ORIGINAL ARTICLE

Value of Serum Galectin 3 in Patients with Hepatocellular Carcinoma: A Meta-Analysis

L Zhang, X-J Chen, D He, T-Y Zhou

ABSTRACT

Objective: *To investigate the connection of Galectin 3 with hepatocellular carcinoma (HCC) risk.*

Methods: *Publications were searched using PubMed, MEDLINE, EMBASE and the Chinese databases (including CNKI and WanFang) up to October 2015.*

Results: *A total of four studies were included in this analysis. The pooled mean difference for HCC versus hepatitis was (1.98 (95% CI: 1.13, 2.83, Z = 4.57,* $p < 0.00001$*)) and for HCC versus healthy person was (2.29 (95% CI: 2.09, 2.5, Z = 21.78,* $p < 0.00001$*).. The serum Galectin 3 level in HCC was significantly higher than that in hepatitis and healthy person. The pooled sensitivity and specificity were 0.93 (95% CI: 0.86, 0.97) and 0.83 (95% CI: 0.74, 0.90), the pooled diagnostic odds ratio were 116.78 (95% CI: 0.13, 102122.46), the pooled positive likelihood ratio were 12.71 (95% CI: 0.12, 1374.27), and the pooled negative LR were 0.11 (95% CI: 0.00, 12.51).*

Conclusion: *The serum Galectin 3 level in HCC is higher than that in hepatitis and healthy person. Serum Galectin 3 may be a possible biomarker for diagnosis of HCC.*

Keywords: Hepatocellular carcinoma, meta-analysis, serum Galectin 3

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer, and the third most common cause of cancer-related mortality overall in the world (1). Prognosis of HCC is very poor with a 14% five-year survival rate because of rapid progression and high grade of malignancy (2, 3). Lacking novel biomarkers, HCC is frequently found in late stages. Commonly, CT, ultrasound, MRI and blood chemistry tests are used to diagnose HCC. Histopathologic assessment is necessary for confirmation and when the imaging tests and blood chemistry tests are atypical. However, biopsy of liver tissue suspected of harbouring HCC is invasive and difficult. So it would be helpful if new biomarkers can be found to improve the pre-biopsy diagnostic efficiency of HCC. In the clinic serum alpha-fetoprotein (AFP), with low sensitivity, is used to support the diagnosis of HCC (4). However, a new serum biomarker needs to be found with better performance than AFP, which is not which is not satisfactory.

Galectins are a family of β-galactoside-binding animal lectins, composed of 2 domains: a carboxyl-terminal domain and an amino-terminal domain (5). Studies suggest that Galectin 3, a unique chimaera-type member of the β-galactoside-binding soluble lectin family, has multifaceted functions including cell growth, proliferation, adhesion, differentiation, immune responses, angiogenesis, apoptosis, metastasis and tumour progression (6–8) . Expression of Galectin 3 is a promising diagnostic indicator for several kinds of carcinomas, such as carcinomas stomach (9), colon (10) and thyroid (11). However, the relationship between Galectin 3 and HCC is unclear. Our aims are to analyse the expression of serum Galectin 3 in different stages of liver diseases and evaluate the diagnostic accuracy of serum Galectin 3 in HCC patients.

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SUBJECTS AND METHODS

Search strategy

Publications searched were PubMed, MEDLINE, EMBASE and the Chinese databases (including CNKI and WanFang database) until October 2015, by using the following search terms: HCC or liver cancer or liver cell carcinoma or HCC and Galectin 3 or gal-3.

Study selection

Studies included in this meta-analysis met the following criteria::

(1) Original articles that directly directly explored serum Galectin 3 expression in different stages of diseases (including HCC, hepatic cirrhosis, hepatitis, or healthy person);
(2) Original articles that directly directly explored the diagnostic performance of serum Galectin 3 for HCC;
(3) Used ELISA to examine serum Galectin 3 expression;
(4) Sufficient information was reported to estimate a mean difference (MD), 95% confidence interval (CI), true positive (TP), false positive (FP), false negative (FN) and true negative (TN).

Studies were excluded as follows: (a) case reports, reviews, letters and editorial articles; (b) articles in which sufficient data were not reported or calculated.

Data extraction

Two independent investigators (LZ and DH) extracted all data from eligible studies to minimize bias; a third researcher (XJC) resolved disagreements through discussion. For each article, the following characteristics were recorded: first author, publication year, number of patients, test method, TP, FP, FN, PN and cut-off value.

Statistical analysis

All analysis was performed using Review Manager 5.3 and MetaDisc. Extracted data included serum Galectin 3 levels of HCC versus serum Galectin 3 levels of hepatic cirrhosis, hepatitis and healthy person in each article. Mean difference and 95% CI were applied to provide the effective values. And in order to evaluate the diagnostic efficiency of serum Galectin 3 in HCC, we also extracted the TP, FP, FN and PN to estimate the sensitivity and specificity. Initially, we retrieved 191 studies from PubMed, EMBASE and the Chinese databases (including CNKI and WanFang database) up to October 2015.

One hundred and eighty one abstracts were excluded, because they were reviews, experimental research, reports, duplicate articles or not relevant. After reading the remaining 10 full-text articles, 6 were excluded, because they used other test methods than ELISA. Finally, four articles were included for conducting the meta-analysis (see Fig. 1). One hundred and twenty patients with HCC, 68 patients with hepatic cirrhosis, 47 patients with hepatitis and 24 healthy persons in these four articles were used to explore serum Galectin 3 levels in different stages of diseases. TP, FP, FN and PN were acquired to estimate the sensitivity and specificity of HCC for detecting serum Galectin 3 expression in HCC and non-tumour. ELISA was used to detect the serum Galectin 3. A random-effects model for $I^2 > 50\%$, a fixed-effects model for $I^2 < 50\%$, and statistical significance defined as a p-value less than 0.05 (12) (Tables 1 and 2) were adopted.

Table 1: Serum Galectin 3 levels in patients with HCC, cirrhosis, hepatitis and healthy people

Reference	Year	HCC	Cirrhosis	Hepatitis	Healthy people
Nada (13)	2015	50	30	0	10
Yasunori (14)	2008	51	16	23	14
Mehmet (15)	2015	19	22	24	0

HCC = hepatocellular carcinoma.

Table 2: Galectin 3 expression in HCC and non-tumour

Reference	**Year**	**TP**	**FP**	**FN**	**TN**	**Cut-off**	**HCC/ Non-tumour**	**Detection method**
Qing-Qing Fang (16)	2011	40	1	1	89	0.62 ng/l	62/90	ELISA
Yasunori (14)	2008	34	7	14	14	2.76 ng/ml	48/21	ELISA

TP = True positive; FP = false positive; FN = false negative; TN = true negative; HCC = hepatocellular carcinoma.

RESULTS

In the four studies, the meta-analysis results (mean difference: 0.63 (95% CI: −0.61–1.87, $Z = 0.99$, $p = 0.325$)) indicated that there were no significant differences for serum Galectin 3 level between HCC and hepatic cirrhosis with an obvious heterogeneity (Tau-square = 0.92, chi-square = 9.83, $I^2 = 80\%$, $p = 0.007$) (Fig. 2A). However, we also found the serum Galectin 3 level in HCC was significantly higher than that in hepatitis and healthy person. The pooled mean difference for HCC versus hepatitis was (1.98 (95% CI: 1.13, 2.83, $Z = 4.57$, $p < 0.00001$)) without heterogeneity (chi-square = 0.21, $I^2 = 0\%$, $p = 0.64$) (Fig. 2B). The pooled mean difference

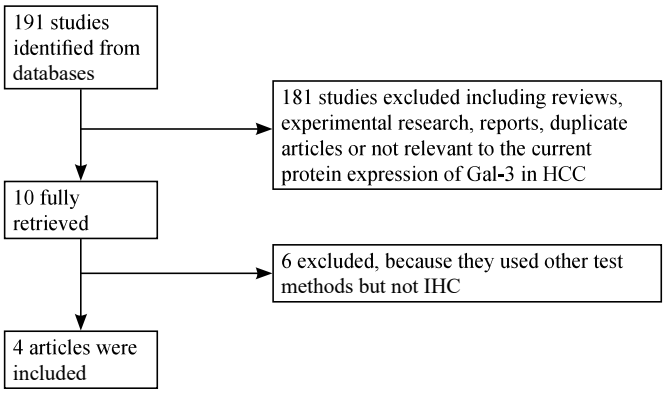

Fig. 1: The study selection process.

respectively, the pooled DOR was 116.78 (95% CI: 0.13, 102122.46), the pooled positive LR was 12.71 (95% CI: 0.12, 1374.27), and the pooled negative LR was 0.11 (95% CI: 0.00, 12.51). All the results indicated that Galectin 3 may be a useful biomarker for the diagnosis of HCC (Fig. 3).

DISCUSSION

Prognosis of HCC is very poor because of rapid progression and high grade of malignancy. Radiotherapy, chemotherapy and surgery are the main treatment methods for HCC patients in the clinic. Although therapies

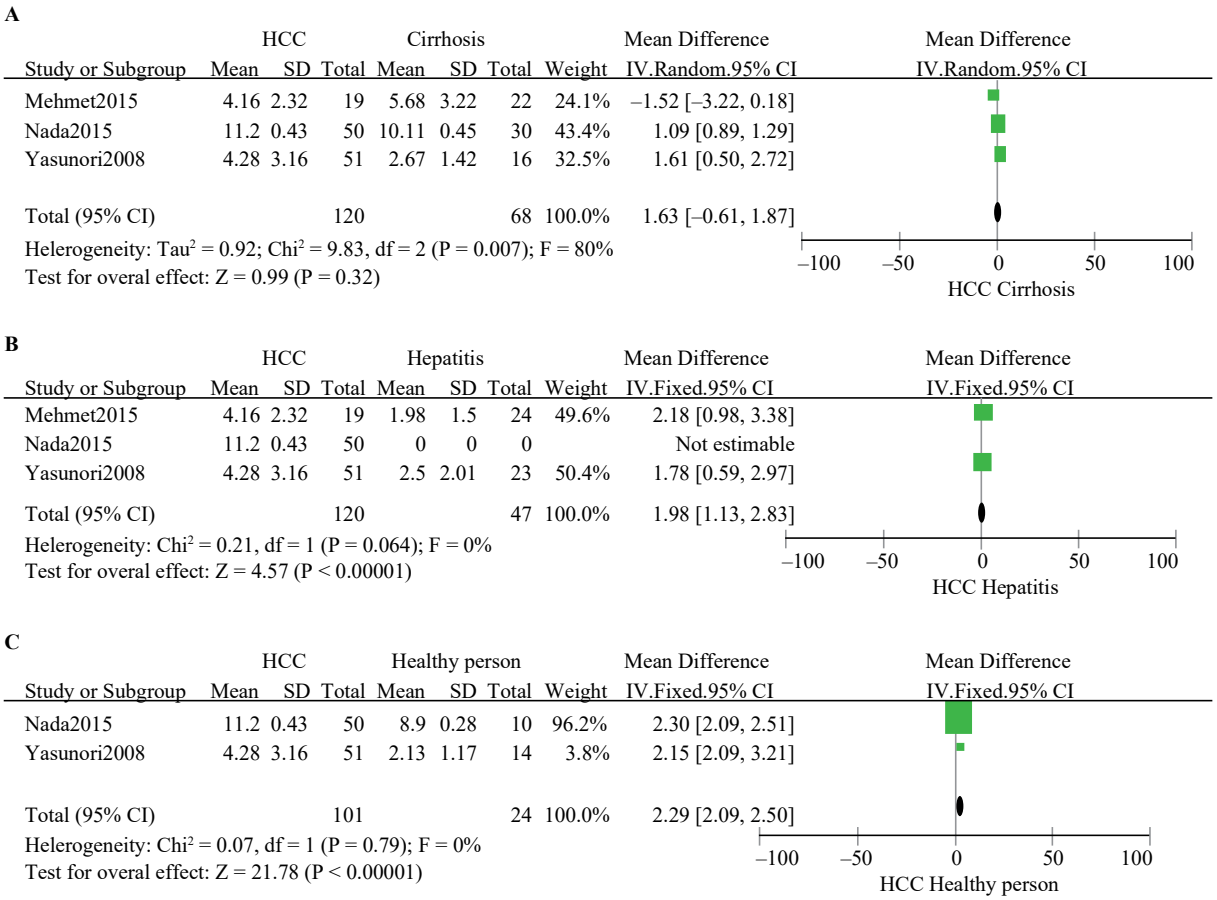

Fig. 2: (A) Forest plot for serum Galectin 3 in HCC and hepatic cirrhosis. (B) Forest plot for serum Galectin3 in HCC and hepatitis. (C) Forest plot for serum Galectin3 in HCC and healthy person. HCC = hepatocellular carcinoma.

for HCC versus healthy person was (2.29 (95% CI: 2.09, 2.5, $Z = 21.78$, $p < 0.00001$)) without heterogeneity (chi-square = 0.07, $I^2 = 0\%$, $p = 0.79$) (Fig. 2C).

In our analysis, a total of 110 HCC patients and 111 non-tumour patients were included in this meta-analysis to evaluate the diagnostic usefulness of serum Galectin 3. The overall sensitivity and specificity were 0.93 (95% CI: 0.86, 0.97) and 0.83 (95% CI: 0.74, 0.90) have been improved, the cure rate is still poor. Therefore, it is urgent to engage in finding potent factors for earlier diagnosis of HCC.

Four studies were included in this study to derive a more precise estimation of serum Galectin 3 levels in HCC patients versus serum Galectin levels in hepatic cirrhosis, hepatitis, and healthy person. The diagnostic effect of serum Galectin 3 for HCC was also estimated.

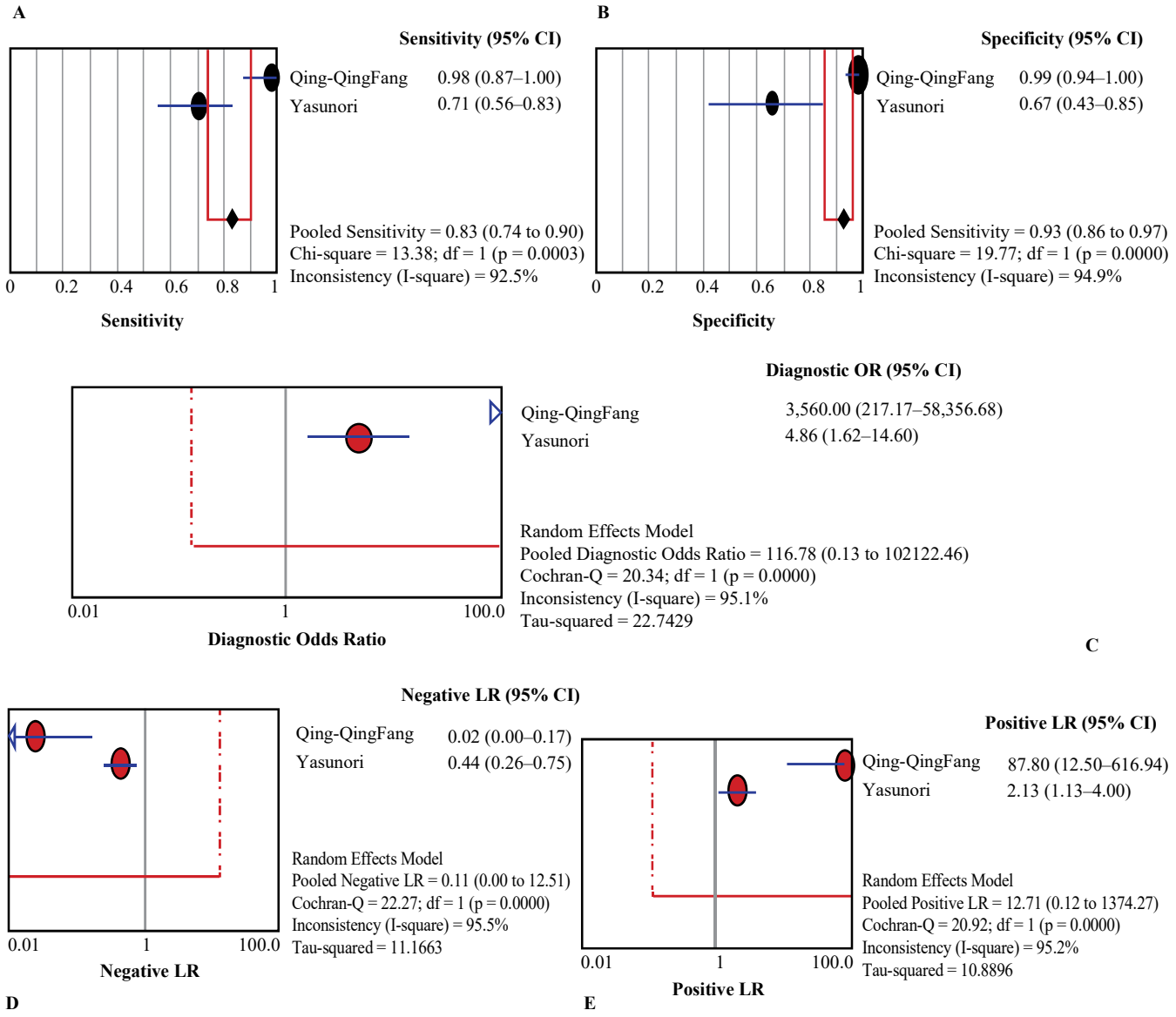

Fig. 3: (A) Forest plot of the sensitivity of serum Galectin 3 in HCC diagnosis. (B) Forest plot of the specificity of serum Galectin 3 in HCC diagnosis. (C) Forest plot of the DOR of serum Galectin 3 in HCC diagnosis. (D) Forest plot of the pooled negative LR of serum Galectin 3 in HCC diagnosis. (E) Forest plot of the pooled positive LR of serum Galectin 3 in HCC diagnosis. HCC = hepatocellular carcinoma.

The results indicated serum Galectin 3 levels in HCC were significantly increased compared to those in hepatitis and healthy persons, suggesting Galectin 3 played an important role in the pathogenesis of HCC. But there was no significant difference for serum Galectin 3 level between HCC and hepatic cirrhosis. In the study titled 'galectin 3 expression is induced in cirrhotic liver and hepatocellular carcinoma', Galectin-3 was abundantly expressed in cirrhotic liver in peripheral distribution within regenerating nodules (17). Such Galectin 3 expression in rapidly proliferating hepatocytes in cirrhotic liver may be a result of the high mitotic index. Alternatively, it is possible that proliferating cells expressing galectin-3 are in the process of being transformed, thus may indicate an early neoplastic event. Higher Galectin 3 level may be a potential biomarker for disease diagnosis. The meta-analysis showed that the overall sensitivity and specificity were 0.93 and 0.83 respectively, which implies clinical value to evaluate the diagnosis of HCC, used as an auxiliary diagnostic method. The pooled diagnostic odds ratio (DOR) reflects the accuracy of diagnostic tests as a reliable indicator; the greater its value, the stronger the diagnostic ability to distinguish. In our study the pooled DOR was 116.78, which suggested the efficiency of diagnosis was relatively high. The pooled positive LR was 12.71,

indicating the rate of detection of HCC was 12.71 times higher that of non-HCC.

The pooled negative LR implied that once the detection of Galectin 3 was negative, the risk of liver cancer is 11%. Overall, full consideration of the clinical symptoms, combined with serum Galectin 3, is helpful for early diagnosis. Zhou's study (4) included eight studies of serum AFP for diagnosis of HCC and reported as follows: sensitivity 70%, specificity 89%, and DOR 18.00 (9.41–34.46), which indicates that serum Galectin 3 may be a more useful diagnostic biomarker for HCC. The problem in our analysis is that there was no significant difference between serum Galectin 3 levels in HCC and hepatic cirrhosis, with an obvious heterogeneity. However, we did not analyse for publication bias, because the studies included were just four.

CONCLUSION

Our meta-analysis indicates that galectin3 may have good diagnostic accuracy for making the diagnosis of HCC. More studies should be done to evaluate the diagnostic accuracy of Galectin 3.

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AUTHORS' NOTE

LZ collected data and wrote the manuscript and approved the final version. XJC conducted data analysis and approved the final version. DH looked for the papers and collected the useful data and approved the final version, TYZ critically revised the manuscript and approved the final version. The authors declare that they have no conflicts of interest.

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; **61:** 69–90.
2. Yamashita T, Wang XW. Cancer stem cells in the development of liver cancer. J Clin Investigat 2013; **123:** 1911–8.
3. Cao K, Lu C, Han S, Zou Q, Li J, Xie D, et al. Expression of Girdin in primary hepatocellular carcinoma and its effect on cell proliferation and invasion. Int J Clin Exp Pathol 2015; **8:** 551–9.
4. Zhou Y, Yin X, Ying J, Zhang B. Golgi protein 73 versus alpha-fetoprotein as a biomarker for hepatocellular carcinoma: a diagnostic meta-analysis. BMC Cancer 2012; **12:** 17.
5. Nita-Lazar M, Banerjee A, Feng CG, Vasta GR. Galectins regulate the inflammatory response in airway epithelial cells exposed to microbial neuraminidase by modulating the expression of SOCS1 and RIG1. Mol Immunol 2015; **68:** 194–202.
6. Nangia-Makker P, Balan V, Raz A. Regulation of tumor progression by extracellular galectin-3. Cancer Microenviron 2008; **1:** 43–51.
7. Liu FT, Patterson RJ, Wang JL. Intracellular functions of galectins. Bba-Gen Subjects 2002; **1572:** 263–73.
8. Liu FT, Rabinovich GA. Galectins as modulators of tumour progression. Nat Rev Cancer 2005; **5:** 29–41.
9. Lotan R, Ito H, Yasui W, Yokozaki H, Lotan D, Tahara E. Expression of a 31-kDa lactoside-binding lectin in normal human gastric mucosa and in primary and metastatic gastric carcinomas. Int J Cancer 1994; **56:** 474–80.
10. Schoeppner HL, Raz A, Ho SB, Bresalier RS. Expression of an endogenous galactose-binding lectin correlates with neoplastic progression in the colon. Cancer 1995; **75:** 2818–26.
11. Cvejic D, Savin S, Golubovic S, Paunovic I, Tatic S, Havelka M. Galectin-3 and carcinoembryonic antigen expression in medullary thyroid carcinoma: possible relation to tumour progression. Histopathology 2000; **37:** 530–5.
12. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; **21:** 1539–58.
13. Eisa NH, Ebrahim MA, Ragab M, Eissa LA, El-Gayar AM. Galectin-3 and matrix metalloproteinase-9: perspective in management of hepatocellular carcinoma. J Oncol Pharm Pract 2015; **21:** 323–30.
14. Matsuda Y, Yamagiwa Y, Fukushima K, Ueno Y, Shimosegawa T. Expression of galectin-3 involved in prognosis of patients with hepatocellular carcinoma. Hepatol Res 2008; **38:** 1098–111.
15. Ulu M, Alacacioglu A, Yuksel E, Pamukk BO, Bozkaya G, Ari A, et al. Prognostic significance of serum galectin-3 levels in patients with hepatocellular cancer and chronic viral hepatitis. Saudi J Gastroenterol 2015; **21:** 47–50.
16. Fang Q-q. Serum and tissue expressions of galectin-3 in hepatocellular carcinoma and the clinical significances. Chin J Hepatol 2011; **19:** 527–31.
17. Hsu DK, Dowling CA, Jeng KC, Chen JT, Yang RY, Liu FT. Galectin-3 expression is induced in cirrhotic liver and hepatocellular carcinoma. Int J Cancer. 1999 May 17; 81(4): 519-26.