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Original Article

Serum isthmin-1 levels in chronic hepatitis B: association with viral replication and hepatic dysfunction

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Abstract

Introduction: Chronic hepatitis B virus (HBV) infection remains a major global health problem, underscoring the need for biomarkers that reflect viral replication and liver function. Isthmin-1 (ISM-1), an immunometabolic adipokine, has not been adequately studied in chronic HBV infection. This study evaluated serum ISM-1 levels in patients with chronic HBV to assess its potential as a complementary marker of viral activity and hepatic dysfunction.

Methodology: In this cross-sectional study, 100 patients with histologically mild chronic hepatitis B and 60 healthy controls were enrolled. Serum ISM-1 levels were measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit alongside comprehensive virological and biochemical assessments.

Results: Serum ISM-1 concentrations were significantly lower in patients with chronic HBV than in healthy controls (102.74 ± 15.64 vs. 194.62 ± 187.59 pg/mL; $p < 0.001$). ISM-1 levels demonstrated a significant downward trend as HBV DNA categories increased ($p = 0.001$), indicating an inverse relationship with viral replication. Multiple linear regression identified direct bilirubin as a positive independent predictor of ISM-1 levels. ROC analysis showed moderate overall performance (AUC = 0.656); the marker exhibited a remarkably high sensitivity (97.0%) but limited specificity (38.7%).

Conclusions: Serum ISM-1 levels are significantly reduced in chronic HBV infection and are inversely associated with viral replication. The positive correlation with direct bilirubin may reflect an adaptive cellular response to hepatocellular stress rather than simple dysfunction. Despite its limited specificity, the high sensitivity of ISM-1 suggests that it could be a valuable complementary tool for monitoring disease progression and viral status in clinical practice.

Key words: isthmin-1; HBV; HBV DNA; biomarker; bilirubin.

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Introduction

Hepatitis B virus (HBV) remains a major global cause of liver-related morbidity and mortality [1]. Despite vaccination and antiviral therapy, chronic HBV infection still leads to nearly 1 million deaths annually through progression to cirrhosis and hepatocellular carcinoma [2]. Current serological and biochemical markers have limited value in predicting disease progression, viral activity, and treatment timing [3], highlighting the need for biomarkers that better reflect viral replication and host immune responses [4].

Isthmin-1 (ISM-1) is an adipokine involved in glucose metabolism, angiogenesis, and immune regulation [5]. Although increasingly studied in metabolic and hepatic disorders [6], its role in chronic HBV infection remains undefined. This study evaluated serum ISM-1 levels in patients with chronic HBV to assess its potential as a biomarker of viral replication and hepatic dysfunction.

Methodology

Study design and participants

This cross-sectional study included 100 patients with chronic hepatitis B (HBsAg positivity > 6 months and detectable HBV DNA by real-time polymerase chain reaction (RT-PCR)) and 60 age- and gender-matched healthy controls. Only patients with early-stage disease were enrolled; the patients were determined to have steatosis < 5%, fibrosis stages F0–F2, and mild necroinflammatory activity according to the meta-analysis of histological data in viral hepatitis (METAVIR) scoring system. Liver biopsies were evaluated by a hepatopathologist blinded to clinical data. Patients with hepatitis C virus (HCV) or hepatitis D virus (HDV) co-infection, autoimmune or alcoholic liver disease, Wilson's disease, hepatotoxic drug use, cirrhosis, or hepatocellular carcinoma were excluded. Controls had normal biochemistry and negative HBV/HCV serology.

Ethical approval

The study was approved by the Non-Interventional Research Ethics Committee of Fırat University (Approval No: 2025/08-22). All procedures complied with the principles of the Declaration of Helsinki.

Sample collection

After an overnight fast of at least 8 hours, 5 mL of venous blood was collected from each participant between 8:00 and 10:00 a.m. The samples were drawn into gel-containing serum separator tubes, centrifuged, and the serum was aliquoted into Eppendorf tubes and stored at –80 °C until analysis. All samples were processed in a single batch, and repeated freeze-thaw cycles were avoided to ensure analytical reliability.

Measurement of serum ISM-1

Serum ISM-1 levels were measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit (SunLong Biotechnology Co., Ltd., Hangzhou, China; Cat. No. SL3926Hu) according to the manufacturer's instructions. The assay sensitivity was 6 pg/mL, with a detection range of 33–2000 pg/mL. Optical density was measured at 450 nm using a BioTek ELx800 reader (BioTek Instruments, Winooski, VT, USA).

Virological evaluation

Quantitative HBV DNA was determined using a COBAS AmpliPrep/COBAS TaqMan HBV Test, v 2.0 (Roche Diagnostics GmbH, Mannheim, Germany) with a lower limit of detection of 20 IU/mL. The 'negative' HBV DNA levels referred to in the results section correspond to values below this lower limit of detection (< 20 IU/mL). HBsAg, HBeAg, anti-HBe, and anti-HBs levels were measured using chemiluminescent microparticle immunoassay (CMIA) on the Abbott Alinity i (Abbott Laboratories, Abbott Park, IL, USA). The results were reported in international units per milliliter (IU/mL).

Histopathological evaluation

All biopsy specimens were fixed in formalin, paraffin-embedded, and stained with hematoxylin-eosin and Masson's trichrome. Histopathological scoring was performed according to the METAVIR scoring system, in which fibrosis was staged from F0 to F4 and necroinflammatory activity was graded from A0 to A3. Only cases with F0–F2 and A1–A2 were included in the study.

Statistical analysis

Statistical evaluations were performed utilizing IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). The distribution of data was analyzed through visual examination and normality assessments. Continuous variables were represented as mean ± standard deviation, while categorical variables were expressed as frequencies and percentages. Comparisons between groups were conducted using the independent samples t-test or one-way analysis of variance (ANOVA) with Fisher's least significant difference (LSD) post hoc test, as appropriate. Categorical variables were analyzed using the Chi-square test. Effect sizes were computed utilizing Cohen's d and eta-squared (η^2). The relationships between serum ISM-1 levels and biochemical or virological parameters were assessed via Pearson correlation analysis. Independent predictors of ISM-1 levels were identified through multiple linear regression analysis. The discriminative efficacy of ISM-1 was investigated through receiver operating characteristic (ROC) curve analysis, which included calculations of the area under the curve (AUC), sensitivity, specificity, and the Youden index. A two-tailed p value < 0.05 was considered statistically significant.

Results

There was no statistically significant difference between the groups regarding gender distribution (χ^2 = 1.875, p = 0.113). The control group consisted of 58.3% males and 41.7% females, whereas the patient group included 47.0% males and 53.0% females. The mean age was 40.11 ± 10.22 years in healthy controls and 43.12 ± 10.28 years in patients, with no significant difference between groups (p = 0.074) (Table 1).

Table 1. Demographic and laboratory characteristics of healthy controls and patients with chronic HBV infection.

Variable	Healthy controls (n = 60)	Chronic HBV patients (n = 100)	*p*
Age (years)	40.11 ± 10.22	43.12 ± 10.28	0.074
Gender (male/female), n (%)	35 (58.3%) / 25 (41.7%)	47 (47.0%) / 53 (53.0%)	0.113
ISM-1 (pg/mL)	194.62 ± 187.59	102.74 ± 15.64	< 0.001
Virological/serological status	Negative HBV / HCV serology	HBsAg positivity > 6 months and detectable HBV DNA by RT-PCR; HCV/HDV co-infection excluded	–

Data are presented as mean ± standard deviation or n (%). HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; ISM-1: isthmin-1; RT-PCR: real-time polymerase chain reaction.

Serum ISM-1 levels were compared between groups using an independent samples t-test. The mean ISM-1 concentration was significantly higher in healthy controls (194.62 ± 187.59 pg/mL) than in patients with chronic HBV infection (102.74 ± 15.64 pg/mL; t = 4.879, df = 160, $p < 0.001$) (Table 1). The effect size was large, with a Cohen's d value of 0.789.

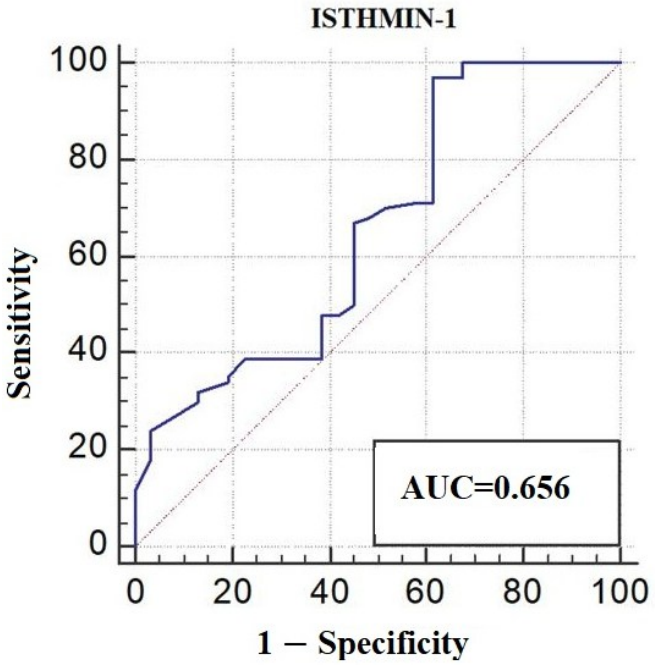
The discriminative performance of ISM-1 was evaluated using ROC curve analysis. The area under the curve (AUC) was 0.656 (standard error: 0.0455; 95% confidence interval: 0.577–0.729; z = 3.425; p = 0.0006). The optimal cut-off value was ≤ 131 pg/mL, yielding a sensitivity of 97.0% and a specificity of 38.71%. The Youden index was calculated as 0.3571 (Figure 1).

The biochemical and hematological characteristics of patients with chronic HBV infection are summarized descriptively. The mean levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were 25.07 ± 8.13 U/L and 29.71 ± 21.14 U/L, respectively. Alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) levels were 72.89 ± 20.24 U/L and 25.46 ± 16.27 U/L. The mean platelet count was 246.10 ± 72.07 ×10³/µL. Total bilirubin and direct bilirubin levels were 0.576 ± 0.231 mg/dL and 0.126 ± 0.084 mg/dL, respectively. Mean albumin concentration was 42.31 ± 3.03 g/L, and the international normalized ratio (INR) was 1.039 ± 0.074.

The C-reactive protein (CRP) levels showed a wide distribution (mean: 19.41 ± 78.90 mg/L; range: 0.5–381 mg/L), likely reflecting concomitant subclinical inflammatory conditions unrelated to chronic HBV infection.

Based on virological evaluation, HBV DNA was undetectable (< 20 IU/mL) in 44% of patients, while 23% had HBV DNA levels below 1000 IU/mL and 33% had levels ≥ 1000 IU/mL. One-way ANOVA demonstrated a statistically significant difference in ISM-1 levels across HBV DNA categories (F = 7.407, p = 0.001), with a moderate effect size (η^2 = 0.132). Post hoc analysis (LSD test) showed that patients with undetectable HBV DNA had significantly higher ISM-1 levels (108.52 ± 15.52 pg/mL) compared to those with HBV DNA ≥ 1000 IU/mL (95.50 ± 13.88 pg/mL). No significant difference was observed between patients with undetectable HBV DNA and those with HBV DNA < 1000 IU/mL (Table 2).

Figure 1. Receiver operating characteristic (ROC) curve analysis of serum isthmin-1 (ISM-1) levels for differentiating patients with chronic hepatitis B virus (HBV) infection from healthy controls.



The area under the curve (AUC) was 0.656 (95% CI: 0.577–0.729; p = 0.0006). The sensitivity was 97.0% and the specificity was 38.71% at the optimal cut-off value of ≤ 131 pg/mL.

Pearson correlation analysis revealed a significant positive correlation between serum ISM-1 levels and direct bilirubin (r = 0.225, p = 0.024). No significant correlations were observed between ISM-1 and AST, ALT, ALP, GGT, total bilirubin, albumin, INR, alpha-fetoprotein (AFP), CRP, or virological serological markers ($p > 0.05$) (Table 3). Multiple linear regression analysis identified direct bilirubin as an independent predictor of serum ISM-1 levels. The regression model was statistically significant (F = 3.024, p = 0.021), with an R^2 value of 0.076. The Durbin-Watson coefficient was 1.637, indicating no autocorrelation. Direct bilirubin was positively associated with ISM-1 levels (B = 39.792, p = 0.030), indicating that a one-unit increase in direct bilirubin corresponded to an approximate 39.79 pg/mL increase in ISM-1 concentration.

Table 2. Comparison of serum ISM-1 levels according to HBV DNA subgroups.

	Groups	n	Mean	SD	F	*p*	η^2
ISM-1	Negative	44	108.52	15.52	7.407	*0.001*	0.132
	< 1000 IU/mL	23	102.09	14.27			
	≥ 1000 IU/mL	33	95.50	13.88			

One-way ANOVA; post hoc: LSD; η^2: effect size. Negative HBV DNA indicates values below the lower limit of detection of the assay (< 20 IU/mL). HBV: hepatitis B virus; ISM-1: isthmin-1.

Table 3. Factors affecting ISM-1 levels.

Independent Variable	Unstandardized coefficients		Standardized coefficients	t	*p*	95% CI	
	B	SE	β			Lower	Upper
Constant	84.886	7.558		11.231	< 0.001	69.881	99.892
Direct Bilirubin	39.792	18.096	0.213	2.199	0.030	3.867	75.716

Dependent variable: ISM-1. R = 0.336; R^2 = 0.076; F = 3.024; p = 0.021; Durbin-Watson = 1.637. ISM-1: isthmin-1; CI: confidence interval; B: unstandardized regression coefficient; SE: standard error; β: standardized regression coefficient.

Discussion

This study evaluated serum ISM-1 levels in patients with chronic hepatitis B infection and explored its potential clinical relevance in relation to viral replication and hepatic dysfunction. The principal finding was that serum ISM-1 concentrations were significantly lower in patients with chronic HBV infection compared with healthy controls. This observation suggests that ISM-1 may reflect disease-related alterations rather than representing a purely metabolic marker, and it supports a possible role for ISM-1 within the complex host–virus interaction in chronic HBV infection.

ROC analysis showed high sensitivity (97.0%) but low specificity (38.7%) for ISM-1 in distinguishing patients from controls. Although this performance limits its role as a standalone diagnostic marker, the high sensitivity supports its potential utility in screening settings. ISM-1 may therefore be more informative when used in combination with established virological and biochemical markers, consistent with the multi-marker approach increasingly adopted for emerging host-derived biomarkers in chronic hepatitis [4].

A significant finding of this study is the negative correlation between serum ISM-1 levels and HBV DNA levels. Patients with undetectable HBV DNA had higher ISM-1 levels compared to those with viral loads ≥ 1000 IU/mL, indicating that increased viral replication correlates with diminished ISM-1 levels. This observation supports the hypothesis that HBV influences host immunometabolic pathways to sustain chronic infection. Previous research indicates that HBV disrupts innate immune signaling and alters cellular metabolism, thereby promoting immune tolerance and viral persistence [7–10]. In this framework, diminished ISM-1 levels in patients with heightened viral loads may signify modifications in host metabolic pathways pertinent to immune regulation.

The biological role of ISM-1 appears to be context-dependent. Increased ISM-1 levels have been reported in some metabolic disorders, whereas reduced levels have been observed in type 2 diabetes, reflecting its complex and disease-specific regulation [6,11]. The inverse association observed in chronic HBV infection suggests that ISM-1 may be regulated differently in infectious versus metabolic conditions and may reflect immunometabolic responses to persistent viral infection rather than general metabolic status.

Autophagy plays a role in HBV replication and immune evasion, as viral modulation of autophagy promotes immune tolerance and persistence [12]. Although a direct link between ISM-1 and autophagy has not been established, its involvement in apoptosis and cell survival suggests potential interaction with HBV-regulated pathways [13,14]. Chronic HBV infection increases the risk of hepatocellular carcinoma through sustained immune dysregulation and inflammation [15–17]. Given the reported pro-apoptotic and pro-tumorigenic effects of ISM-1 in cancer models [6,18,19], reduced ISM-1 levels in patients with higher viral loads may reflect viral suppression of host protective mechanisms. These findings should be considered hypothesis-generating and require validation in mechanistic and longitudinal studies.

An additional finding of this study was the significant positive correlation between ISM-1 levels and direct bilirubin observed during multivariate analysis. Direct bilirubin is a recognized indicator of hepatocellular dysfunction and compromised biliary excretion [20]. However, emerging evidence indicates that bilirubin may also provide antioxidant and cytoprotective benefits. Despite lower overall ISM-1 levels in chronic HBV patients, their correlation with direct bilirubin may signify a response to hepatocellular stress. Given ISM-1's role in apoptosis and cellular survival, this relationship may suggest the activation of adaptive cellular mechanisms in response to liver injury. In agreement with prior research, ISM-1 regulation seems to vary based on disease severity and clinical context [6]. Further research is required to ascertain whether ISM-1 has a direct role in hepatic injury responses or merely mirrors changes resulting from liver dysfunction.

Conclusions

Serum ISM-1 levels are decreased in chronic HBV infection and show an inverse association with viral replication. The correlation with direct bilirubin indicates a relationship between ISM-1 and hepatic dysfunction. Despite its limited specificity, ISM-1 may serve as a complementary marker when evaluated with

established virological and biochemical indicators. Additional longitudinal and mechanistic investigations are necessary to elucidate its regulation in chronic HBV infection and its prospective role in disease monitoring and therapeutic decision-making.

Limitations

The main limitation of this study is its cross-sectional design, which prevents causal interpretation. Although an inverse association between serum ISM-1 levels and HBV viral load was identified, it remains uncertain whether reduced ISM-1 is a consequence of viral replication, a host factor contributing to persistence, or the result of unmeasured confounding variables. The relatively small sample size may also limit generalizability.

Furthermore, the interindividual variability observed in ISM-1 concentrations among healthy control subjects underscores the context-sensitive modulation of this adipokine. The regression model's relatively modest explanatory power (R^2 = 0.076) implies that, although direct bilirubin serves as a significant predictor, a substantial proportion of the variability in ISM-1 levels remains inadequately accounted for by the variables incorporated in this investigation. This finding suggests that additional unquantified clinical, metabolic, or immunological determinants, such as specific cytokine profiles, markers of insulin sensitivity, or indices of oxidative stress, are likely to play a role in the intricate regulation of ISM-1 within the framework of chronic HBV infection.

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Conflict of interest

No conflict of interest is declared.

References

1. Liu Y, Wu D, Zhang K, Ren R, Liu Y, Zhang S, Zhang X, Cheng J, Chen L, Huang J (2024) Detection technology and clinical applications of serum viral products of hepatitis B virus infection. Front Cell Infect Microbiol 14: 1402001. doi: 10.3389/fcimb.2024.1402001.
2. Boora S, Sharma V, Kaushik S, Bhupatiraju AV, Singh S, Kaushik S (2023) Hepatitis B virus-induced hepatocellular carcinoma: a persistent global problem. Braz J Microbiol 54: 679–689. doi: 10.1007/s42770-023-00970-y.
3. Hao K-y, Fan Y, Zhang Y-q, Yu Y-c (2025) Coexisting patterns and significance of serum HBV RNA and HBV DNA in patients with treatment-naïve chronic hepatitis B virus infection. Front Med 11: 1525476. doi: 10.3389/fmed.2024.1525476.
4. Kramvis A, Chang KM, Dandri M, Farci P, Glebe D, Hu J, Janssen HLA, Lau DTY, Penicaud C, Pollicino T, Testoni B, Van Bömmel F, Andrisani O, Beumont-Mauviel M, Block TM, Chan HLY, Cloherty GA, Delaney WE, Geretti AM, Gehring A, Jackson K, Lenz O, Maini MK, Miller V, Protzer U, Yang JC, Yuen MF, Zoulim F, Revill PA (2022) A roadmap for serum biomarkers for hepatitis B virus: current status and future outlook. Nat Rev Gastroenterol Hepatol 19: 727–745. doi: 10.1038/s41575-022-00649-z.
5. Hu M, Zhang X, Hu C, Teng T, Tang QZ (2022) A brief overview about the adipokine: isthmin-1. Front Cardiovasc Med 9: 939757. doi: 10.3389/fcvm.2022.939757.
6. Li M, Yang Y, Ma Q, Zhang N, Cao S, Chang B, Yi XJ (2023) Advances in research of biological functions of isthmin-1. J Cell Commun Signal 17: 507–521. doi: 10.1007/s12079-023-00732-3.
7. Ma Z, Cao Q, Xiong Y, Zhang E, Lu M (2018) Interaction between hepatitis B virus and toll-like receptors: current status and potential therapeutic use for chronic hepatitis B. Vaccines (Basel) 6: 6. doi: 10.3390/vaccines6010006.
8. Kayesh MEH, Kohara M, Tsukiyama-Kohara K (2021) Toll-like receptor response to hepatitis B virus infection and potential of TLR agonists as immunomodulators for treating chronic hepatitis B: an overview. Int J Mol Sci 22: 10462. doi: 10.3390/ijms221910462.
9. Li Y, Li S, Duan X, Yang C, Xu M, Chen L (2020) Macrophage phenotypes and hepatitis B virus infection. J Clin Transl Hepatol 8: 424–431. doi: 10.14218/JCTH.2020.00046.
10. Bei J, Chen Y, Zhang Q, Wang X, Lin L, Huang J, Huang W, Cai M, Cai W, Guo Y, Zhu K (2023) HBV suppresses macrophage immune responses by impairing the TCA cycle through the induction of CS/PDHC hyperacetylation. Hepatol Commun 7: e0294. doi: 10.1097/HC9.0000000000000294.
11. Alshawaf E, Marafie SK, Abu-Farha M, Albatineh AN, Alramah T, Albuhairi A, Al Qassar Y, Zinoun R, Shalabi R, Behbehani S, Mohammed D, Alajmi F, Abdalla MA, Al-Ozairi E, Shehab M, Abdul-Ghani M, Al-Mulla F, Abubaker J (2025) Circulating isthmin-1 levels and their relationship with diabetes and metabolic diseases in Kuwaiti adults. Biomedicines 13: 101. doi: 10.3390/biomedicines13010101.
12. Chuang YC, Ou JHJ (2023) Regulation of hepatitis B virus replication by autophagic membranes. Autophagy 19: 1357–1358. doi: 10.1080/15548627.2022.2117974.
13. Lam TYW, Nguyen N, Peh HY, Shanmugasundaram M, Chandna R, Tee JH, Ong CB, Hossain MZ, Venugopal S, Zhang T, Xu S, Qiu T, Kong WT, Chakarov S, Srivastava S, Liao W, Kim JS, Teh M, Ginhoux F, Wong WSF, Ge R (2022) ISM1 protects lung homeostasis via cell-surface GRP78-mediated alveolar macrophage apoptosis. Proc Natl Acad Sci USA 119: e2019161119. doi: 10.1073/pnas.2019161119.
14. Sahiri V, Caron J, Roger E, Desterke C, Ghachem K, Mohamadou I, Serre J, Prakoura N, Fellahi S, Placier S, Adriouch S, Zhang L, Chadjichristos CE, Chatziantoniou C, Lorenzo HK, Boffa JJ (2023) The angiogenesis inhibitor isthmin-1 (ISM1) is overexpressed in experimental models of

glomerulopathy and impairs the viability of podocytes. Int J Mol Sci 24: 2723. doi: 10.3390/ijms24032723.
15. Hwang SY, Danpanichkul P, Agopian V, Mehta N, Parikh ND, Abou-Alfa GK, Singal AG, Yang JD (2025) Hepatocellular carcinoma: updates on epidemiology, surveillance, diagnosis and treatment. Clin Mol Hepatol 31 Suppl: S228–254. doi: 10.3350/cmh.2024.0824.
16. Teng CF, Wu HC, Su IJ, Jeng LB (2020) Hepatitis B virus pre-S mutants as biomarkers and targets for the development and recurrence of hepatocellular carcinoma. Viruses 12: 945. doi: 10.3390/v12090945.
17. Shen C, Jiang X, Li M, Luo Y (2023) Hepatitis virus and hepatocellular carcinoma: recent advances. Cancers (Basel) 15: 533. doi: 10.3390/cancers15020533.
18. Chen M, Zhang Y, Yu VC, Chong YS, Yoshioka T, Ge R (2014) Isthmin targets cell-surface GRP78 and triggers apoptosis via induction of mitochondrial dysfunction. Cell Death Differ 21: 797–810. doi: 10.1038/cdd.2014.3.
19. Zhou X, Zhang K, Wang C, Teng Y, Yu P, Cai W, Gao W, Li M, Ding Y, Sun P, Chen F, Wang Y, Ma J, Maeshige N, Ma X, Li Q, Liang X, Zhang Y, Su D (2024) Isthmin-1 promotes growth and progression of colorectal cancer through the interaction with EGFR and YBX-1. Cancer Lett 590: 216868. doi: 10.1016/j.canlet.2024.216868.
20. Ma Y, Du L, Zhou S, Bai L, Tang H (2023) Association of direct bilirubin to total bilirubin ratio with 90-day mortality in patients with acute-on-chronic liver failure. Front Med (Lausanne) 10: 1286510. doi: 10.3389/fmed.2023.1286510.