



慢性乙型肝炎患者的血清标志物基线水平对 干扰素治疗效果的预测价值*

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【摘要】目的 研究长效干扰素治疗核苷经治及初治慢性乙型肝炎(简称慢乙肝)病例的血清标志物变化及对临床预后的评价价值。**方法** 收集2019年10月-2022年4月411例慢乙肝加用长效干扰素病例的临床资料,对经治组及初治组病例的血清标志物进行比较,其中经治病例为HBV感染半年以后经核苷(酸)类治疗半年以上,初治病例为HBV感染半年以后未治疗或停止核苷(酸)类治疗半年以上。采用受试者工作特征曲线(ROC曲线),评价基线HBsAg和HBV前基因组RNA(HBV pgRNA)对两组病例临床治愈的预测价值。**结果** 经治组与初治组治愈率无明显差异。两组中治愈病例的基线HBV DNA、HBsAg及HBeAg水平均低于未治愈病例($P<0.0001$)。在治疗48周时,经治及初治组治愈病例的血清HBsAb水平(mIU/mL)高于未治愈病例(经治: 78.97 ± 22.57 vs. 0.99 ± 0.38 , $P<0.0001$; 初治: 235.50 ± 175.00 vs. 1.32 ± 0.88 , $P<0.0001$),初治治愈病例的血清HBsAb水平(mIU/mL)高于经治治愈病例(235.50 ± 175.00 vs. 78.97 ± 22.57 , $P<0.0001$)。治疗0~60周内两组治愈病例的HBV pgRNA水平比未治愈组低($P<0.0001$)。多因素logistic回归及ROC曲线分析显示:血清基线HBsAg是影响经治和初治病例干扰素疗效的影响因素和预测指标,其曲线下面积分别为0.80[95%置信区间(confidence interval, CI): 0.7423~0.8615, $P<0.0001$]和0.74(95%CI: 0.6283~0.8604, $P=0.0079$),其最佳截断值分别为244.60 IU/mL和934.40 IU/mL。而初治病例的血清基线HBV pgRNA水平 <1340.00 copies/mL时有较好的敏感性和特异性预判疗效,其基线HBV pgRNA的曲线下面积为0.9649(95%CI: 0.9042~1.000, $P<0.0001$)。**结论** 经治和初治病例中获得临床治愈的患者其基线HBV DNA、HBsAg、HBeAg以及治疗期间HBV pgRNA水平更低,第48周HBsAb水平更高。基线HBsAg水平能有效预测经治及初治患者的临床治愈结局,基线HBV pgRNA水平对初治患者的治疗结局也呈现较高的预测价值。

【关键词】 乙型肝炎病毒 前基因组RNA HBsAg HBeAg 预后

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【Abstract】 Objective To study the changes in the serum markers in chronic hepatitis B patients who have had previous treatment with long-acting interferon therapy of nucleoside and those who have not and to assess the value of the serum markers for clinical prognosis evaluation. **Methods** The clinical data of 411 cases of chronic hepatitis B were collected. All cases were given the additional treatment of long-acting interferon between October 2019 to April 2022. The cases were divided into two groups, a previously treated group consisting of patients who had been treated with nucleoside and nucleotide analogues (NAs) for more than 6 months after they became infected with hepatitis B virus (HBV) for over 6 months and an initial treatment group, or treatment naïve group, consisting of patients who had HBV infection for over 6 months and received no treatment or patients who have stopped NAs therapy for more than 6 months. The serum marker levels of the previously treated group and the initial treatment group, i.e., the previously treatment-naïve patients, were compared, and the receiver operating characteristics (ROC) curve was used to evaluate the value of the baseline levels of hepatitis B surface antigen (HBsAg) and HBV pregenomic RNA (pgRNA) for predicting the rate of cured cases in the two groups. **Results** There was no significant difference in the rate of cured cases between the previously treated group and the initial treatment group. The baseline HBV DNA, HBsAg, and hepatitis B e antigen (HBeAg) levels of the cured cases in both groups were significantly lower than those in the uncured cases ($P<0.0001$). After 48 weeks of treatment, the serum HBsAb levels (mIU/mL) of the cured cases in both the previously treated and initial treatment groups were significantly higher than those of the uncured cases in the two groups (previously treated group: 78.97 ± 22.57 vs.

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0.99±0.38, $P<0.0001$; initial treatment group: 235.50±175.00 vs. 1.32±0.88, $P<0.0001$). The serum HBsAb levels (mIU/mL) of the cured cases in the initial treatment groups were significantly higher than that of cured cases in the previously treated group (235.50±175.00 vs. 78.97±22.57, $P<0.0001$). Within 0 to 60 weeks of treatment, HBV pgRNA levels of cured cases in both groups were significantly lower than those of the uncured cases in both groups ($P<0.0001$). Multivariate logistic regression and ROC curve analysis showed that baseline serum HBsAg was the influencing factor and predictor of interferon efficacy in both the previously treated cases and the initial treatment cases, with the area under the curve (AUC) being 0.80 (95% confidence interval [CI]: 0.7423-0.8615, $P<0.0001$) and 0.74 (95% CI: 0.6283-0.8604, $P=0.0079$), respectively, and the optimal cut-off values being 244.60 IU/mL and 934.40 IU/mL, respectively. However, the baseline serum HBV pgRNA level of under 1340.00 copies/mL in the initial treatment cases led to better sensitivity and better specificity in efficacy prediction, with the AUC of the baseline HBV pgRNA being 0.9649 (95% CI: 0.9042-1.0000, $P<0.0001$). **Conclusion** Among the previously treated cases and the initial treatment cases, patients who achieve clinical cure have lower levels of HBV DNA, HBsAg, and HBeAg at baseline, lower level of HBV pgRNA over the course of their treatment, and higher level of HBsAb at week 48. Baseline HBsAg levels can be used to effectively predict the clinical cure outcomes in previously treated cases and initial treatment cases. Baseline HBV pgRNA levels also exhibit a high predictive value for treatment outcomes in initial treatment cases.

【Key words】 Hepatitis B virus Pregenomic RNA HBsAg HBeAg Prognosis

乙型肝炎病毒(hepatitis B virus, HBV)感染是全球重要的公共卫生问题,约有2.4亿人为慢性HBV感染,每年65万人死于HBV感染引起的并发症^[1]。目前,使用核苷(酸)类(nucleoside and nucleotide analogues, NAs)联合干扰素治疗可以显著降低血清HBV表面抗原(HBsAg)和肝脏HBV共价闭合环状DNA(HBV cccDNA)的水平,并促使HBV表面抗体(HBsAb)产生,实现临床治愈^[2]。宿主的cccDNA半衰期较长,难以彻底从体内清除,其定量水平在预测肝癌发生风险方面有着重要的价值^[3]。HBV前基因组RNA(HBV pgRNA)由HBV cccDNA直接转录产生,可反映cccDNA的转录活性,是慢性乙型肝炎(简称慢乙肝)患者预后的潜在生物学标志物。

慢乙肝临床治愈(或功能性治愈)是指停止治疗后仍保持HBsAg阴性,伴或不伴HBsAb阳性、HBV DNA基因检测为阴性、肝功能的指标正常、肝组织病理的病变得改善^[4]。目前,临床治愈研究处于扩大研究阶段,大部分学者认为NAs经治的慢乙肝病例才是临床治愈的理想人群,该人群的病毒载量已得到有效的控制,并且可能已出现HBV e抗原(HBeAg)转阴。而NAs初治人群的临床治愈研究目前仍处于初级阶段,主要集中在非活动性HBsAg携带状态人群^[5-7],并以回顾性研究为主^[8-9]。本研究通过回顾性比较研究,分析了长效干扰素治疗NAs经治和初治慢乙肝病例的抗病毒效果,以及病毒血清标志物——基线HBsAg和HBV pgRNA对临床治愈的预测价值。

1 对象与方法

1.1 研究对象

选取2019年10月-2022年4月无锡市第五人民医院(无锡市传染病医院)入组使用聚乙二醇干扰素 α -2b(Peg-

IFN α -2b)进行免疫治疗的NAs经治及初治慢乙肝病例。所有病例按《慢性乙型肝炎防治指南(2019年版)》的诊断标准^[4],其中经治病例为HBV感染半年以后经NAs治疗半年以上,初治病例为HBV感染半年以后未治疗或停止NAs治疗半年以上。其他入组标准包括:①年龄18~60岁;②无干扰素治疗禁忌证,同意接受96周的Peg-IFN α -2b治疗,剂量为180 μ g/周,签署干扰素治疗知情同意书。排除标准:①干扰素过敏者;②谷丙转氨酶大于10倍正常值上限(ULN),总胆红素 $>2\times$ ULN;③肝硬化失代偿期,或曾经出现过肝硬化失代偿者;④外周血白细胞数和/或血小板数低于正常值下限者;⑤存在严重的心血管、肺、肾、脑病变者及眼底病变者;⑥合并自身免疫性疾病、精神病、糖尿病、甲状腺功能异常;⑦确诊或疑似肝癌及其他恶性肿瘤者;⑧器官移植术后或准备行器官移植者;⑨正在使用免疫抑制剂者;⑩妊娠或计划2年内妊娠者;⑪酗酒或药瘾者;⑫合并人类免疫缺陷病毒感染;⑬主管医生认为存在其他不宜使用干扰素治疗情况。本研究经无锡市第五人民医院伦理委员会审核批准(伦理编号:2021-019-1)。

1.2 试验设计

所有患者根据指南进行治疗并判断慢乙肝临床治愈^[4,10]。将研究组划分为慢乙肝经治和初治两组。入组干扰素治疗的条件包括:①有乙型肝炎、肝癌家族史的病例,同意NAs治疗联合干扰素抗病毒;②HBsAg低于2000~3000 IU/mL,追求临床治愈的情况下联合使用干扰素抗病毒;③HBsAg高于3000 IU/mL,长期NAs治疗后仍大三阳和/或低病毒血症病例,联合干扰素抗病毒。干扰素使用剂量按体质量分为90、135、180 μ g/周,一周一次,根据身高、体质量和不良反应评价使用剂量的适用

性,48周/疗程,至少完成一个疗程的治疗。在第0、4、12、24、36、48、60周时进行血常规、肝功能、高灵敏度病毒DNA、乙肝五项检测和pgRNA定量检测等,比较经治组及初治组的临床治愈情况及血清标志物。

1.3 检测指标

样本来自于本院的临床生物样本库。定期随访病例并收集血清样品,HBsAg、HBeAg(试剂购自苏州新波生物技术有限公司)均采用新鲜血液进行检测,方法为双抗体夹心时间分辨免疫荧光分析法,阳性临界值0.05 IU/mL、0.1 PEIU/mL。采集干扰素治疗病例的血样本,采用荧光PCR法定量检测高灵敏度HBV DNA载量[试剂购自罗氏诊断产品(上海)有限公司],检测下限为20 IU/mL。保存血清集中进行病毒RNA定量检测,试剂购自北京全式金生物技术有限公司;HBV病毒pgRNA检测采用HBV核酸测定试剂盒(RNA捕获探针法)(购自上海仁度生物科技股份有限公司);DNA酶和反转录试剂盒购自美国ThermoFisher Scientific公司,检测下限为50 copies/mL。

1.4 统计学方法

采用SPSS Statistics 22.0和GraphPad Prism 9.0统计学软件进行数据分析,所有临床指标以 $\bar{x} \pm SE$ 表示,两组间比较采用Student's *t*检验、单因素方差分析和重复测量数据的方差分析;将HBV DNA载量和HBV pgRNA的定量值经过对数转换后再进行统计学分析^[11]。计数资料比较采用卡方检验和构成比分析。采用Bonferroni方法对*P*值进行校正,通过比较调整*P*值,用多因素logistic回归模型分析影响疗效的相关因素,采用受试者工作特征曲线(ROC曲线)及曲线下面积(area under the curve, AUC)分析血清标志物对免疫治疗预后的价值。*P*<0.05为差异有统计学意义。

2 结果

2.1 经治及初治慢乙肝病例参与干扰素治疗的入组及临床治愈情况

共入组慢乙肝病例443例,经过一个疗程以上的干扰素治疗及观察,因不良反应和HBsAg转阴效果不良而放弃跟踪治疗分别为15例和17例,获得随访完整的经治和初治病例分别为341例和70例。2019年入组经治、初治病例分别为4例、1例,无治愈病例;2020年共入组经治病例122例,治愈率为15.57%(19/122);2021年入组经治、初治病例分别为127例、50例,治愈率分别为16.54%(21/127)、22.00%(11/50);2022年入组经治、初治病例分别为88例、19例,治愈率分别为20.45%(18/88)、5.26%(1/19)(图1)。研究结束时所有患者的总体临床治愈率为17.03%(70/411),

其中经治组和初治组患者的临床治愈率分别为17.01%(58/341)和17.14%(12/70),两组临床治愈率差异无统计学意义($\chi^2 = 0.001, P = 0.9783$)。

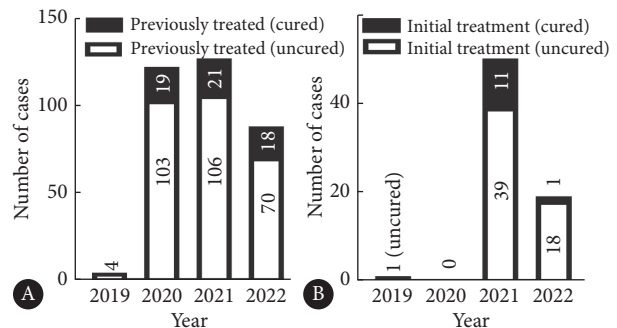


图1 经治组(A)和初治组(B)的临床治愈数

Fig 1 Clinical cured cases in the previously treated group (A) and the initial treatment group (B)

Previously treated group consists of chronic hepatitis B patients who have been treated with nucleoside or nucleotide analogues (NAs); initial treatment group consists of patients who have not received any previous treatment or have stopped NAs therapy for more than half a year.

2.2 不同人群的基线指标比较

初治治愈和未治愈病例的女性比例均高于经治组($P < 0.05$),初治治愈和未治愈病例的基线病毒DNA定量水平均高于经治组($P < 0.0001$);初治和经治组治愈病例的基线DNA、HBsAg及HBeAg水平低于未治愈病例($P < 0.0001$);初治未治愈病例的基线HBsAg水平高于经治未治愈病例($P < 0.0001$);其余指标差异无统计学意义,详见表1。从血清HBeAg状态来看,16.13%(55/341)的经治病例为基线HBeAg阳性,其中7.27%(4/55)实现临床治愈,92.73%(51/55)未治愈。另外,15.71%(11/70)的初治病例为基线HBeAg阳性,无治愈病例。

2.3 不同人群干扰素治疗0~48周血清HBsAg和HBsAb的定量比较

见图2。经治治愈病例在治疗0~24周内血清HBsAg水平(IU/mL)降低[0周(62.29 ± 24.27)>12周(20.28 ± 8.14)>24周(2.83 ± 1.56), $P < 0.0001$]。在0~48周HBsAb观察期的早期,经治组和初治组治愈病例抗体出现明显增高($P < 0.05$)。治愈病例在48周时可产生较高水平的血清HBsAb,最高达1279.80 mIU/mL;而未治愈组血清HBsAb水平较低,最高达19.30 mIU/mL。治疗48周时,经治及初治组治愈病例的血清HBsAb水平(mIU/mL)均高于未治愈病例(经治: 78.97 ± 22.57 vs. 0.99 ± 0.38 , $P < 0.0001$;初治: 235.50 ± 175.00 vs. 1.32 ± 0.88 , $P < 0.0001$);初治治愈病例的血清HBsAb水平高于经治治愈病例($P < 0.0001$)。

2.4 不同人群干扰素治疗0~60周HBV pgRNA定量比较

收集127例有2次以上血清HBV pgRNA定量结果的

表 1 入组不同人群的基线指标比较

Table 1 Comparison of baseline indicators in the different populations enrolled

Group	n	Male/case (%)	Body mass index/(kg/m ²)	Age/yr.	DNA/(lg IU/mL)	HBsAg/(IU/mL)	HBeAg/(PEIU/mL)
Previously treated							
Cured	58	50 (86.21)	24.96±1.15	39.02±1.01	2.57±2.21	252.70±65.30	0.02±0.01
Uncured	283	234 (82.69)	23.51±0.57	39.10±0.50	6.19±5.86	2812.00±450.60	3.28±1.49
P		0.5126	0.4349	0.1307	<0.000 1	<0.000 1	<0.000 1
Initial treatment							
Cured	12	7 (58.33) ^a	23.65±0.85	40.00±2.45	4.06±3.87 ^b	198.80±92.89	0
Uncured	58	35 (60.34) ^b	23.26±1.06	35.30±1.41	6.80±6.55 ^b	8 164.00±2 639.00 ^b	4.04±3.81
P		0.8970	0.8870	0.3156	<0.000 1	<0.000 1	<0.000 1

^a P<0.05, ^b P<0.000 1, vs. the corresponding cases in the previously treated group. The baseline HBV DNA normal range is 0-20 IU/mL. The normal range of HBsAg is 0-10 IU/mL. The normal range of HBeAg is 0-0.1 PEIU/mL.

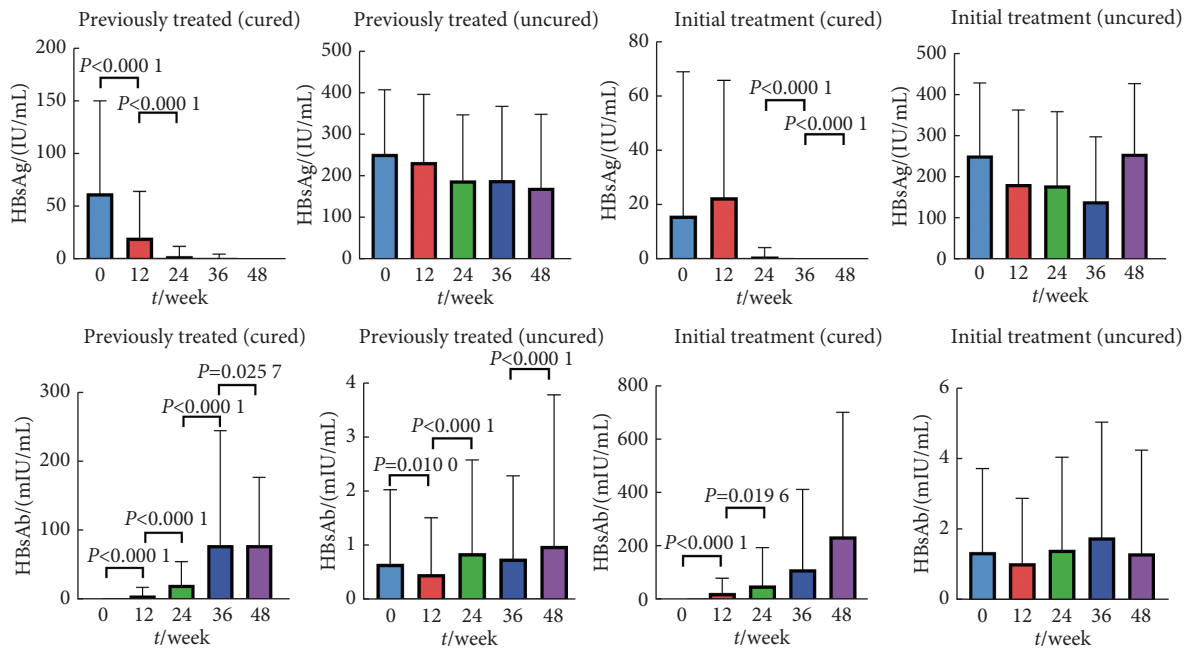


图 2 不同人群随访病例干扰素治疗后的HBsAg和HBsAb水平比较

Fig 2 Comparison of HBsAg and HBsAb levels after interferon treatment among the follow-up cases in different populations

Previously treated (cured), n=58; previously treated (uncured), n=283; initial treated (cured), n=12; initial treated (uncured), n=58.

病例, 分析发现, 无论经治组还是初治组, 治疗后临床治愈病例HBV pgRNA水平比未治愈组低, 各组病例治疗后HBV pgRNA水平亦降低(P<0.05)(图3)。

2.5 logistic回归分析影响慢乙肝干扰素疗效的基线指标

logistic回归分析显示, 基线HBsAg和HBV pgRNA水

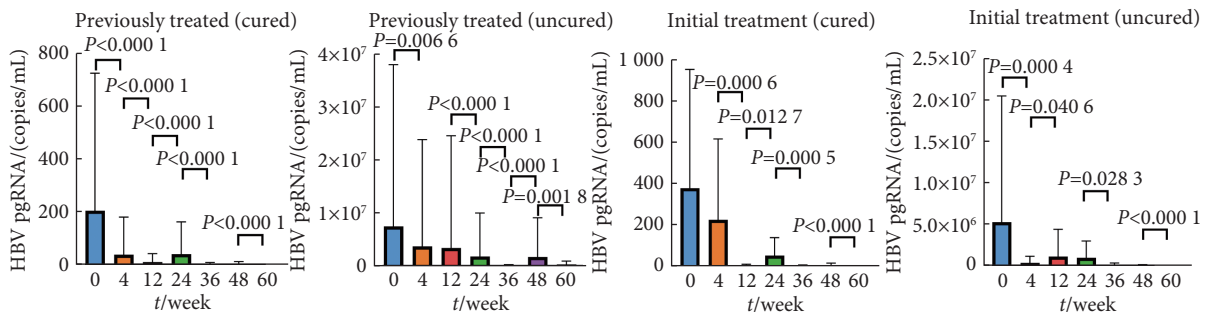


图 3 不同人群干扰素治疗0~60周HBV pgRNA水平比较 (n=127)

Fig 3 Comparison of HBV pgRNA levels in different populations after 0-60 weeks of interferon treatment (n=127)

平是经治病例干扰素治疗效果的影响因素, 基线HBsAg水平也是初治病例干扰素治疗效果的影响因素($P < 0.05$), 性别、年龄、基线血清病毒DNA和HBeAg均不影响干扰素治疗效果。见表2。

2.6 基线HBsAg和HBV pgRNA水平评价慢乙肝干扰素疗效的ROC曲线

以经治及初治治愈病例基线HBsAg和HBV pgRNA定量数值为阳性, 未治愈病例定量数值为阴性, 绘制基线

HBsAg和HBV pgRNA预测干扰素疗效的ROC曲线。结果显示(表3、图4), 经治和初治病例的基线HBsAg ROC曲线的AUC分别为0.80[95%置信区间(confidence interval, CI): 0.742 3 ~ 0.861 5, $P < 0.000 1$]和0.74(95%CI: 0.628 3 ~ 0.860 4, $P = 0.007 9$), Cut-off值分别为244.60 IU/mL和934.40 IU/mL。初治病例的HBV pgRNA ROC曲线的AUC为0.96(95%CI: 0.904 2 ~ 1.000 0, $P < 0.000 1$), Cut-off值为1 340.00 copies/mL。基线HBsAg水平是经治病例

表 2 logistic回归分析基线指标水平影响不同人群干扰素疗效的统计结果

Table 2 Statistical results of the logistic regression of the effect of baseline index levels on the efficacy of interferon in different populations

Group	Index	β	SE	χ^2	OR	95% CI	P
Previously treated	Sex	-1.60	0.14	0.33	0.20	0.1515-0.2667	0.5670
	Age	0.016	0.02	0.81	1.02	0.9810-1.0520	0.3690
	DNA	0.00	0.00	1.30	1.00	1.0000-1.0000	0.5680
	HBsAg	-0.00	0.00	0.38	1.00	0.9970-0.9990	<0.0001
	HBeAg	0.074	0.11	0.42	1.08	0.8690-1.3340	0.4980
	HBV pgRNA	-2.02	0.30	15.65	0.13	0.0702-0.2253	<0.0001
Initial treatment	Sex	-0.01	0.63	0.00	1.00	0.2900-3.4120	0.9900
	Age	0.06	0.04	3.10	1.06	0.9890-1.1450	0.0980
	DNA	0.00	0.00	1.58	1.00	1.0000-1.0000	0.7080
	HBsAg	-0.01	0.08	23.43	0.99	0.9820-1.0010	0.0140
	HBeAg	-90.42	1 669.25	2.90	0.22	0.1138-0.3815	0.9570
	HBV pgRNA	-0.59	0.56	18.25	0.56	0.1558-1.4070	0.5560

β : partial regression coefficient; SE: standard error; OR: odds ratio; CI: confidence interval.

表 3 不同人群血清HBsAg和HBV pgRNA水平判断干扰素疗效的ROC分析

Table 3 ROC analysis of interferon efficacy according to the serum HBsAg and HBV pgRNA levels in different populations

Group	Index	AUC	95% CI	Optimal cut-off value	Sensitivity/%	Specificity/%	P
Previously treated	HBsAg	0.80	0.7423-0.8615	244.60 IU/mL	77.78	72.39	<0.0001
	HBV pgRNA	0.58	0.4586-0.7024	3 955.00 copies/mL	77.78	42.13	0.2606
Initial treatment	HBsAg	0.74	0.6283-0.8604	934.40 IU/mL	100.00	50.85	0.0079
	HBV pgRNA	0.96	0.9042-1.0000	1 340.00 copies/mL	94.74	88.89	<0.0001

AUC: area under thecurve; CI: confidence interval.

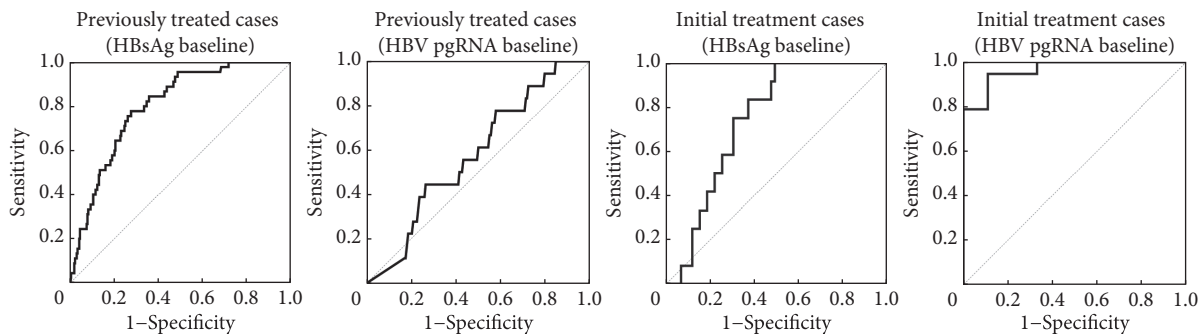


图 4 血清基线HBsAg和HBV pgRNA水平预测慢乙肝患者干扰素疗效的ROC曲线

Fig 4 ROC curves of using baseline serum HBsAg and HBV pgRNA levels to predict interferon efficacy in patients with chronic hepatitis B

干扰素疗效的预判指标,基线HBsAg和基线HBV pgRNA水平是初治病例干扰素疗效的预判指标。

3 讨论

慢乙肝的临床治愈是通过合理的抗病毒治疗后获得生物化学和病毒学应答,谷丙转氨酶复常、HBsAg清除、HBV DNA持续低于检测下限,最终获得肝组织学改善并降低肝硬化和肝癌的发生风险^[10, 12]。目前大部分研究都集中在经治病例^[13],其HBV DNA在入组时已得到有效的控制。本研究尝试对病毒载量高的初治病例进行长效干扰素治疗,评价临床治愈效果,并与经治病例的相关指标进行比较。

在2019-2022年的观察期内,从基线病毒DNA水平来看,经治组治愈和未治愈病例的基线病毒DNA定量水平均明显低于初治组病例,但仅发现初治未治愈病例基线HBsAg水平明显高于经治未治愈组,初治和经治治愈组HBsAg水平均不高,说明基线HBsAg水平差异不与DNA水平差异有直接的联系,说明治愈病例在HBsAg不高的情况下宿主可能产生较好的抗病毒效果,可能也提示基线HBsAg水平在预后评价中可能起着重要的作用。另外值得说明的是,SARS-CoV-2病毒流行期间慢乙肝患者按疗程治疗部分有所中断,因不良反应停药主要发生在2019-2021年间,同时,入组患者的依从性逐年增高,经治病例的治愈率在2022年达到了最高水平(20.45%)。根据以往的治疗指南^[14],曾报道女性的抗病毒效果优于男性,本课题组亦曾报道本地经治的慢乙肝病例男性显著高于女性^[15-16],但本研究中初治组的女性病例比例明显高于经治组,入组偏差与宿主的依从性和免疫应答能力相关,作为效果因素值得深入研究。

成功的免疫治疗对HBeAg阴转应有所帮助^[4],从本研究的血清HBeAg阴转率来看,有少数HBeAg阳性经治病例实现了阴转且完成了临床治愈,且初治患者的基线HBeAg阳性无一例临床治愈,同时,基线HBeAg阴性患者实现临床治愈的比例更高,提示了HBeAg阴性患者实现临床治愈的概率更大。从血清HBsAb应答定量水平来看,WU等^[13]发现,慢乙肝临床治愈后有6.19%~9.66%病例会复发,并且提出HBsAg持续阴性和HBsAb持续应答与肝癌发生率呈负相关。本研究发现,我中心的70例临床治愈病例至2022年10月底仍为HBsAg持续阴性,血清HBsAb持续应答,无临床复发病例(包括HBV pgRNA均阴性)。WU等^[13]研究发现HBsAb>100 IU/mL病例是临床治愈后复发率最低的人群,因此,为了达到中长期的临床治愈效果并降低肝癌发生,除了按照临床治愈实现HBsAg

转阴等标准,还应进一步追求HBsAb>100 IU/mL以及肝内cccDNA清除。随着国内多个中心开展慢乙肝临床治愈的实践及研究,近期许多学者采用慢乙肝相关的血清学指标及肝cccDNA指标评价临床治愈和病毒学治愈的效果。GAN等^[8]分析了临床治愈后短期(6个月)、小规模肝cccDNA定量,有27%(13/48)病例已实现HBV完全清除,达到了病毒学治愈,但临床治愈病例的中长期cccDNA清除情况仍需要进一步研究。虽然,肝组织中cccDNA含量直接反映了HBV复制的基因储存库情况,有助于HBV复发及肝癌的发生风险评价,但由于肝组织活检技术要求较高,难以成为常规评价指标^[17]。本课题组将对本研究中未实现此类标准的患者进一步干预并长期随访,措施包括:达临床治愈后巩固用药3个月、半年复查、HBsAb>100 IU/mL和肝组织cccDNA检测^[2, 8, 13]。

HBV pgRNA是3.5 kb大小的HBV前基因组,其唯一来源是HBV感染的肝细胞核内cccDNA,是cccDNA转录活性的标志物,可以更好地反映cccDNA活性状态^[18-19]。因此,学者提出HBV pgRNA可能成为慢乙肝疗效的间接指标^[20-21]。在长期NAs治疗下,HBV DNA水平并不能真实反映肝细胞中cccDNA的状态,pgRNA产生过程不受NAs抗病毒药物的直接影响,评价研究证实,临床治愈停药点(HBsAg阴性或<0.05 IU/mL)的HBV pgRNA量值与停药后病毒学反弹相关^[19]。综合分析干扰素治疗经治和初治的优势人群,其共同点是基线HBsAg、HBeAg转换和HBV pgRNA水平对评价临床治愈结局均有重要意义;不同的是初治病例的基线病毒DNA水平、HBsAg水平和HBeAg阳性率较高,致使这些劣势人群的治疗周期需要延长,或者改变用药频次,相应的方法值得进一步探索。有报道称^[22],基线HBsAg水平可以有效预测慢乙肝的抗病毒治疗效果以及肝癌发生风险。本研究经logistic回归分析及绘制两组病例基线HBsAg的ROC曲线,同样证明其可影响经治、初治两组病例的干扰素治疗效果($P < 0.05$),当经治病例基线HBsAg<244.60 IU/mL时有较高的敏感度(77.78%)和特异度(72.39%),可预测临床治愈,经治病例的基线HBsAg可以作为较可靠的预测指标;当初治病例HBsAg<934.40 IU/mL时也可以预测临床疗效,该指标的敏感度较高(100.00%)而特异度偏低(50.85%)。两组病例血清基线HBV pgRNA的统计分析显示,经治病例在logistic回归分析中该指标是疗效的影响因素,不是初治病例疗效的影响因素,但是ROC分析显示对于经治病例疗效的预测效果并不理想,特异性较低,而在初治病例HBV pgRNA<1340.00 copies/mL时有较好的敏感性和特异性来预测疗效,说明基线血清HBV pgRNA可作为预判

初治病例干扰素治疗疗效理想的标志物。

综上, 基线HBsAg水平可作为慢乙肝经治及初治患者干扰素疗效评价的血清标志物, 基线HBV pgRNA水平可作为慢乙肝初治患者干扰素疗效评价的血清标志物, 以上结论有助于指导患者的临床治疗。本研究也存在不足之处, 包括试验设计为单臂, 未根据患者的基线特征进行分层分析, 以及回顾性研究本身可能带来的结果偏倚, 尚需更多大样本、多中心的随机对照试验来验证本研究结论。

* * *

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