

· 病毒性肝炎 ·

DOI: 10.12449/JCH260311

慢性乙型肝炎低病毒血症患者HBV RNA的表达及临床意义

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摘要: **目的** 探讨低病毒血症(LLV)患者血清乙型肝炎病毒(HBV)RNA的表达特征,并评估其对LLV的辅助诊断价值。**方法** 选取2023年12月—2025年5月在遵义医科大学附属医院就诊的402例慢性乙型肝炎(CHB)患者,根据不同病毒载量分为完全病毒学应答(CVR)组($n=190$, HBV DNA < 20 IU/mL)和LLV组($n=212$, 20 IU/mL $\leq$ HBV DNA $< 2\,000$ IU/mL)。对两组患者年龄、性别、疾病类型、血清HBV RNA、乙型肝炎病毒e抗原(HBeAg)、丙氨酸氨基转移酶(ALT)、天冬氨酸氨基转移酶(AST)及总胆红素(TBil)等指标进行分析,同时根据LLV组中HBeAg状态分为HBeAg阴性组($n=140$)和HBeAg阳性组($n=72$)。计数资料两组间比较采用 χ^2 检验;计量资料两组间比较采用Mann-Whitney U 检验。通过多因素Logistic回归分析CHB患者发生LLV的影响因素。运用Spearman秩相关分析LLV组中HBV RNA与HBV DNA、ALT、AST及TBil的相关性。应用受试者操作特征(ROC)曲线评估HBV RNA对LLV的诊断效能。**结果** 与CVR组相比,LLV组患者的血清HBV RNA水平更高[$3(1 \sim 5)$ log₁₀ copies/mL vs $2(1 \sim 3)$ log₁₀ copies/mL, $Z=-2.346$, $P=0.019$],乙型肝炎肝硬化(31.13% vs 22.11%, $\chi^2=4.155$, $P=0.042$)及肝细胞癌(9.91% vs 4.74%, $\chi^2=3.876$, $P=0.049$)患者占比均较高。多因素Logistic回归分析显示,HBV RNA是CHB患者发生LLV的独立危险因素(比值比=1.163, 95%置信区间:1.058 ~ 1.278, $P=0.002$)。在LLV患者中,HBeAg阳性者HBV RNA水平显著高于HBeAg阴性者[$6(4 \sim 7)$ log₁₀ copies/mL vs $2(1 \sim 3)$ log₁₀ copies/mL, $Z=-9.962$, $P<0.001$]。相关性分析结果显示,LLV患者HBV RNA水平与HBV DNA、ALT、AST及TBil均无显著相关性(P 值均 >0.05)。ROC曲线分析表明,HBV RNA诊断LLV的曲线下面积为0.567($P=0.021$),最佳截断值为4.5 log₁₀ copies/mL,灵敏度为30.7%,特异度为85.8%。**结论** 血清HBV RNA水平是CHB患者发生LLV的独立危险因素,尤其在HBeAg阳性患者中表达显著升高,可作为临床风险评估的潜在生物学标志物。

关键词: 慢性乙型肝炎; 低病毒血症; RNA, 病毒; 诊断**基金项目:** 贵州省科学技术基金项目(黔科合基础-zk[2025]面上384)

Expression and clinical significance of HBV RNA in chronic hepatitis B patients with low-level viremia

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Abstract: Objective To investigate the expression characteristics of serum HBV RNA in patients with low-level viremia (LLV) and its value in the diagnosis of LLV. **Methods** A total of 402 chronic hepatitis B (CHB) patients who attended Affiliated Hospital of Zunyi Medical University from December 2023 to May 2025 were enrolled, and according to their viral load, they were divided into complete virologic response (CVR) group (190 patients with HBV DNA < 20 IU/mL) and LLV group (212 patients with an HBV DNA level of ≥ 20 IU/mL and $< 2\,000$ IU/mL). The two groups were analyzed in terms of age, sex, disease type, serum HBV RNA, HBeAg, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBil), and according to HBeAg status, the patients in the LLV group were further divided into HBeAg-negative group with 140 patients and HBeAg-positive group with 72 patients. The chi-square test was used for comparison of categorical data between two groups, and the Mann-Whitney U test was used for comparison of continuous data between two groups. A multivariate Logistic regression

analysis was used to investigate the influencing factors for LLV in CHB patients, and a Spearman's rank correlation analysis was used to analyze the correlation of HBV RNA with HBV DNA, ALT, AST, and TBil in the LLV group. The receiver operating characteristic (ROC) curve was plotted to evaluate the efficacy of HBV RNA in the diagnosis of LLV. **Results** Compared with the CVR group, the LLV group had a significantly higher serum level of HBV RNA [$3(1-5) \log_{10}$ copies/mL vs $2(1-3) \log_{10}$ copies/mL, $Z=-2.346$, $P=0.019$] and a significantly higher proportion of patients with hepatitis B cirrhosis (31.13% vs 22.11%, $\chi^2=4.155$, $P=0.042$) or hepatocellular carcinoma (9.91% vs 4.74%, $\chi^2=3.876$, $P=0.049$). The multivariate Logistic regression analysis showed that HBV RNA (odds ratio=1.163, 95% confidence interval: 1.058—1.278, $P=0.002$) was an independent risk factor for the onset of LLV in CHB patients. Among the patients with LLV, HBeAg-positive patients had a significantly higher level of HBV RNA than HBeAg-negative patients [$6(4-7) \log_{10}$ copies/mL vs $2(1-3) \log_{10}$ copies/mL, $Z=-9.962$, $P<0.001$]. The correlation analysis showed that HBV RNA level had no significant correlation with HBV DNA, ALT, AST, or TBil in the patients with LLV (all $P>0.05$). The ROC curve analysis showed that HBV RNA had an AUC of 0.567 for the diagnosis of LLV ($P=0.021$), with an optimal cut-off value of $4.5 \log_{10}$ copies/mL, a sensitivity of 30.7%, and a specificity of 85.8%. **Conclusion** Serum HBV RNA level is an independent risk factor for the development of LLV in CHB patients, and there is a significant increase in the expression of HBV RNA in HBeAg-positive patients. Therefore, it may serve as a potential biomarker for clinical risk assessment.

Key words: Hepatitis B, Chronic; Low-Level Viremia; RNA, Viral; Diagnosis

Research funding: Science and Technology Research Foundation of Guizhou Province (QKHJC-zk[2025]MS384)

乙型肝炎病毒(hepatitis B virus, HBV)感染是全球范围内一项重大公共卫生挑战。据统计,全球约有2.96亿人感染HBV,其中部分患者进展为慢性乙型肝炎(chronic hepatitis B, CHB)^[1],每年导致死亡人数超过82万^[2]。尽管核苷(酸)类似物和聚乙二醇干扰素等一线抗病毒药物已显著改善CHB患者的临床预后^[3],但部分患者在接受规范治疗后仍未能实现完全病毒学应答(complete virological response, CVR),表现为血清HBV DNA持续低水平阳性,即低病毒血症(low-level viremia, LLV)^[4-5]。多项研究显示,与达到CVR的患者相比,LLV不仅可能提示病毒耐药,还与持续肝脏炎症、肝纤维化进展及肝细胞癌等不良结局密切相关,因而成为CHB治疗的关键难题^[6-8]。根据国内外相关报道,在接受一线抗病毒治疗的CHB患者中,LLV的发生率为17.8%~40.0%^[9-10]。LLV形成机制复杂,涉及共价闭合环状DNA(covalently closed circular DNA, cccDNA)的长期存留、宿主免疫调节及药物抑制效能等多方面因素,其中cccDNA难以彻底清除是核心原因^[3]。cccDNA是评估CHB患者预后的重要指标,其检测依赖肝脏活组织检查,因而在临床应用中受限。血清HBV RNA作为cccDNA的直接转录产物,可间接反映其转录活性,成为潜在的理想替代标志物^[11-12]。相关研究提示,血清HBV RNA水平可能与抗病毒治疗应答相关,在LLV患者中,其水平或可预测疗效、停药后病毒学反弹风险及长期病毒抑制能力,对于评估感染状态与疾病进展具有

重要临床价值^[13]。本研究拟探讨HBV RNA与LLV的关系,以期HBV感染者的临床管理提供理论依据。

1 资料与方法

1.1 研究对象 选取2023年12月—2025年5月于本院就诊的CHB患者402例,收集年龄、性别、疾病类型(包括CHB、乙型肝炎肝硬化及乙型肝炎相关肝细胞癌)、血清HBV RNA、HBV DNA、乙型肝炎病毒e抗原(HBV e antigen, HBeAg)、丙氨酸氨基转移酶(alanine amino-transferase, ALT)、天冬氨酸氨基转移酶(aspartate transferase, AST)、总胆红素(total bilirubin, TBil)及抗病毒药物种类和抗病毒时长等指标。根据病毒载量,将患者分为CVR组($n=190$, HBV DNA <20 IU/mL)和LLV组($n=212$, $20 \text{ IU/mL} \leq \text{HBV DNA} < 2\,000 \text{ IU/mL}$)两组。LLV患者进一步按照HBeAg状态分为HBeAg阴性组($n=140$)及HBeAg阳性组($n=72$)。

1.2 纳入及排除标准 纳入标准:(1)年龄 >18 岁;(2)CHB诊断和LLV诊断均符合《慢性乙型肝炎防治指南(2022年版)》^[14]中的标准,乙型肝炎相关肝细胞癌依据《原发性肝癌诊疗指南(2024年版)》^[15]中的诊断标准确诊。排除标准:(1)因联合使用两种抗病毒药物而获得CVR者不纳入CVR组;(2)正在接受或曾经接受干扰素或免疫制剂治疗者;(3)合并其他类型病毒性肝炎、酒精性肝炎或自身免疫性肝病等;(4)临床资料不完整者。

1.3 LLV、CVR判定 将接受恩替卡韦(entecavir,

ETV)、富马酸替诺福韦二吡呋酯(tenofovir disoproxil fumarate, TDF)、富马酸丙酚替诺福韦(tenofovir alafenamide fumarate, TAF)或艾米替诺福韦(tenofovir amibufenamide, TMF)且依从性良好的CHB患者,治疗48周及以上,若血清仍可检测到HBV DNA,但 $<2\,000\text{ IU/mL}$ 定义为LLV^[14]。将CVR定义为抗病毒治疗48周及以上,血清HBV DNA持续检测不到^[16]。

1.4 检测方法 采用逆转录实时荧光定量聚合酶链式反应检测HBV RNA,引物序列为5'-TAATACGACTCACT ATAGGG-3',最低检出限为50 copies/mL;HBV DNA检测采用实时荧光定量聚合酶链式反应,最低检出限为15 IU/mL。所有测定均由本院专业技术人员操作完成。

1.5 统计学方法 应用SPSS 27.0软件进行数据分析,使用Graphpad Prism 10.5软件绘制统计图。非正态分布的计量资料以 $M(P_{25} \sim P_{75})$ 表示,两组间比较采用Mann-Whitney U 检验。计数资料两组间比较采用 χ^2 检验。通过多因素Logistic回归分析CHB患者发生LLV的影响因素。相关性检验采用Spearman相关性分析。采用受试者操作特征(receiver operator characteristic, ROC)曲线评估HBV RNA的诊断效能。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 CVR组和LLV组患者基线特征及临床指标比较 LLV组患者的血清HBV RNA载量、乙型肝炎肝硬化及肝细胞癌患者占比均高于CVR组,差异均有统计学意义(P 值均 <0.05);两组患者年龄、性别、HBeAg阳性、ALT、AST及TBil水平差异均无统计学意义(P 值均 >0.05)(表1)。

2.2 CVR组和LLV组患者抗病毒治疗情况 在抗病毒药物使用方面,ETV在两组患者中的使用比例均最高。LLV组中,TDF、TAF和TMF的使用比例分别为21.70%、20.75%和0.47%,联合用药者占10.85%;CVR组中,TDF、TAF和TMF的使用比例分别为10.00%、37.37%和10.53%。在抗病毒治疗时长方面,LLV组中治疗 ≥ 48 周 ~ 96 周、 ≥ 96 周 ~ 144 周及 ≥ 144 周的患者分别占68.40%、24.06%和7.55%(表2)。

2.3 多因素Logistic回归分析 将单因素分析中有统计学意义的指标纳入多因素Logistic回归分析,结果显示,HBV RNA载量是CHB患者发生LLV的独立危险因素($P<0.05$)(表3)。

2.4 LLV患者中HBeAg阴性组和HBeAg阳性组的指标比较 HBeAg阳性组的HBV RNA载量显著高于HBeAg阴性组($P<0.001$);两组在乙型肝炎肝硬化和乙型肝炎相关肝细胞癌比例、HBV DNA载量、ALT、AST及TBil水平方面,差异均无统计学意义(P 值均 >0.05)(表4)。

2.5 LLV组患者血清HBV RNA与HBV DNA、ALT、AST及TBil的相关性分析 Spearman相关性分析结果显示,HBV RNA与HBV DNA($r=0.051, P=0.462$)、ALT($r=0.121, P=0.080$)、AST($r=0.125, P=0.070$)及TBil($r=-0.011, P=0.871$)水平均无显著相关性。

2.6 血清HBV RNA对LLV的诊断效能 HBV RNA的曲线下面积(area under the curve, AUC)为0.567(95%置信区间:0.511 $\sim$ 0.623, $P=0.021$),通过计算约登指数,得出血清HBV RNA诊断LLV的最佳截断值为4.5 log₁₀ copies/mL,灵敏度为30.7%,特异度为85.8%,阳性预测值为70.7%,阴性预测值为52.6%(图1)。

表1 CVR组和LLV组患者的基线特征及临床指标比较

Table 1 Comparison of baseline characteristics and clinical indicators between CVR and LLV groups

指标	CVR组($n=190$)	LLV组($n=212$)	统计值	P 值
年龄(岁)	42.5(35.0 $\sim$ 50.0)	40.0(31.0 $\sim$ 50.7)	$Z=-1.628$	0.104
≥ 60 岁[例(%)]	12(6.32)	13(6.13)	$\chi^2=0.006$	0.939
性别[例(%)]			$\chi^2=0.273$	0.601
男	116(61.05)	124(58.49)		
女	74(38.95)	88(41.51)		
乙型肝炎肝硬化[例(%)]	42(22.11)	66(31.13)	$\chi^2=4.155$	0.042
乙型肝炎相关肝细胞癌[例(%)]	9(4.74)	21(9.91)	$\chi^2=3.876$	0.049
HBV RNA(log ₁₀ copies/mL)	2(1 $\sim$ 3)	3(1 $\sim$ 5)	$Z=-2.346$	0.019
HBeAg阳性[例(%)]	50(26.32)	72(33.96)	$\chi^2=2.772$	0.096
ALT(U/L)	29.00(21.00 $\sim$ 40.00)	31.00(20.00 $\sim$ 46.00)	$Z=-1.034$	0.301
AST(U/L)	29.00(24.00 $\sim$ 35.00)	30.00(24.00 $\sim$ 40.00)	$Z=-1.914$	0.056
TBil($\mu\text{mol/L}$)	14.45(11.17 $\sim$ 18.85)	14.30(10.63 $\sim$ 19.50)	$Z=-0.219$	0.827

注:CVR,完全病毒学应答;LLV,低病毒血症;HBV,乙型肝炎病毒;HBeAg,乙型肝炎病毒e抗原;ALT,丙氨酸氨基转移酶;AST,天冬氨酸氨基转移酶;TBil,总胆红素。

3 讨论

LLV的形成与HBV独特的生物学特性密切相关,其核心在于cccDNA在肝细胞内的持续存在。在LLV状态下,cccDNA的稳定性与转录活性受表观遗传修饰、宿主细胞因子及病毒蛋白反馈等多因素调控^[17],提示其动态平衡可能是LLV发生与维持的关键机制。近年来,作为cccDNA的非侵入性替代标志物,血清HBV RNA在LLV的评估中发挥了重要作用^[18]。

本研究结果显示,LLV组患者的血清HBV RNA水

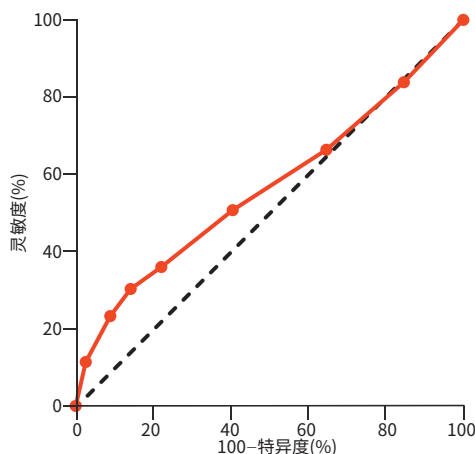
平显著高于CVR组;多因素 Logistic 回归分析证实,HBV RNA 载量为发生 LLV 的独立危险因素。血清 HBV RNA 水平较高的经治 CHB 患者发生 LLV 的概率是低水平患者的 1.163 倍,该结论与国内多项研究结果一致^[19-20]。ROC 曲线分析表明,血清 HBV RNA 诊断 LLV 的 AUC 仅为 0.567,诊断灵敏度较低,提示其作为独立诊断指标的判别能力有限。这种“统计学显著但判别效能不高”的矛盾现象,可能是因为在本研究,尽管 LLV 组 HBV RNA 水平整体高于 CVR 组,但 LLV 组中占比较高的 HBeAg 阴性患者其 HBV RNA 水平普遍较低,从而影响了该指标的整体识别灵敏度。虽然血清

表2 CVR组和LLV组患者抗病毒情况

Table 2 Comparison of antiviral regimens between patients in the CVR and LLV groups

指标	CVR组(n=190)	LLV组(n=212)
抗病毒药物[例(%)]		
ETV	80(42.11)	98(46.23)
TDF	19(10.00)	46(21.70)
TAF	71(37.37)	44(20.75)
TMF	20(10.53)	1(0.47)
联合用药	0(0.00)	23(10.85)
抗病毒治疗时间[例(%)]		
≥48周~96周	—	145(68.40)
≥96周~144周	—	51(24.06)
≥144周	—	16(7.55)

注:CVR,完全病毒学应答;LLV,低病毒血症;ETV,恩替卡韦;TDF,富马酸替诺福韦二吡呋酯;TAF,富马酸丙酚替诺福韦;TMF,艾米替诺福韦;—表示未记录。



注:HBV,乙型肝炎病毒;LLV,低病毒血症;ROC,受试者操作特征。

图1 HBV RNA诊断LLV的ROC曲线

Figure 1 ROC curve of HBV RNA for diagnosing LLV

表3 CHB患者发生LLV的多因素Logistic回归分析

Table 3 Multivariate Logistic analysis of factors associated with LLV occurrence in chronic hepatitis B patients

指标	β 值	SE	Wald	OR(95%CI)	P值
肝硬化(无=0,有=1)	0.372	0.260	2.042	1.451(0.871~2.417)	0.153
肝细胞癌(无=0,有=1)	0.505	0.465	1.179	1.657(0.666~4.120)	0.278
HBV RNA($\log_{10}$ copies/mL)	1.151	0.048	9.721	1.163(1.058~1.278)	0.002

注:CHB,慢性乙型肝炎;LLV,低病毒血症;HBV,乙型肝炎病毒;SE,标准误;OR,比值比;95%CI,95%置信区间。

表4 HBeAg阴性组和HBeAg阳性组患者的指标比较

Table 4 Comparison of indicators between patients in the HBeAg-negative group and the HBeAg-positive group

指标	HBeAg 阴性组 (n=140)	HBeAg 阳性组 (n=72)	统计值	P值
乙型肝炎肝硬化[例(%)]	48(34.29)	18(25.00)	$\chi^2=1.912$	0.167
乙型肝炎相关肝细胞癌[例(%)]	16(11.43)	5(6.94)	$\chi^2=1.071$	0.301
HBV RNA($\log_{10}$ copies/mL)	2(1~3)	6(4~7)	$Z=-9.962$	<0.001
HBV DNA($\log_{10}$ IU/mL)	2(1~2)	2(1~2)	$Z=-0.732$	0.464
ALT(U/L)	31.40(19.25~44.75)	31.00(22.00~48.00)	$Z=-0.900$	0.368
AST(U/L)	28.50(24.00~40.75)	30.00(25.00~40.00)	$Z=-0.124$	0.901
TBil(μ mol/L)	14.60(11.00~20.13)	13.70(9.75~18.88)	$Z=-1.202$	0.229

注:HBeAg,乙型肝炎病毒e抗原;HBV,乙型肝炎病毒;ALT,丙氨酸氨基转移酶;AST,天冬氨酸氨基转移酶;TBil,总胆红素。

HBV RNA 诊断效能较低,但在诊断最佳截断值($4.5 \log_{10}$ copies/mL)下,其特异度与阳性预测值较高,使临床医师有相对较高的把握判断可能发展为LLV的群体。这有助于精准地识别出部分需要高度关注的、存在持续低水平病毒复制的患者,从而进行重点管理或干预。值得注意的是,与陈贺等^[21]研究结论不同,本研究未发现LLV组与CVR组的HBeAg阳性率存在统计学差异,这可能与抗病毒药物能高效抑制病毒DNA复制,但对cccDNA无直接清除或降解作用有关。HBeAg阳性通常代表病毒复制更活跃,但在强效药物压制下,其作为病毒复制活跃指标的灵敏度下降,削弱了HBeAg与病毒复制水平的关联。亚组分析显示,在LLV患者中,HBeAg阳性者的血清HBV RNA水平显著高于HBeAg阴性者,这与既往研究结果一致^[22]。HBeAg是由肝细胞修饰和分泌的病毒蛋白,HBeAg阳性患者肝内cccDNA的转录活性可能更高,故监测CHB患者基线及治疗期间的HBeAg状态,有助于早期识别患者对抗病毒治疗的反应^[23]。LLV患者的病毒载量虽保持在较低水平,但肝脏活组织检查发现部分患者的肝脏存在炎症反应及组织学病变,可造成肝脏进一步损伤,甚至发展为肝硬化和肝癌^[24]。本研究结果显示,LLV组乙型肝炎肝硬化和乙型肝炎相关肝细胞癌患者的阳性率均显著高于CVR组,这与多项研究结论相符^[25-27]。LLV已被证实是肝硬化及肝细胞癌发生的独立危险因素^[28-29],故早期干预LLV并降低血清HBV RNA水平,对改善CHB患者长期预后至关重要。相关性分析显示,LLV组患者血清HBV RNA与HBV DNA无显著相关性,这与既往报道的抗病毒治疗后二者相关性降低甚至无相关性的结论一致^[30-31]。其原因可能与药物抑制DNA复制但无法靶向清除cccDNA有关,此时HBV RNA能够更准确地反映肝内病毒模板活性。对于未治疗的患者,血清HBV RNA与HBV DNA则呈正相关^[30],与本团队已发表的研究结果一致^[32]。

综上所述,血清HBV RNA是评估CHB患者病毒学状态的敏感指标。其不仅能更早反映抗病毒治疗中的疗效变化,还可作为LLV的独立预测因子。将血清HBV RNA纳入常规监测,有助于早期识别LLV患者并及时干预,从而降低肝硬化、肝细胞癌等远期风险,对于优化CHB患者的全程管理具有重要临床价值。然而,本研究仍存在一定的局限性:(1)因CVR组未纳入联合抗病毒治疗者,两组抗病毒情况入组条件不一致,故未进行统计分析;(2)血清HBV RNA诊断LLV的AUC

(0.567)较低,限制了其临床适用范围;(3)本研究为单中心回顾性分析,可能存在潜在的选择偏倚;(4)未评估基线血清HBV DNA水平对48周抗病毒药物治疗结局的干扰。因此,本团队计划开展多中心前瞻性队列研究,扩大样本量,覆盖不同基因型及治疗阶段人群,纳入肝组织学数据验证血清HBV RNA与cccDNA活性的关联,建立动态监测模型,进一步探索血清HBV RNA指导个体化治疗的阈值标准。

伦理学声明:本研究方案于2025年8月29日经由遵义医科大学附属医院生物医学研究伦理委员会审批,批号:KLL-2025-353。

利益冲突声明:本文不存在任何利益冲突。

作者贡献声明:陈娅负责提出研究思路,设计研究方案,起草论文;何毅怀负责收集与整理数据,并进行统计学分析;陈应华负责整理数据并绘制统计图;罗亚文负责拟定写作思路,指导撰写文章并最后定稿。

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收稿日期: 2025-09-23; 录用日期: 2025-12-11

本文编辑: 葛俊

引证本文: CHEN Y, HE YH, CHEN YH, et al. Expression and clinical significance of HBV RNA in chronic hepatitis B patients with low-level viremia[J]. J Clin Hepatol, 2026, 42(3): 573-578.

陈娅, 何毅怀, 陈应华, 等. 慢性乙型肝炎低病毒血症患者HBV RNA的表达及临床意义[J]. 临床肝胆病杂志, 2026, 42(3): 573-578.