increase the vasoactive substances such as renin-aldosterone, vasopressin and endothelin, which leads to the aggravation of liver cirrhosis and causes hepatorenal syndrome.[3] Acute kidney injury (AKI) occurs when there is severe liver cirrhosis.[4] The incidence of AKI in hospitalized patients with decompensated liver cirrhosis is as high as 20% to 30%.[5] The most common types of AKI include prerenal azotemia, hepatorenal syndrome and acute tubular necrosis, with incidence rates of 68%, 25%, and 33%, respectively.[5,6] The mortality of patients with liver cirrhosis is closely related to the severity of renal impairment.[7–9] Therefore, accurate and early diagnosis of renal dysfunction in patients with liver cirrhosis is essential.[10]

According to the recommendations of the Kidney Disease Improving Global Outcomes (KDIGO)[11] and the International Club of Ascites (ICA),[12] the diagnostic criteria for AKI are usually defined based on serum creatinine (sCr). Since sCr detection has the advantages of low cost and simple operation, it has been widely used in clinical laboratories. In clinical practice, physicians also use sCr-based glomerular filtration rate (eGFR) to assess renal function. Although sCr is a routine and important

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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indicator of renal function, it still has some limitations. For example, its level is affected by diet, age, gender, bilirubin levels, muscle mass and tubular excretion or malignancy, and it has limited potential for the diagnosis of early kidney injury. Therefore, when using sCr to diagnose AKI in patients with cirrhosis, it may lead to missed diagnosis, which may further cause treatment failure.[10]

Neutrophil gelatinase-associated lipocalin (NGAL), a protein covalently bound to gelatinase, has molecular weights of approximately 25 kD.[13] NGAL is expressed by immune cells, hepatocytes and renal tubular cells under various disease states.[14] Urine and plasma/serum NGAL are strong independent predictors of AKI, which are the first recommend potential biomarker of AKI by acute dialysis quality initiative of the 10th international consensus conference.[15]

Cystatin C (CysC) is a member of the family of cysteine protease inhibitors with a low molecular weight (13 kD), which is produced by all nucleated cells. Due to its small size and basic pH, and non-adherence to plasma proteins, CysC can be freely filtered by the glomerulus and subsequently reabsorbed and catabolized in proximal tubular cells.[16] Additionally, CysC level is independent of age, sex, or muscle mass.[17] Therefore, Cys C level in plasma or serum mainly depends on the GFR, and it is an endogenous marker for kidney filtration function recommended by FDA in 2002.[18]

Thus, NGAL and CysC may become two potential markers for renal function evaluation in patients with liver cirrhosis. In recent years, some studies have confirmed that NGAL and CysC are superior to sCr in the diagnosis of AKI secondary to liver cirrhosis.[19,20] Here, in this study, the serum NGAL (sNGAL), urine NGAL (uNGAL), and serum CysC were measured in liver cirrhosis patients. Then, the eGFR was calculated based on serum CysC. Finally, we evaluated the diagnostic efficacy of sNGAL and uNGAL, CysC and its eGFR, and sCr and its c-aGFR in the diagnosis of secondary AKI in liver cirrhosis patients.

2. Materials and methods

2.1. Ethics

Written informed consent was obtained from every patient and the study was approved by the ethics review board of Mianyang Central Hospital (Reference Number S2014048 and S2018085).

2.2. Subjects

A total of 540 hepatitis B virus patients receiving treatment in Mianyang Central Hospital (Mianyang City, China) from January 2015 to December 2018 were enrolled into this study. All patients with liver fibrosis were diagnosed by percutaneous liver biopsy or abdominal ultrasound, according to consensus guidelines of the Asian-Pacific Association for the Study of the Liver.[21] Ultrasound evaluation was based on liver size, bluntness of liver edge, coarseness of liver parenchyma, nodularity of liver surface, size of the lymph nodes around the hepatic artery, irregularity and narrowness of inferior vena cava, portal vein velocity, or spleen size. Finally, the fibrosis index >3.6 was used to differentiate cirrhosis from chronic hepatitis, which was calculated as follows: hepatic artery resistive index/portal vein peak velocity × 100. Among these patients, 210 were diagnosed with AKI secondary to liver cirrhosis (AKI group) and 330 patients were with simple liver cirrhosis (LC group). In the AKI group, 148 were male and 62 were female. Their age ranged from 26 to 88 years, and the average age was 55.3 ± 13.5 years. The inclusion criteria for the AKI group were:

(1) Patients met the criteria in the 2016 Asian Pacific Association for the Study of the Liver guideline.[21]
(2) Patients did not take medications that could cause an impaired renal function or severe cardiopulmonary insufficiency, including immunomodulators, glucocorticoids, and statins.
(3) Patients had no combined primary kidney disease, malignant tumors, blood system disease, neurological disease, autoimmune disease, diabetes, coronary heart disease, hypertension, severe infection or urinary tract infection, or complications.
(4) Patients met the criteria of the 2012 Kidney Disease: Improving Global Outcome (KDIGO) guideline:[11]
    a. the increase in the sCr level of patients within 48 hour was higher than 26.5 μmol/L; or
    b. the sCr level of patients within 7 days was higher than 1.5 times of the baseline value; or
    c. the patients had urine output per hour lower than 0.5 ml/kg and such situation lasted for more than 6 h. According to the above KDIGO guideline,[11] the AKI group was subdivided into AKI-S1 group (112 patients), AKI-S2 group (54 patients) and AKI-S3 group (44 patients). The severity of AKI followed the order: AKI-S1 < AKI-S2 < AKI-S3.
(5) All the patients with liver cirrhosis did not receive surgical treatment before sampling.

In the LC group, there were 229 male patients and 101 female patients. Their age ranged from 21 to 89 years, with an average age of 54.3 ± 12.2 years. The inclusion criteria for the LC group were the same as the inclusion criteria 1), 2) and 3) for the AKI group.

A total of 285 healthy subjects with normal hepatorenal functions and normal urinalysis results were also enrolled and considered as the healthy control group (HC group). In this group, 180 were male and 105 were female. Their age ranged from 23 to 87 years and the average age was 53.7 ± 11.8 years.

2.3. Sample collection

Venous blood (5 mL) was collected from each subject and centrifuged (3000 rpm, 15 min) to isolate the serum. The levels of NGAL, Cr and CysC in the serum were detected within 2 h. Midstream urine (10 mL) from each of the subjects was collected and centrifuged (3000 rpm, 10 min). The supernatant was taken for the detection of uNGAL and uCr within 2 hour.

2.4. Laboratory detection

CysC, sNGAL/uNGAL and sCr were detected using corresponding kits provided by Maccura Biotechnology Company (Chengdu, China). The detections were performed on the LST008 automatic biochemical analyzer (Hitachi, Japan). The uCr was detected using kits provided by Biostec Company (Chongqing, China) on the BioSystems A25 fully automatic specific protein analyzer (BioSystems, Spain).

2.5. eGFR calculation

The eGFR equation was a CysC equation suitable for Chinese developed by our team,[22] and the c-aGFR equation was an

improved MDRD equation suitable for Chinese.[22] The 2 equations were as follows:

$$e^{GFR} = 78.64 \times CysC(mg/L)^{-0.964}$$

$$c-a^{GFR} = 186 \times Cr(mg/dl)^{-1.154} \times Age(years)^{-0.203} \times 0.742(if\ Female) \times 1.233(if\ Chinese)$$

2.6. Statistical analysis

SPSS19.0 (SPSS Inc., Somers, NY) was used to process data. Normality of data was analyzed with one-sample Kolmogorov-Smirnov normality test. Normally distributed measurement data were presented as average ± standard deviation and analyzed by One-way ANOVA. Measurement data that were not normally distributed were presented as median [M (min, max)] and subjected to comparison with multiple independent samples Kruskal-Wallis H test or ordered Jonckheere-Terpstra nonparametric test and their Post Hoc Multiple Comparisons. For correlation analysis, a nonparametric Spearman test was used. ROC curve was used to analyze the diagnostic values of the indicators in liver cirrhosis with AKI. The diagnostic value was represented by area under the curve (AUC). The difference between AUCs was analyzed by DeLong test. Risk analysis of the above six indicators in predicting the occurrence of AKI was performed by a stepwise binary logistic regression method. A P value <.05 was considered statistically significant.

3. Results

3.1. Comparison of indicators among AKI, LC and HC groups

There were no significant differences in age (F=1.014, P=.363) or gender (χ2=3.838, P=.147) among the AKI, LC and HC groups. One-sample Kolmogorov-Smirnov normality test indicated that sNGAL, uNGAL, sCr, CysC, c-aGFR and eGFR levels were of non-normal distribution (z=1.383–6.926, P<.05). Therefore, multiple independent samples Kruskal-Wallis H nonparametric test was used to analyze multi-group differences. The results showed that the differences in the indicators among the three groups were statistically significant (χ2=360.104–424.203, P<.001) (Fig. 1). Compared with LC and HC groups, the sNGAL, uNGAL, sCr and CysC levels of AKI group were significantly higher (z=13.407~20.560, P<0.001), whereas the c-aGFR and eGFR levels of AKI group were significantly lower (z=-13.408—20.558, P<.001). Compared with HC group, LC group had significantly higher sNGAL, uNGAL and CysC levels (z=1.986~8.596, P<.05), whereas significantly lower eGFR levels (z=-8.593, P<.001). However, there were no statistical differences in the sCr and c-aGFR levels between the LC group and HC group

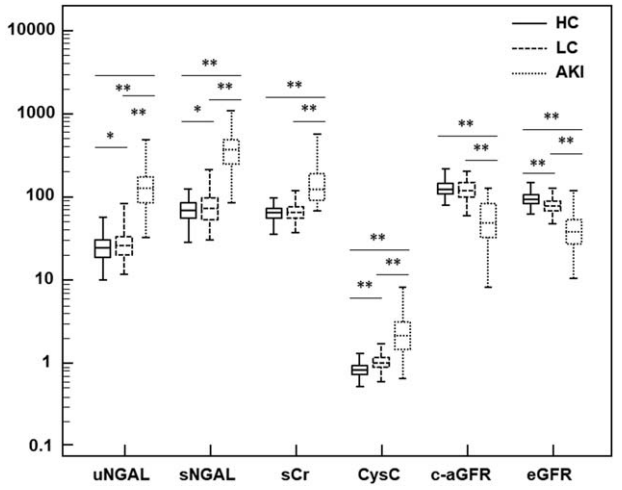

Figure 1. Comparison of indicators among AKI, LC and HC groups. Differences were tested by Kruskal-Wallis H nonparametric test and Post Hoc Multiple Comparisons. $^{**}P$<.001, $^{*}P$<.05. uNGAL (μg/gCr), urine neutrophil gelatinase-associated lipocalin; sNGAL (μg/L), serum neutrophil gelatinase-associated lipocalin; sCr (μmol/L), serum creatinine; CysC (mg/L), cystatin C; c-aGFR (ml/min/1.73m^2), estimated glomerular filtration rate by improved MDRD equation suitable for Chinese; eGFR (ml/min/1.73m^2), estimated glomerular filtration rate by CysC equation suitable for Chinese.

3.2. Comparison of indicators among different AKI subgroups

Ordered Jonckheere-Terpstra nonparametric test results demonstrated that the sNGAL, uNGAL, sCr and CysC levels of AKI patients increased significantly with the progression of AKI (z=4.718~12.715, P<.001), whereas the c-aGFR and eGFR levels decreased with the progression of AKI (z=-12.523 and -10.932, P<.001) (Fig. 2). Compared with AKI-S2 group, the sNGAL, uNGAL, sCr and CysC levels of AKI-S3 group were significantly higher (z=3.089 – 7.475, P<.01), while the c-aGFR and eGFR levels were significantly lower than (z=-7.496 and -6.197, P<.01). The AKI-S2 group had significantly higher sCr and CysC (z=8.637 and 6.799, P<.01) levels, while significantly lower c-aGFR and eGFR (z=-8.329 and -6.799, P<.01) levels than AKI-S1 group. However, there was no statistical difference in uNGAL level (z=1.473, P=.211) and sNGAL (z=1.907, P=.085) between AKI-S2 and AKI-S1 groups.

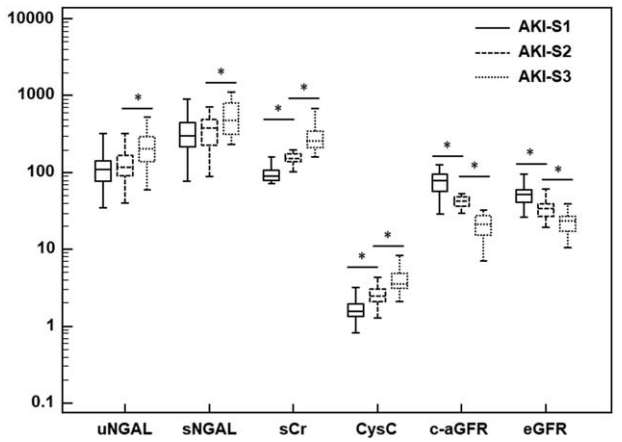

Figure 2. Comparison of indicators among different AKI subgroups (AKI-S1, AKI-S3, and AKI-S3). Trend analysis was performed by Ordered Jonckheere-Terpstra nonparametric test and Post Hoc Multiple Comparisons, $^{*}P$<.01. uNGAL (μg/gCr), urine neutrophil gelatinase-associated lipocalin; sNGAL (μg/L), serum neutrophil gelatinase-associated lipocalin; sCr (μmol/L), serum creatinine; CysC (mg/L), cystatin C; c-aGFR (ml/min/1.73m^2), estimated glomerular filtration rate by improved MDRD equation suitable for Chinese; eGFR (ml/min/1.73m^2), estimated glomerular filtration rate by CysC equation suitable for Chinese.

3.3. Correlation analysis of indicators

Spearman correlation results indicated that sNGAL, uNGAL and CysC levels were positively correlated with sCr level (r = 0.638, 0.635 and 0.650, $P < .001$), but negatively correlated with c-aGFR level (r = -0.617, -0.606 and -0.655, $P < .001$) (Fig. 3). The eGFR level was negatively correlated with sCr level (r = -0.650, $P < 0.001$), but positively correlated with c-aGFR level (r = 0.655, $P < .001$).

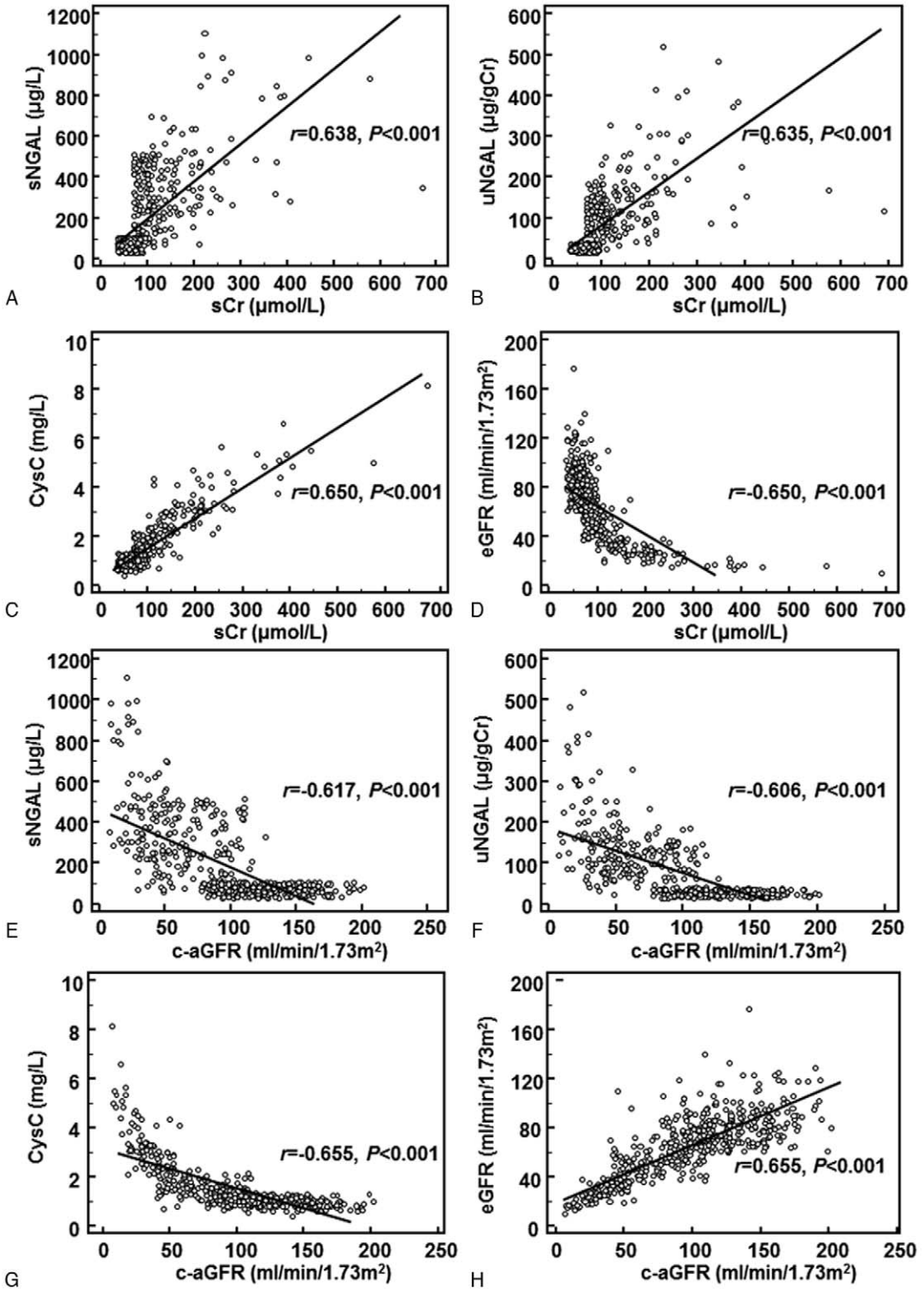

Figure 3. Spearman correlation analysis between the two observed indicators. The correlation between the observed indicators was similar (r: 0.606-0.655, all $P < .001$). A: Correlation of sNGAL and sCr; B: Correlation of uNGAL and sCr; C: Correlation of CysC and sCr; D: Correlation of eGFR and sCr; E: Correlation of sNGAL and c-aGFR; F: Correlation of uNGAL and c-aGFR; G: Correlation of CysC and c-aGFR; H: Correlation of eGFR and c-aGFR. Among them, Fig. A, B, C, and H showed a positive correlation, and Fig. D, E, F, and G showed a negative correlation.

Table 1

Performances of indicators in terms of diagnosis of AKI in patients with liver cirrhosis.

Indicator	AUC (95% CI)	Cutoff value	Se (%)	Sp (%)	YI
uNGAL	0.976 (0.957, 0.989)	41 μg/gCr	97.5 (94.0, 99.4)	93.2 (90.1, 95.7)	0.907
sNGAL	0.967 (0.947, 0.982)	109 μg/L	94.0 (89.5,97.0)	93.0 (89.8, 95.5)	0.870
sCr	0.945 (0.921, 0.964)	77.7 μmol/L	91.5 (86.5, 95.1)	81.0 (76.3, 84.4)	0.725
CysC	0.940 (0.915, 0.961)	1.24 mg/L	92.0 (86.3, 96.3)	91.9 (88.7, 94.3)	0.839
c-aGFR	0.945 (0.921, 0.964)	96.1 ml/min/1.73m^2	89.5 (84.1, 93.6)	83.9 (79.9, 87.5)	0.734
eGFR	0.940 (0.915, 0.961)	63.4 ml/min/1.73m^2	92.0 (87.0, 95.6)	91.9 (88.8, 94.4)	0.839

AKI = acute kidney injury, AUC = area under curve of ROC analysis, c-aGFR = estimated glomerular filtration rate by improved MDRD equation suitable for Chinese, CysC = cystatin C, eGFR = estimated glomerular filtration rate by CysC equation suitable for Chinese, sCr = serum creatinine, Se = sensitivity, sNGAL = serum neutrophil gelatinase-associated lipocalin, Sp = specificity, uNGAL = urine neutrophil gelatinase-associated lipocalin, YI = Youden index. Because eGFR was calculated by CysC and c-aGFR is calculated by sCr, their AUCs were equal.

3.4. ROC curve analysis of the diagnostic values of indicators in AKI secondary to liver cirrhosis

ROC curves for the six indicators are shown in Figure 2. The AUCs for uNGAL, sNGAL, sCr, CysC, c-aGFR and eGFR levels were 0.976, 0.967, 0.945, 0.940, 0.945, and 0.940, respectively (Table 1 and Fig. 4). The differences in AUC between uNGAL and sNGAL were not statistically significant (z = 1.538, P = 0.124). The AUC for uNGAL and sNGAL were significantly higher than those for sCr, CysC, c-aGFR and eGFR (z = 1.992~3.957, $P < .05$). The differences in AUC among sCr, CysC, c-aGFR and eGFR were not statistically significant (z = 0.000~0.371, $P > .05$).

The optimal cutoff value, which was the detection value of each indicator corresponding to the maximum Youden index (YI = Se +Sp-1), of sNGAL, uNGAL, sCr, CysC, c-aGFR and eGFR was 109 μg/L, 41 μg/gCr, 77.7 μmol/L, 1.24 mg/L, 96.1 ml/min/1.73m^2 and 63.4 ml/min/1.73m^2, respectively. The uNGAL had the best diagnostic performance (YI 0.907), followed by sNGAL (YI 0.870) (Table 1).

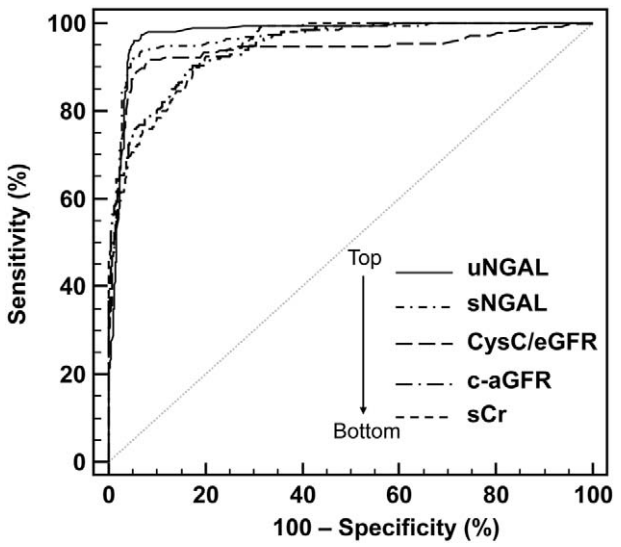

Figure 4. Receiver operating characteristic (ROC) curve analysis of the observed indicators. The diagnostic performance of each observed indicator, in terms of sensitivity and specificity, are presented after ROC curve analysis. The area under the ROC curve (AUC) of sNGAL and uNGAL were larger than those of CysC/eGFR and sCr/c-aGFR.

3.5. Risk degree analysis of the indicators in predicting the occurrence of AKI secondary to liver cirrhosis

Taking the above optimal threshold as abnormal, the stepwise binary logistic regression method was used to analyze the risk degree of serum levels and abnormal rate of the above 6 indicators in predicting the occurrence of AKI in patients with liver cirrhosis (Table 2). The results showed that only uNGAL, sNGAL, sCr and eGFR were risk factors (OR = 0.960–1.021, $P < .05$), but the correlations with AKI were all weak when using serum levels for analysis. However, only uNGAL, sNGAL and eGFR were the risk factors (OR = 3.047–54.524, $P < .05$), and the correlations with AKI were all strong when using abnormal rates for analysis.

4. Discussion

Renal dysfunction severely affects the natural development of liver cirrhosis.[23] If renal dysfunction can be diagnosed at an early stage and positive interventions are administrated, the treatment and prognosis of patients with cirrhosis may be improved.[5] Four standards have been subsequently proposed for the diagnosis of AKI, including RIFLE, AKIN, KDIGO,[11] and ICA.[12] These standards have been applied to kidney disease diagnosis in clinical practice. However, it remains unclear whether these standards can help improve the diagnosis of AKI secondary to liver cirrhosis. Additionally, acute dialysis quality initiative[15,24] and KIDGO[11] point out that there is no clinical evidence to support the use of certain biomarkers as indicators of AKI. Therefore, further research is needed.

In the past decade, NGAL has become the most promising and widely studied biomarker for kidney injury.[25] It is highly expressed in damaged renal tubules. A possible mechanism for early diagnosis of AKI secondary to cirrhosis using NGAL is that damaged renal tubular epithelial cells may lead to the up-regulation of NGAL expression. Up-regulated expression of NGAL can be taken up by early primitive renal epithelial cells, which then mediate iron transport and promote maturation of primitive renal epithelial cells.[26] The results of this study indicate that in the early stage of AKI (S1 phase), the level of NGAL increased significantly, but not sCr. As the kidney has a strong compensatory ability, when the damage is light, the patient may have no obvious discomfort. However, when the clinical symptoms are obvious, the kidney damage has become more severe, and at this time, the sCr is obviously increased.[27] In this study, we found that both the LC and AKI groups experienced an increase in sNGAL and uNGAL levels compared to the HC group. AKI group experienced a significant increase in

Table 2

Risk degree of the indicators in predicting the occurrence of AKI in patients with liver cirrhosis.

	Serum levels			Abnormal rate		
Indicators	**OR**	***95%*CI**	***P***	**OR**	***95%*CI**	***P***
uNGAL	1.021	1.010, 1.031	<.001	54.524	9.644, 308.247	<.001
sNGAL	1.007	1.004, 1.011	<.001	5.115	1.408, 18.587	.013
sCr	1.020	1.004, 1.036	.013	-	-	-
eGFR	0.960	0.940, 0.980	<.001	3.047	1.116, 8.317	.030

AKI = acute kidney injury, CI = confidence interval, eGFR = estimated glomerular filtration rate by CysC equation suitable for Chinese, OR = odds ratio, sCr = serum creatinine, sNGAL = serum neutrophil gelatinase-associated lipocalin, uNGAL = urine neutrophil gelatinase-associated lipocalin.

Table 3

Performances of indicators in terms of diagnosis of AKI in patients with liver cirrhosis.

Indicator	AUC (95% CI)	Cutoff value	Se (%)	Sp (%)	YI
uNGAL	0.976 (0.957, 0.989)	41 μg/gCr	97.5 (94.0, 99.4)	93.2 (90.1, 95.7)	0.907
sNGAL	0.967 (0.947, 0.982)	109 μg/L	94.0 (89.5,97.0)	93.0 (89.8, 95.5)	0.870
sCr	0.945 (0.921, 0.964)	77.7 μmol/L	91.5 (86.5, 95.1)	81.0 (76.3, 84.4)	0.725
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c-aGFR	0.945 (0.921, 0.964)	96.1 ml/min/1.73m^2	89.5 (84.1, 93.6)	83.9 (79.9, 87.5)	0.734
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AKI = acute kidney injury, AUC = area under curve of ROC analysis, c-aGFR = estimating glomerular filtration rate by improved MDRD equation suitable for Chinese, CysC = cystatin C, eGFR = estimating glomerular filtration rate by CysC equation suitable for Chinese., sCr = serum creatinine, Se = sensitivity, sNGAL = serum neutrophil gelatinase-associated lipocalin, Sp = specificity, uNGAL = urine neutrophil gelatinase-associated lipocalin, YI = Youden index. Because eGFR was calculated by CysC and c-aGFR is calculated by sCr, their AUCs were equal.

sNGAL and uNGAL levels compared to LC and HC groups. With the development of AKI and when the renal damage becomes more severe, sNGAL and uNGAL levels are further increased. In addition, in patients with liver cirrhosis, sNGAL and uNGAL levels were positively correlated with sCr levels, but negatively correlated with c-aGFR levels. These results indicate that sNGAL and uNGAL could reflect the severity of renal dysfunction and might be used as diagnostic indicators of AKI in patients with liver cirrhosis. The sensitivity and specificity of uNGAL for AKI diagnosis were greater or higher than the other five indicators including sNGAL. Additionally, its abnormal rate had the highest risk of AKI (OR = 54.524). These findings suggest that the diagnostic performance of uNGAL is not only better than those of sCr, CysC and eGFR, but also slightly better than that of sNGAL (OR = 5.115). Therefore, uNGAL is considered an independent, early diagnostic indicator of AKI in patients with liver cirrhosis. It not only can be used to identify and diagnose the type of AKI in patients, but it is also conducive to the risk-stratification management of patients with liver cirrhosis during hospitalization.[20,28,29]

KDIGO guideline states that markers used for the estimation of GFR should be reported as eGFR and not merely as a concentration of the analyte, and clinical laboratories also report eGFR and that clinicians also use eGFR to evaluate kidney function for all patients.[11] A large number of studies have shown that CysC is a good indicator of glomerular filtration,[30,31] but these previous studies only considered CysC detection as a means to overcome the shortcomings of Cr detection.[32,33] Several studies have shown that smoking, thyroid dysfunction and high C-reactive protein levels can promote the production and/or metabolism of CysC.[34] Therefore, CysC tends to be a marker for glomerular filtration function[35] rather than a biomarker for AKI.[34] Although the sensitivity and specificity of CysC detection in AKI diagnosis is lower than that of NGAL, it can provide some useful information for early diagnosis of AKI in patients with liver cirrhosis. Here, we showed that the specificity and sensitivity of AKI diagnosis through CysC detection were both higher than 90% when the cutoff value was determined at 1.24 mg/L, and YI reached 0.839. Thus, the diagnostic performance of CysC is better than those of conventional indicators such as sCr and c-aGFR. Serum CysC detection is necessary when testing renal damage in the laboratory.

Theoretically, the diagnostic performances of CysC and eGFR, as well as the diagnostic performances of sCr and c-aGFR should be the same. However, we observed differences in diagnostic performance between CysC and eGFR as well as between sCr and

Table 4

Risk degree of the indicators in predicting occurrence of AKI in patients with liver cirrhosis.

	Serum levels			Abnormal rate		
Indicators	**OR**	***95%*CI**	***P***	**OR**	***95%*CI**	***P***
uNGAL	1.021	1.010, 1.031	<.001	54.524	9.644, 308.247	<.001
sNGAL	1.007	1.004, 1.011	<.001	5.115	1.408, 18.587	.013
sCr	1.020	1.004, 1.036	.013	–	–	–
eGFR	0.960	0.940, 0.980	<.001	3.047	1.116, 8.317	.030

AKI = acute kidney injury, CI = confidence interval, eGFR = estimating glomerular filtration rate by CysC equation suitable for Chinese, OR = odds ratio, sCr = serum creatinine, sNGAL = serum neutrophil gelatinase-associated lipocalin, uNGAL = urine neutrophil gelatinase-associated lipocalin.

c-aGFR. The possible reason may be that the methods used for detecting CysC and sCr in this study might be different from those required by eGFR and c-aGFR equations. Sampling error (i.e. individual differences) is also a possible explanation.

5. Conclusions

In conclusion, NGAL is highly sensitive and highly specific for the diagnosis of AKI in patients with liver cirrhosis. It is a better biomarker for AKI than sCr and CysC. In addition, the diagnostic performance of uNGAL is better than that of sNGAL. Consequently, uNGAL detection might be applied to the early diagnosis of AKI in patients with liver cirrhosis. However, further studies in multiple centers and with larger sample sizes are needed for further validation.

Author contributions

Yuwei Yang, Bin Ge and Jiafu Feng performed the experiments. Yuwei Yang, Bin Ge and Yan Liu participated in experiment preparation. Yuwei Yang, Jiafu Feng and Bin Ge performed the data analyses. Jiafu Feng participated in the study design and final review of the manuscript. Yuwei Yang, Bin Ge and Jiafu Feng wrote and edited the manuscript. All authors read and approved the manuscript.

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