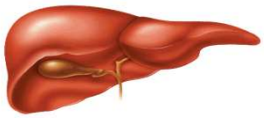
GIÁ TRỊ CỦA HBcrAg

TRONG CHẨN ĐOÁN VÀ TIÊN LƯỢNG VIÊM GAN VIRUS B.



PGS. TS. BS. Phạm Thị Thu Thủy
Trung Tâm Y Khoa MEDIC, TP. Hồ Chí Minh

Oct 2023

1

NỘI DUNG

I, Tổng quan các dấu ấn (Marker) chẩn đoán HBV.

II, Dấu ấn mới HBcrAg.

* Giới thiệu xét nghiệm HBcrAg.

* Ứng dụng HBcrAg trong thực hành lâm sàng.

III, Vai trò quan trọng của HBcrAg trong HCC/HBVI.

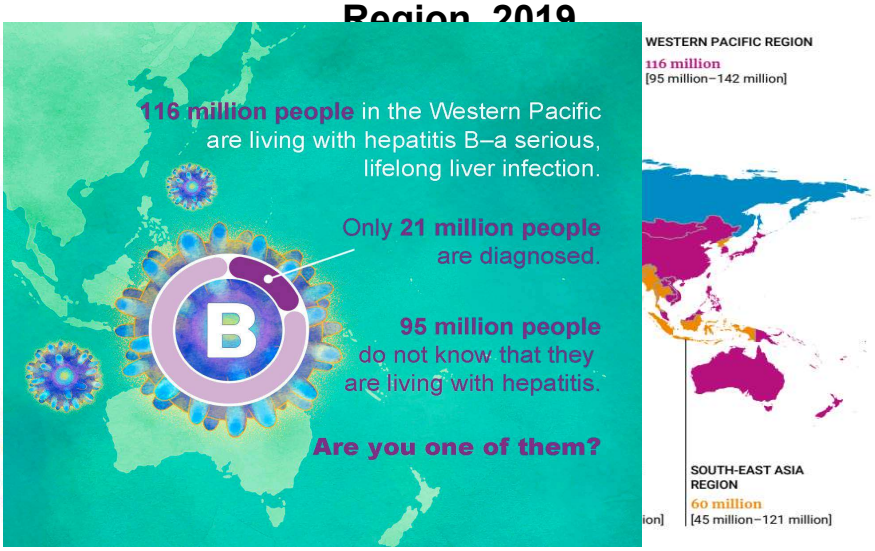
IV, Các trường hợp lâm sàng.

V, Kết luận.

2

I, Tổng quan các dấu ấn (Marker) chẩn đoán HBV.

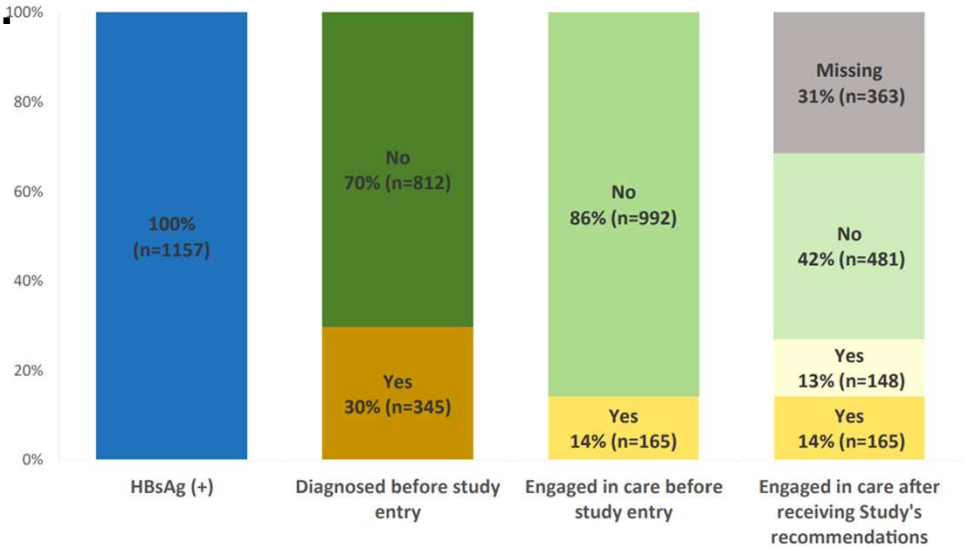
Burden of chronic hepatitis B infection (HBsAg positivity) by WHO Region, 2019



WHO-INTERIM GUIDANCE FOR COUNTRY VALIDATION OF VIRAL HEPATITIS ELIMINATION. JUNE 2021.
https://www.who.int/westernpacific/news-room/multimedia/overview/item/burden-of-hepatitis-b-in-western-pacific

3

Baseline HBV continuum of care in Ho Chi Minh City, Vietnam.



Notes: "Engaged in care" is defined as those who sought medical care by primary care providers or specialists in hepatology/infectious disease for HBV management, irrespective of whether treatment was initiated or not, after being diagnosed with positive HBsAg.

Trang N. D. Pham et al. *The Lancet Regional Health-Western Pacific*. www.thelancet.com Vol 30 January, 2023

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Chủ đề nóng liên quan đến điều trị Viêm gan Siêu vi B

- **Khi điều trị bằng NA, HBV DNA huyết thanh giảm rất nhanh, nhưng thực tế thể virus vẫn còn trong tế bào gan.**

→ **cần một chỉ dấu huyết thanh mới để ước tính được số lượng cccDNA trong tế bào gan khi điều trị VGSV B bằng NA và đâu là thời điểm thích hợp ngưng thuốc.**

- **VGSV B vẫn còn trong tế bào gan thậm chí trong trường hợp nhiễm VGSV B đã hồi phục.**

→ **nguy cơ tái phát VGSV B cao.**

- **VGSV B trong tế bào gan sẽ có cơ hội nhân lên rất nhanh nếu bệnh nhân dùng thuốc ức chế ung thư hoặc thuốc ức chế miễn dịch.**

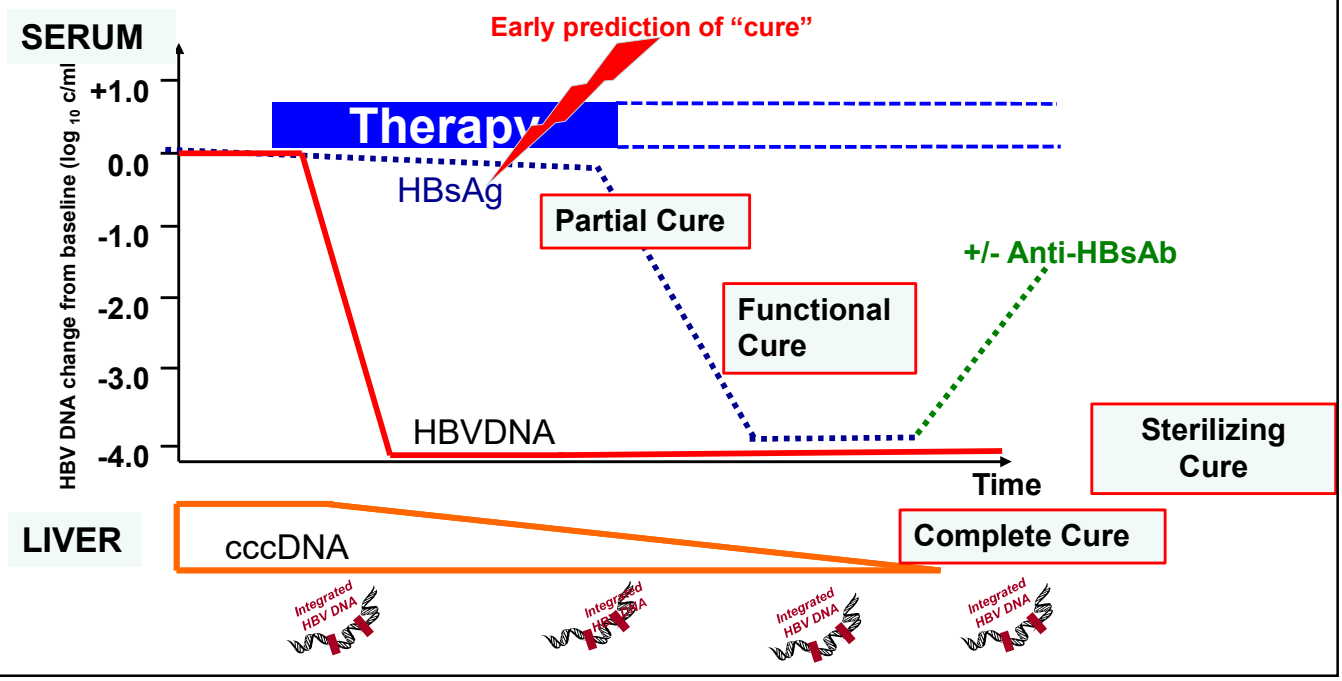
→ **nguy cơ bùng phát VGSV B cao.**

Cần có chỉ dấu huyết thanh mới để giải quyết các chủ đề nóng trên, khi nào là thời điểm thích hợp để dừng thuốc ?

Xét nghiệm Lumipulse G HBcrAg là một trong những giải pháp tối ưu

5

Need for biomarkers to predict the cure of infection



6

Xét nghiệm siêu vi B giữ vai trò then chốt trong chẩn đoán, điều trị và tiên lượng bệnh

CÁC XN MIỄN DỊCH.

1, HBsAg: Định tính, định lượng.

2, AntiHBs: Định tính, định lượng.

3, HBeAg: Định tính, định lượng.

4, Anti HBe: Định tính.

5, AntiHBc IgG: Định tính.

6, AntiHBc IgM: Định tính.

7, HBcrAg: Định lượng.

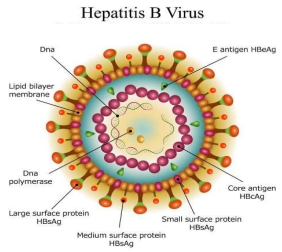
CÁC XN SINH HỌC PHÂN TỬ

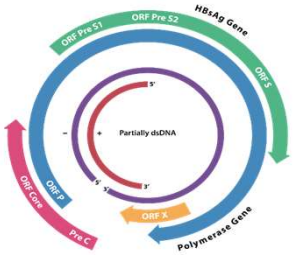
1, HBVDNA: Định tính, định lượng.

2, HBV Genotype.

3, Phát hiện đột biến gene kháng thuốc điều trị, đột biến PC(precore); BCP(basal core promoter)…

4, HBVRNA: Định lượng.





7

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6, AntiHBc IgM: Định tính.

FIRST WORDS

7, HBcrAg: Định lượng.

NEW!

CÁC XN SINH HỌC PHÂN TỬ

1, HBVDNA: Định tính, định lượng.

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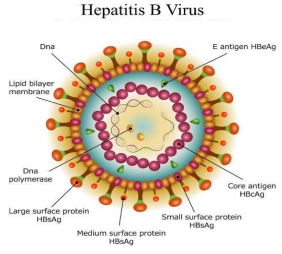

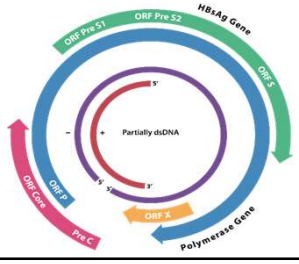

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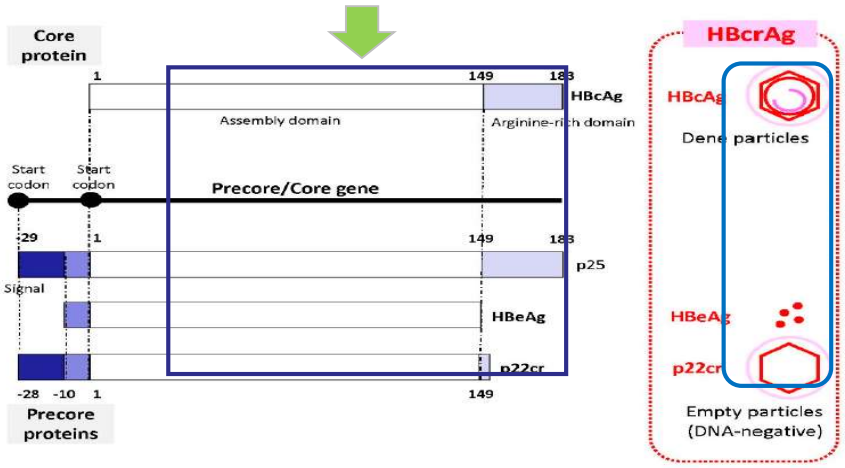
II, Giới thiệu xét nghiệm HBcrAg

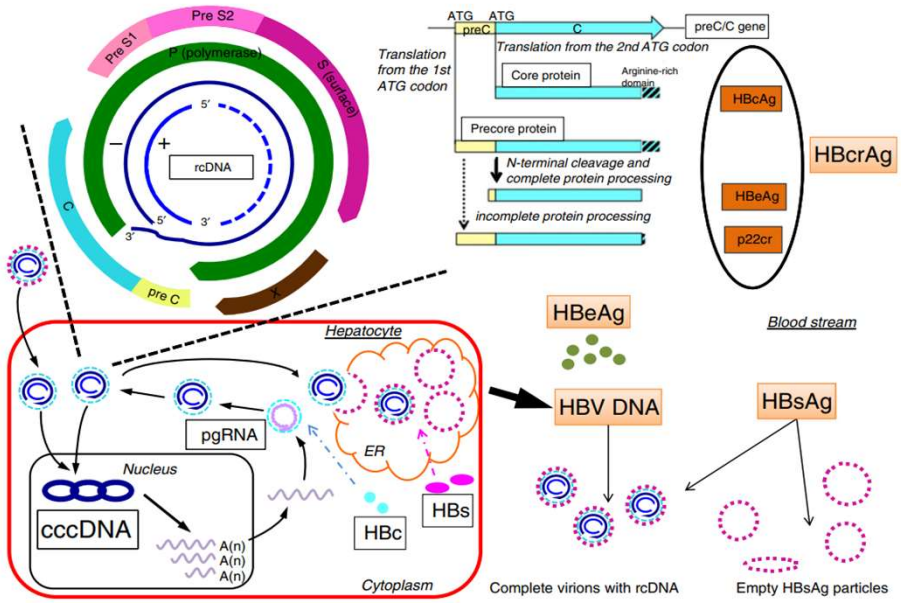
- Xét nghiệm HBcrAg phát hiện đồng thời 3 thành phần: HBcAg, HBeAg và protein p22cr trên cùng gen C của vi rút viêm gan B.
- Cả 3 kháng nguyên này có cùng vị trí nhận diện kháng nguyên 149 acid amin.



- **Ngưỡng phân tích**: 3,0-7,0 LogU/mL (1,0-10.000,0 kU/mL)

9

The viral replication cycle and the origins of HBV DNA, HBsAg, HBeAg and HBcrAg



cccDNA = covalently closed circular DNA, ER = endoplasmic reticulum, HBc = hepatitis B core protein, HBcrAg = hepatitis B core-related antigen, HBeAg = hepatitis B e antigen, HBs = hepatitis B surface protein, HBsAg = hepatitis B virus surface antigen, HBV = hepatitis B virus, p22cr = truncated 22kDa precore protein, pgRNA = pre-genomic RNA, rcDNA = relaxed circular DNA

MAK ET AL. Aliment Pharmacol Ther 2018;47(1):43-54

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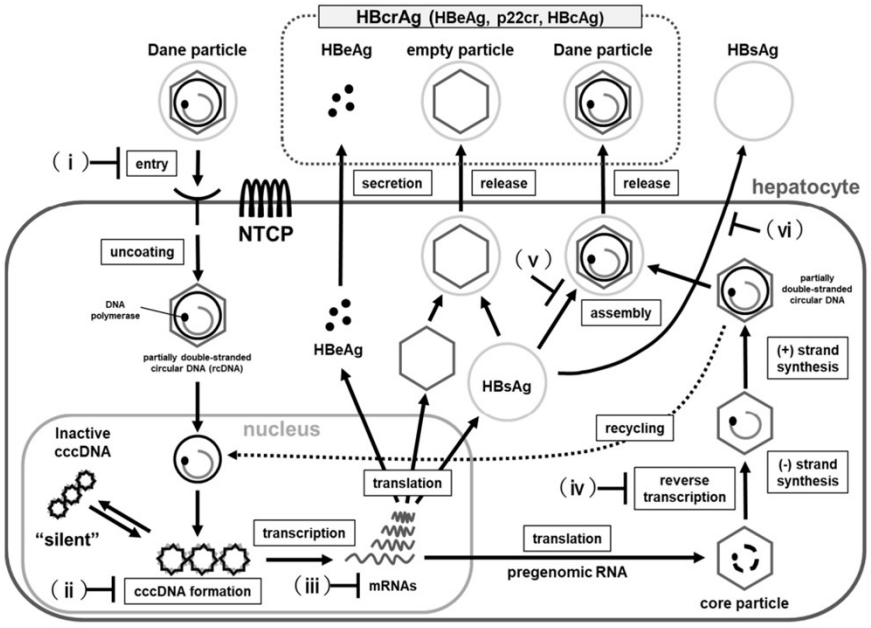
Life cycle of HBV and therapeutic agents



(i) Inhibition of HBV entry into hepatocytes,(ii) Targeting cccDNA, (iii) Targeting viral transcripts, (iv) Inhibition of reverse transcription, (v) Inhibition of capsid formation or nucleocapsid assembly, (vi) HBsAg Inhibitors.

Takehisa Watanabe et al. Microorganisms 2021, 9, 2083

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Ý NGHĨA HBcrAg TRONG THỰC HÀNH.

1. Theo dõi các phase trong HBV.
2. Liên quan HBV DNA.
3. Tương quan cccDNA.
4. Đánh giá hiệu quả điều trị. Quyết định ngưng điều trị.
5. Phát hiện HBV tiềm ẩn.
6. Dự đoán xơ gan.
7. Dự đoán tái hoạt HBV.

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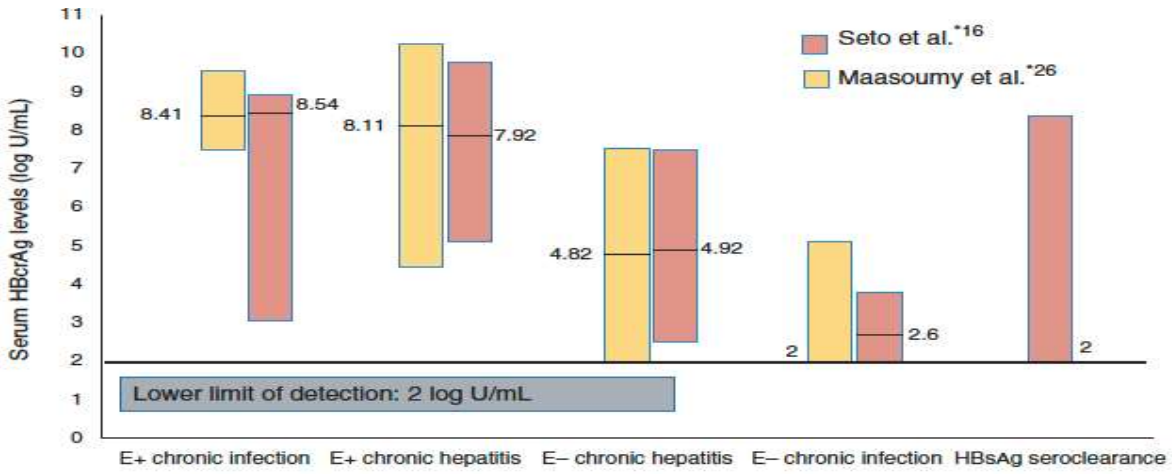
1, HBcrAg in natural history of chronic hepatitis B



MAK ET AL. Aliment Pharmacol Ther 2018;47(1):43-54

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2, Tương quan giữa HBcrAg và HBV DNA huyết thanh, HBV DNA trong gan, cccDNA trong tế bào gan

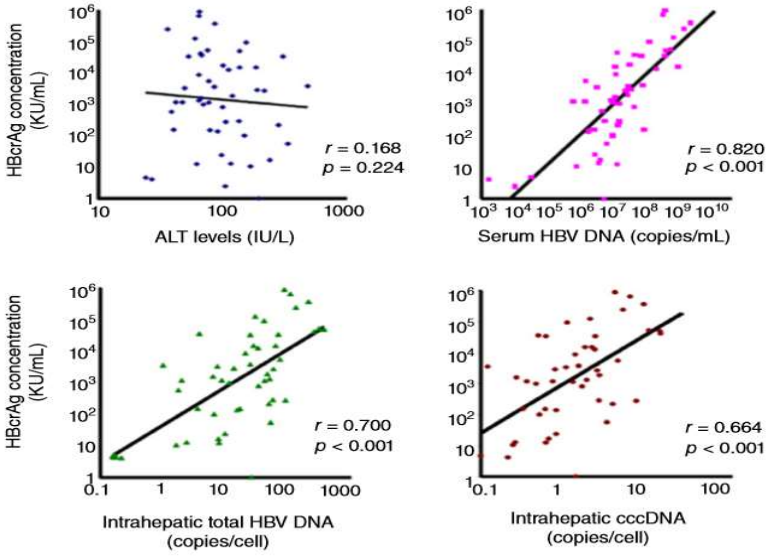

Figure 5 Correlation between HBcrAg, serum HBV DNA levels, and total hepatic HBV DNA and cccDNA.

JSH Guidelines for HBV infection. *Hepatology Research.*, 2014; 44 (Suppl. 1): 1-58

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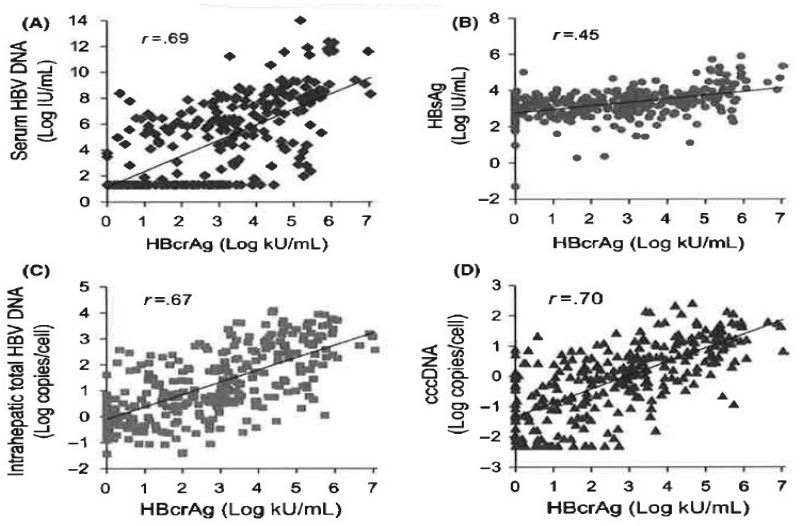
Correlation with HBV-DNA and cccDNA

HBcrAg has excellent correlation with cccDNA and HBV DNA (tế bào gan)



HBcrAg correlated positively with:
(A)Serum HBV DNA(r=.69, P<.0001)
(B) HBsAg(r=.45, P<.0001)
(C) Intrahepatic total HBV DNA (r=.67, P<.0001)
(D) cccDNA (r=.70, P<.0001)

FIGURE 1 Correlation between levels of HBcrAg and serum HBV DNA (A); HBsAg (B); intrahepatic total HBV DNA (C); and cccDNA (D) in the 305 samples tested. The correlation coefficients (r) are shown in the graphs, all with *P*<.0001

Wong, et al, Liver International 2017

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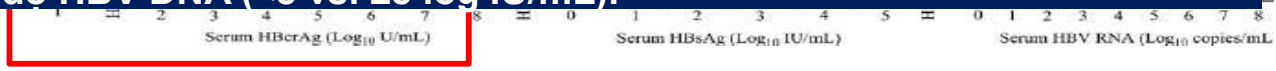
3, Nồng độ HBcrAg huyết thanh tương đương với cccDNA tốt hơn sự tương quan giữa HBV RNA và HBsAg với cccDNA, bất kể HBeAg dương hay âm.

TABLE 4 Correlation of intrahepatic cccDNA with HBcrAg, HBsAg and HBV RNA stratified by inflammatory grade and HBV DNA level among HBeAg-positive patients

	cccDNA				cccDNA			
	G < 2		G ≥ 2		HBV DNA <8 log10 IU/mL		HBV DNA ≥8 log10 IU/mL	
Parameter	*r*	*P*-value	*r*	*P*-value	*r*	*P*-value	*r*	*P*-value
Serum HBcrAg	0.852	0.000	0.743	0.000	0.848	0.000	0.828	0.000
Serum HBsAg	0.650	0.000	0.750	0.000	0.632	0.000	0.926	0.000
Serum HBV RNA	0.513	0.000	0.551	0.006	0.575	0.000	0.417	0.011

HBcrAg tương quan với cccDNA tốt hơn HBsAg và HBV RNA tương quan với cccDNA, bất kể mức độ viêm (G < 2 vs. G ≥ 2) hoặc nồng độ HBV DNA (<8 vs. ≥8 log IU/mL).



Chen EQ et al. J Viral Hepat 2019.

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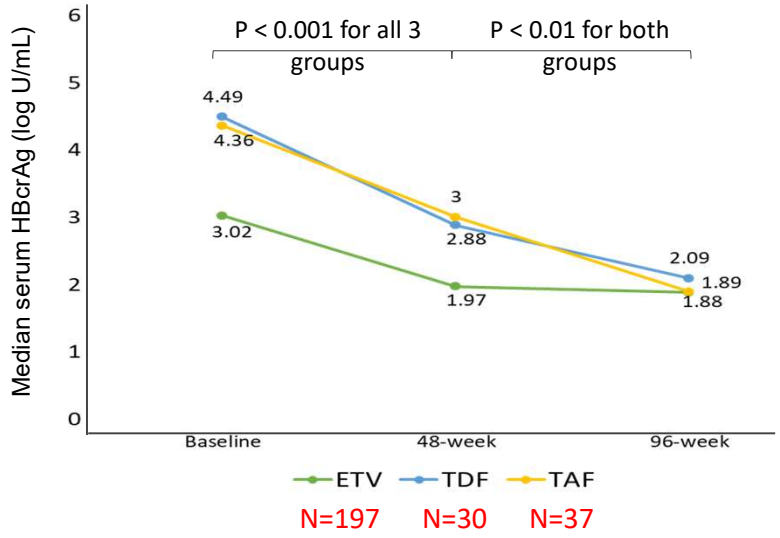
4. Đánh giá hiệu quả điều trị, quyết định ngừng điều trị.

HBcrAg levels on 2-year TDF/ TAF/ ETV treatment.



ETV: entecavir, HBcrAg: hepatitis B core-related antigen,
TAF: tenofovir alafenamide, TDF: tenofovir disoproxil fumarate

Mak, LY et al. The Liver Meeting 2019, Boston, MA, USA, . In Hepatology, 2019, v. 70 n. Suppl. 1, p. 292A, abstract no. 461

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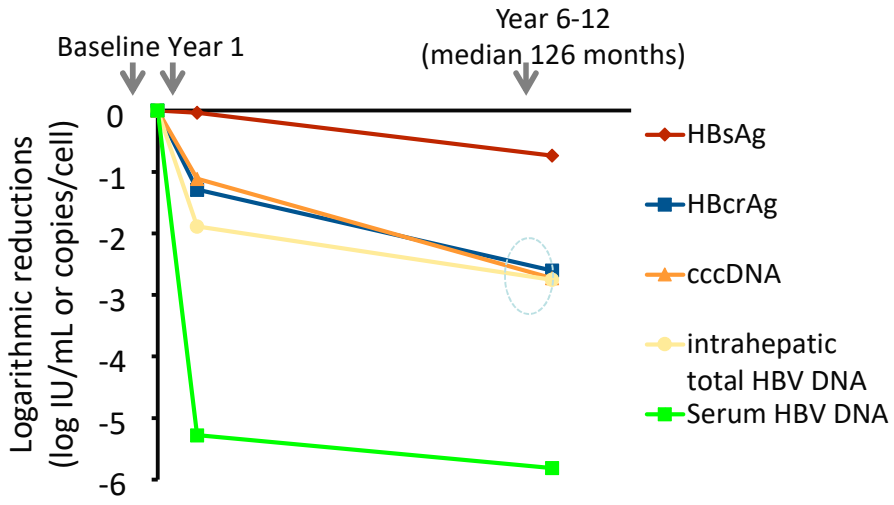
Mức độ giảm của HBcrAg tương đương với mức độ giảm của cccDNA khi điều trị kéo dài bằng NUCs



Lai CLet al. J Hepatol 2017:66(2):275-281

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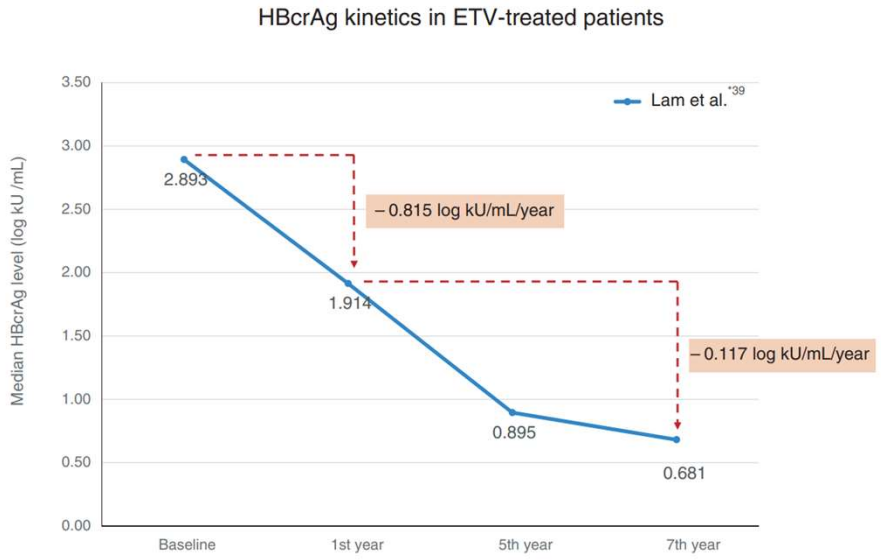
Median HBcrAg levels in CHB patients treated with ETV



ETV = entecavir, HBcrAg = Hepatitis B virus core-related antigen

MAK ET AL. Aliment Pharmacol Ther 2018;47(1):43-54

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Hỗ trợ theo dõi điều trị B khi HBV DNA không phát hiện

genes

MDPI

Review

The Role of Hepatitis B Core-Related Antigen

Takako Inoue [1] and Yasuhito Tanaka [1,2,*]

[1] Department of Clinical Laboratory Medicine, Nagoya City University Hospital, Nagoya 467-8602, Japan; clinoue@med.nagoya-cu.ac.jp

[2] Department of Virology and Liver Unit, Nagoya City University Graduate School of Medical Sciences, Nagoya 467-8601, Japan

* Correspondence: ytanaka@med.nagoya-cu.ac.jp; Tel.: +81-52-853-8191

Received: 2 April 2019; Accepted: 6 May 2019; Published: 9 May 2019

check for updates

Abstract: Hepatitis B virus (HBV) cannot be completely eliminated from infected hepatocytes due to the existence of intrahepatic covalently closed circular DNA (cccDNA). Serological biomarkers reflect intrahepatic viral replicative activity as non-invasive alternatives to liver biopsy. Hepatitis B core-related antigen (HBcrAg) is a novel biomarker that has an important role in chronic hepatitis B (CHB), because it correlates with serum HBV DNA and intrahepatic cccDNA. In clinical cases with undetectable serum HBV DNA or loss of HBsAg, HBcrAg still can be detected and the decrease in HBcrAg levels is significantly associated with promising outcomes for CHB patients. HBcrAg can predict spontaneous or treatment-induced hepatitis B envelope antigen (HBeAg) seroconversion, persistent responses before and after cessation of nucleos(t)ide analogues, potential HBV reactivation, HBV reinfection after liver transplantation, and risk of hepatocellular carcinoma progression or recurrence. In this review, the clinical applications of HBcrAg in CHB patients based on its virological features are described. Furthermore, new potential therapeutic anti-HBV agents that affect intrahepatic cccDNA are under development, and the monitoring of HBcrAg might be useful to judge therapeutic effects. In conclusion, HBcrAg might be a suitable surrogate marker beyond other HBV markers to predict the disease progression and treatment responses of CHB patients.

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Chiến lược ngưng thuốc NUCs

Tiêu chí ngưng thuốc trong liệu pháp kháng vi rút.

1) HBV DNA không phát hiện.
2) Chuyển đổi huyết thanh HBeAg.
3) Giảm HBcrAg (< 3 log U/mL).
4) Giảm HBsAg.
5) Không gồm các xơ hóa nghiêm trọng.

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JSH guideline

Hướng dẫn của Nhật JSH: tính điểm nguy cơ và đánh giá ngưng thuốc NUCs based on HBsAg and HBcrAg.

Cut-offs determined by ROC curve

HBsAg	< 80 IU/ml	score 0
	80～800 IU/ml	score 1
	≥ 800 IU/ml	score 2

Mất HBsAg rất hiếm.

HBcrAg	< 3.0 log U/ml	score 0
	3.0 ～4.0 log U/ml	score 1
	≥ 4.0 log U/ml	score 2

Cut-off = 3 log U/mL

Tổng điểm	0	Nhóm nguy cơ thấp
	1 – 2	Nhóm nguy cơ trung bình
	3 – 4	Nhóm nguy cơ cao

(Matsumoto A et al., Hepatol Res 2012)

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BỘ Y TẾ

CỘNG HÒA XÃ HỘI CHỦ NGHĨA VIỆT NAM
Độc lập - Tự do - Hạnh phúc

Số: 3310/QĐ-BYT

Hà Nội, ngày 29 tháng 7 năm 2019

QUYẾT ĐỊNH

VỀ VIỆC BAN HÀNH HƯỚNG DẪN CHẨN ĐOÁN, ĐIỀU TRỊ BỆNH VIÊM GAN VI RÚT B

BỘ TRƯỞNG BỘ Y TẾ

2.6. Thời gian điều trị

2.6.1. Thời gian điều trị với thuốc NAs kéo dài, có thể suốt đời

- Người bệnh xơ gan phải điều trị suốt đời.

- Người bệnh chưa xơ gan: điều trị lâu dài, có thể xem xét ngưng điều trị trong các trường hợp sau đây:

+ VGVR B mạn với HBeAg dương tính: có thể ngưng điều trị sau khi đã điều trị thêm 12 tháng kể từ khi có chuyển đổi huyết thanh HBeAg (HBeAg âm tính, anti-HBe dương tính và tải lượng HBV DNA dưới ngưỡng) hoặc mất HBsAg

+ VGVR B mạn với HBeAg âm tính: có thể ngưng điều trị khi tải lượng HBV DNA dưới ngưỡng và mất HBsAg

+ Nếu không thể đo tải lượng HBV DNA, có thể cân nhắc ngưng thuốc kháng vi rút khi mất HBsAg kéo dài ít nhất 12 tháng trước khi ngưng điều trị (bất kể tình trạng HBeAg)

+ HBcrAg âm tính.

- Chỉ ngưng điều trị khi người bệnh có điều kiện theo dõi định kỳ trong thời gian dài để đánh giá khả năng tái hoạt HBV sau khi ngưng thuốc. Giải thích và tư vấn cho người bệnh nguy cơ bùng phát VGVR B, bệnh gan mất bù và ung thư gan sau khi ngưng điều trị.

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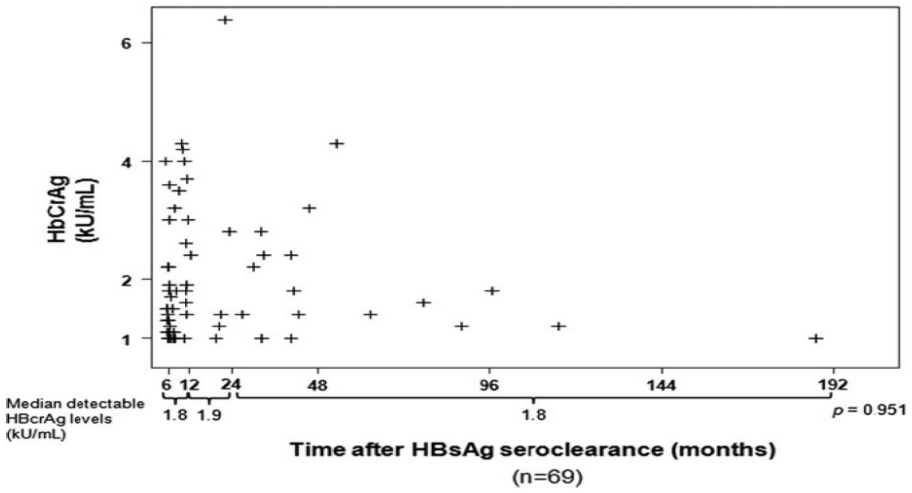
5. Phát hiện HBV tiềm ẩn.

Detectable HBcrAg over long time after HBsAg seroclearance



Seto WK., Yuen MF. Hepatol Int 2013;7(1):98-105

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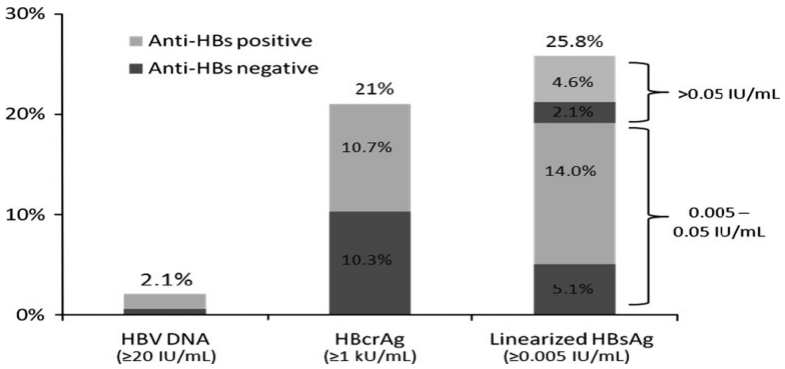
HBcrAg in chronic hepatitis B with HBsAg seroclearance

Using novel HBcrAg and HBsAg-Quant assays, viral serologic activity after HBsAg seroclearance was demonstrated in more than 40% of CHB patients



Patient population: 329 patients with HBsAg seroclearance.

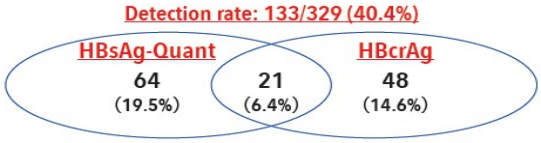


Fig. 2 Percentage of patients with detectable viremia and viral proteins after HBsAg seroclearance documented by a conventional assay ($n = 329$). *HBsAg* hepatitis B surface antigen, *anti-HBs* antibody to the hepatitis B surface antigen, *HBcrAg* hepatitis B core-related antigen

Seto WK et al. Hepatol Int. 2013;7:98-105

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6. Dự đoán xơ gan.

HBcrAg: Development of cirrhosis

529 patients not on treatment FIB-4 > 3.6 to define cirrhosis

Table 3 Multivariate analysis of HBV markers related to the development of cirrhosis

HBV marker	HR	95% CI	*P* value
HBV genotype			
Non-genotype C ($n = 105$)	1	0.48–2.29	0.909
Genotype C ($n = 338$)	1.05		
HBsAg			
< 3.0 log IU/mL ($n = 220$)	1	0.30–0.94	0.031
≥ 3.0 log IU/mL ($n = 284$)	0.53		
HBV DNA			
< 4.3 log IU/mL ($n = 462$)	1	0.52–2.32	0.807
≥ 4.3 log IU/mL ($n = 67$)	1.10		
HBcrAg			
< 3.7 log U/mL ($n = 472$)	1	1.60–6.75	0.001
≥ 3.7 log U/mL ($n = 57$)	3.28		
Precore			
Wild type ($n = 60$)	1	0.76–13.34	0.112
Mutant ($n = 320$)	3.19		
BCP			
Wild type ($n = 119$)	1	0.92–3.95	0.081
Mutant ($n = 224$)	1.91		

Tada T et al., J Gastroenterol Hepatol 2018;33:918-25

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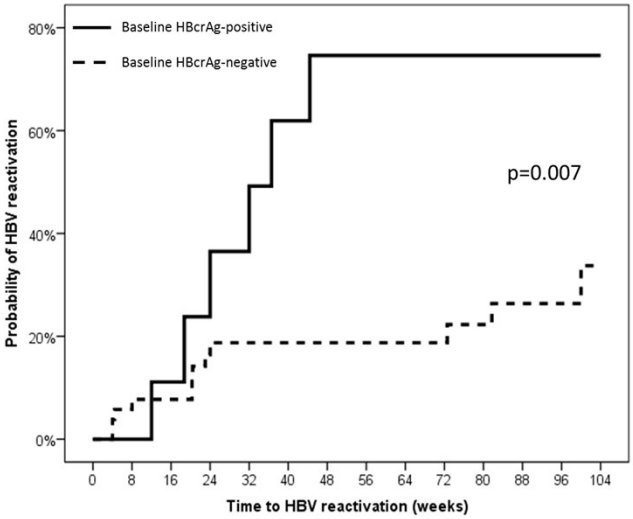
7. Dự đoán tái hoạt HBV khi dùng ức chế miễn dịch

HBcrAg và Nguy cơ bùng phát virus B

Nguy cơ bùng phát viêm gan vi rút B tích lũy trên bệnh nhân nhiễm Viêm gan B tiềm ẩn, khi dùng liệu pháp hóa trị có rituximab.

HBcrAg level < 3 log is considered "Negative".



Seto WK…Yuen MF. Am J Gastroenterol 2016;111(12):1788-95

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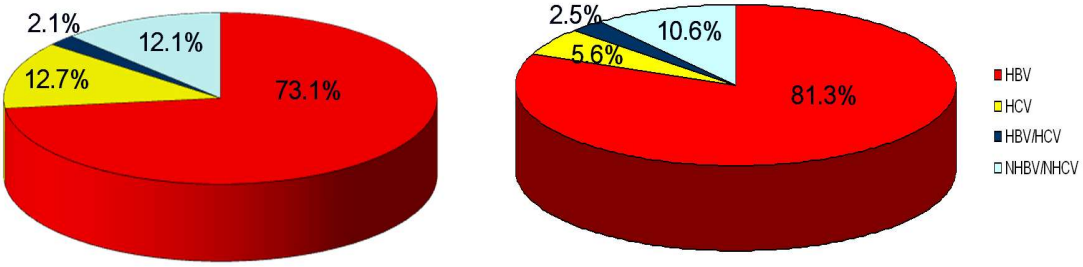
III, Vai trò quan trọng của HBcrAg trong HCC/HBVI.

HBV là nguyên nhân chủ yếu của HCC ở VIỆT NAM



Nguyen et al. [1]

Le et al. [2]

1, Nguyen-Dinh SH et al . Viruses 2022, 14, 2571. https://doi.org/10.3390/v14112571

2, Le et al. Cancer Control Volume 26: 1-6. 2019.

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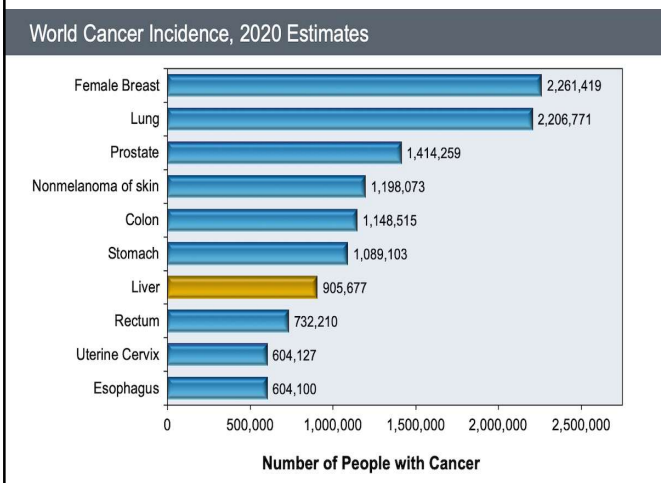
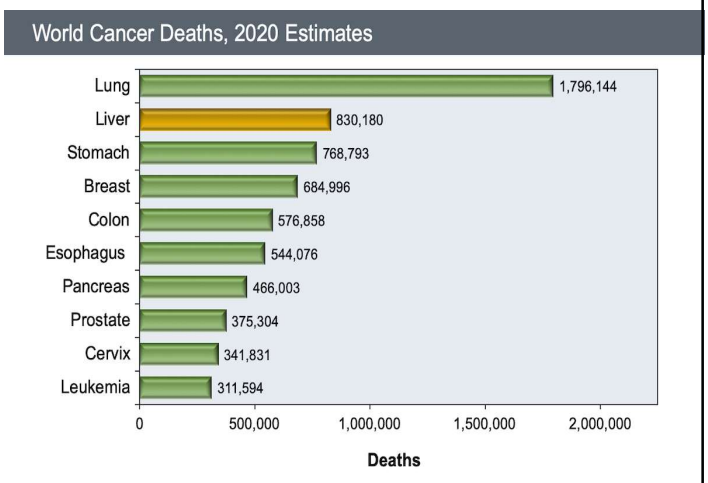
HCC thường phát hiện trễ nên nguy hiểm !

2020 Global Cancer Incidence Estimates



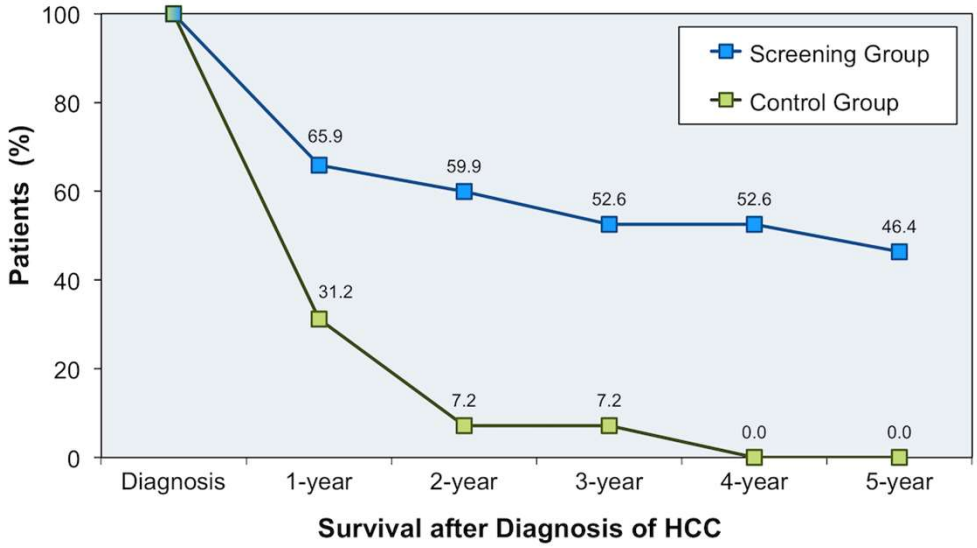
2020 Global Cancer Death Estimates



Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021 Feb 4.

29

Impact of Screening on Survival after Diagnosis of HCC



In this trial, patients with chronic viral hepatitis who underwent screening for HCC had improved survival after the diagnosis of HCC when compared with the control group that did not receive screening for HCC.

Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol. 2004;130:417-22.

30

Stage at Presentation and Survival Curves

Tiên lượng khả năng HCC/HBV để có chiến lược điều trị & theo dõi hiệu quả giữ vai trò rất quan

Serper. Gastroenterology. 2017;152:1954.

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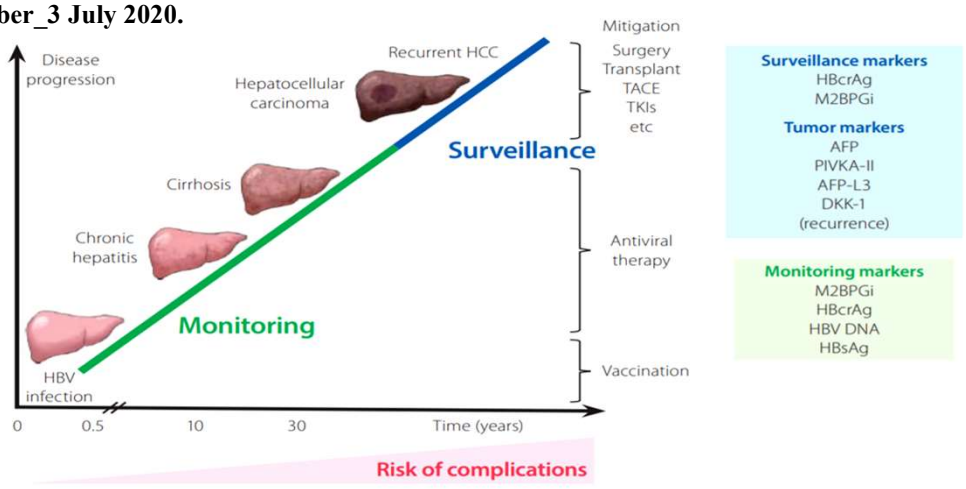
CLINICAL and MOLECULAR HEPATOLOGY
https://doi.org/10.3350/cmh.2020.0032
Clinical and Molecular Hepatology 2020;26:261-279

Novel biomarkers for the management of chronic hepatitis B

Takako Inoue[1] and Yasuhito Tanaka[1-3]

[1]Department of Clinical Laboratory Medicine, Nagoya City University Hospital, Nagoya; [2]Department of Virology and Liver Unit, Nagoya City University Graduate School of Medical Sciences, Nagoya; [3]Department of Gastroenterology and Hepatology, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan

Volume_26 Number_3 July 2020.



The serum biomarkers HBcrAg and M2BPGi provide valuable predictive data for the effective management of CHB. It is important to monitor patients at high risk and to treat them early to prevent liver complications, cirrhosis, and HCC development.

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CLINICAL and MOLECULAR HEPATOLOGY
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Novel biomarkers for the management of chronic hepatitis B

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Volume_26 Number_3 July 2020.

Category	Finding	HBcrAg level (log U/mL) and point	Reference
Natural history	HBeAg seroconversion	<4.92 log U/mL during the clinical course	37
	HBsAg seroclearance	Undetectable (79%), 2.7 log U/mL (median of 21%) during the clinical course	37,48
cccDNA activity	Lower amounts of intrahepatic cccDNA and lower cccDNA activity	<3 log U/mL	38
	Identification of inactive carriers with a high accuracy (any HBV genotype)	HBcrAg ≤3 log U/mL plus HBV DNA ≤2,000 IU/mL	39
Anti-HBV treatment	HBeAg seroconversion by PEG-IFN at 12 weeks	>8 log U/mL (no response) at the beginning of therapy	49
	HBeAg seroconversion by PEG-IFN plus NA for 4 weeks followed by PEG-IFN for 20 weeks	>4.5 log U/mL (no response) at the beginning of therapy	140
	No LAM resistance	<4.6 log U/mL at 6 months of treatment	141
	Virological relapse within 1 year of NA cessation	>3.7 log U/mL at NA cessation	56
	Virological relapse regardless of undetectable HBV DNA for at least 6 months	3.2-3.7 log U/mL at NA (LAM or ETV) cessation	53,54
HCC occurrence/recurrence	At high risk for HCC with intermediate viral load (HBV DNA 2,000-19,999 U/mL)	≥4.0 log U/mL	65
	Cumulative incidence of HCC during NA treatment	≥3.4 log U/mL at the time of HBV DNA disappearance	56
	HCC development during NA treatment	Detectable HBcrAg during NA treatment	63
	Long-term effect of NA treatment on HCC progression	Higher serum levels of HBcrAg and BCP mutations were associated with progression to HCC, independent of NA therapy	62
	Evaluation of HCC occurrence	HBcrAg >3.0 log U/mL and HBsAg >3.0 log IU/mL (cut-off values)	67
	Incidence of HCC for treatment-experienced patients	>4.67 log U/mL at pre-treatment, >3.89 log U/mL at post-treatment	66
	HCC development during NA treatment	Detectable HBcrAg during NA treatment	63
	Incidence of HCC for treatment-naïve patients	>2.9 log U/mL during follow-up period	61,64
	HCC recurrence within 2 years	>4.8 log U/mL at time of HCC diagnosis	61,64
HBV reactivation	HBV reactivation by high-risk immunosuppressive therapy within 2 years	Detectable HBcrAg at baseline	142
HBV reinfection	High levels of post-liver transplantation cccDNA	>4 log U/mL before liver transplantation	143

Clinical applications of HBcrAg in CHB patients

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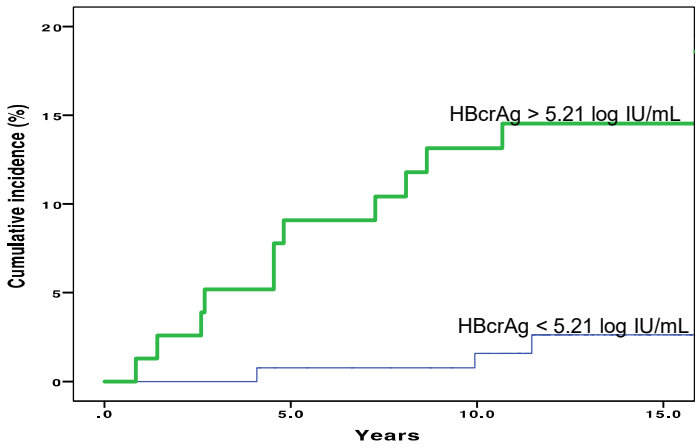
HBcrAg Levels and HCC

Cut-off HBcrAg levels: **5.21 log IU/mL.**

Sensitivity 78.6%
Specificity 65.8%
NPV 97.7%
PPV 14.3%



To WP ... Yuen MF. J Viral Hepat 2019.

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Nghiên cứu ERADICATE-B

3947 bệnh nhân (BN) có HBsAg-positive đăng kí 1985 đến 2000. Tất cả đều có theo dõi thường xuyên trong ít nhất 3 năm

→ Loại 172 BN (đồng nhiễm với HCV: 153, HDV: 13, HCV+HDV: 6)

3775 BN không đồng nhiễm với HCV/HDV

→ Loại 286 BN (không đủ mẫu huyết thanh cho phân tích)

3489 BN đủ huyết thanh cho phân tích

→ Loại 411 BN (có chẩn đoán xơ gan lúc đăng kí)

3078 BN không xơ gan

→ Loại 412 BN (có điều trị kháng vi rút ngay trước khi chẩn đoán HCC và trước khi kết thúc quá trình theo dõi)

2666 BN chưa điều trị trong quá trình theo dõi [HBeAg (+): 523; HBeAg (-): 2165]

Ung thư 209 ca với tỷ lệ mắc hàng năm 0.49% (15.95 năm)

Tseng and Kao et al, Gastroenterology 2012

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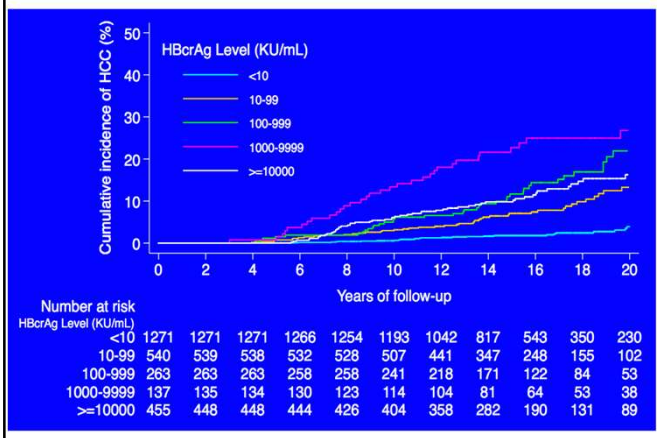
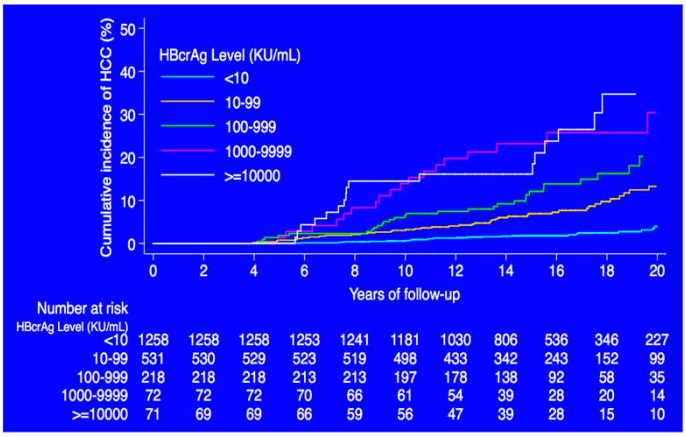
Mối tương quan giữa HBcrAg và HCC

Tất cả bệnh nhân



Bệnh nhân HBeAg-negative



Ngưỡng cắt của HBcrAg: 10KU/ml hay 4 LogU/ml, có nguy cơ HCC rất cao.

Tseng and Kao, Gastroenterology 2012

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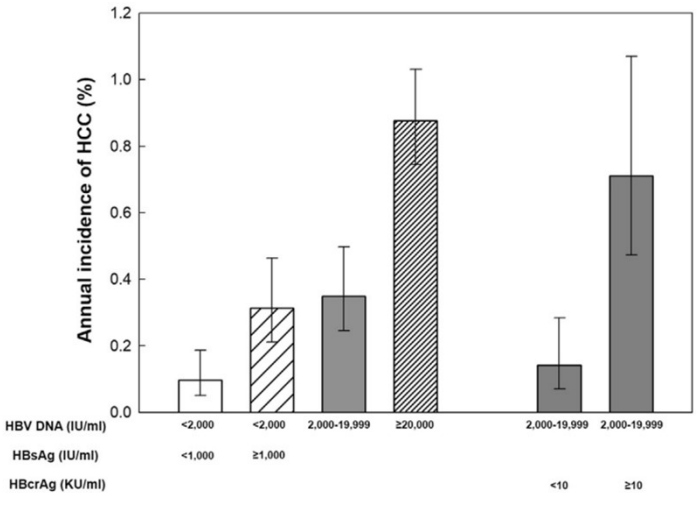
High Level of Hepatitis B Core–Related Antigen Associated With Increased Risk of Hepatocellular Carcinoma in Patients With Chronic HBV Infection of Intermediate Viral Load



Gastroenterology

Tseng et al. Gastroenterology 2019;157:1518–1529

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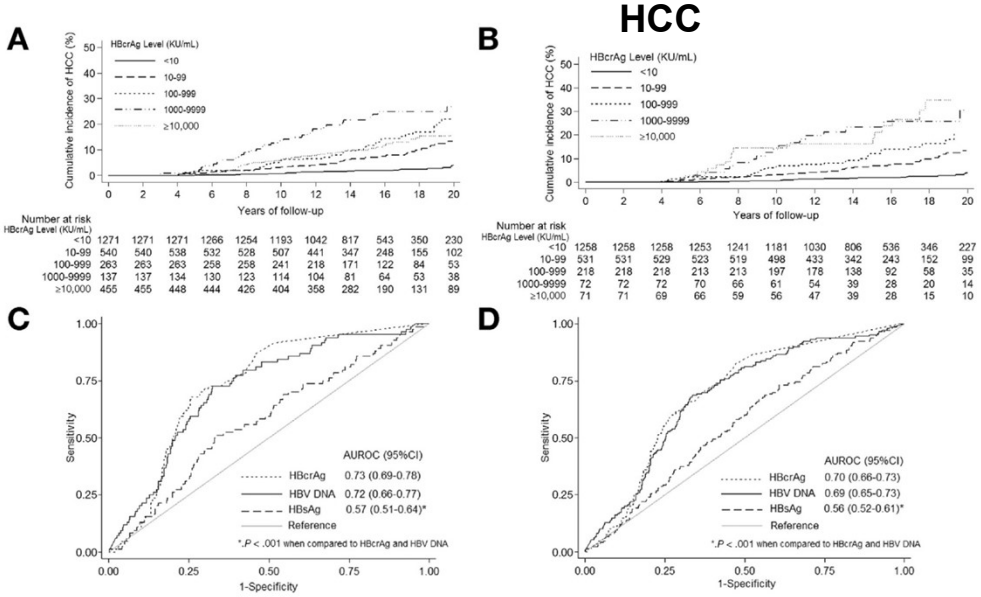
Serum HBcrAg levels are associated with the cumulative incidence of HCC



(A) in the overall cohort of 2666 HBsAg positive patients. (B) in the HBeAg-negative subcohort of 2150 patients. The performance of HCC prediction among HBV DNA, HBsAg, and HBcrAg is compared within (C) 10 years of follow-up (n ¼ 2543; 84 developed HCC) and (D) 15 years of follow-up (n ¼ 1593; 150 developed HCC) using receiver operating characteristic (ROC) curve analysis.

Tseng et al. Gastroenterology 2019;157:1518–1529

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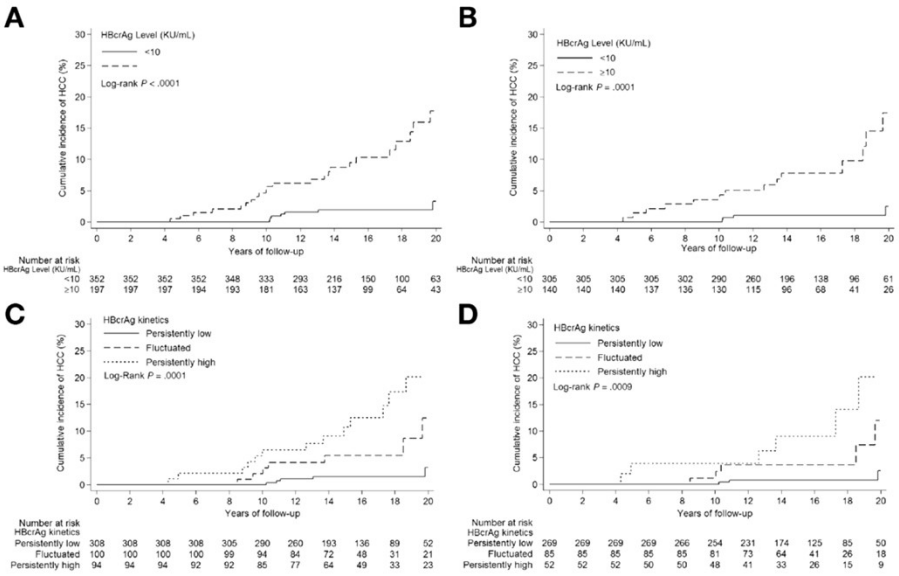
Baseline HBcrAg of 10 KU/mL stratifies the HCC risks



(A) in the patients with intermediate viral load (HBV DNA level: 2000-19,999 IU/mL, IVL), and (B) in the HBeAg-negative patients with IVL and ALT 10 KU/mL), and persistently high group (both >10 KU/mL), increased cumulative incidence of HCC is noted (C) in the IVL patients and (D) HBeAg-negative patients with IVL and ALT

Tseng et al. Gastroenterology 2019;157:1518–1529

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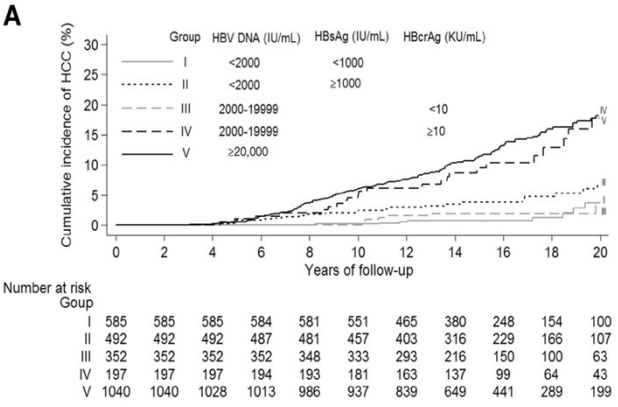
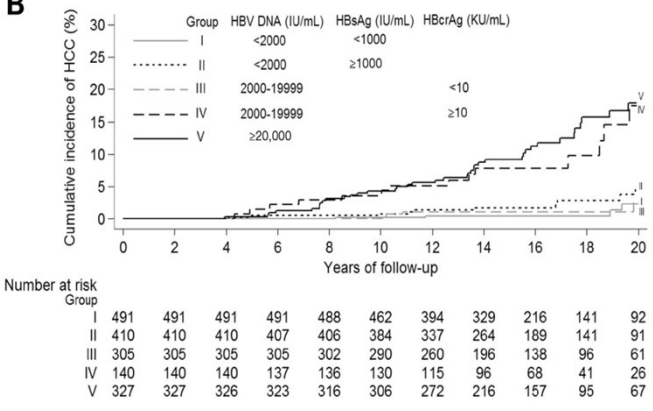
The combination of HBV DNA, HBcrAg, and HBsAg levels is used to reclassify the HBV carriers into 5 groups and 3 clusters of HCC risks



(A) overall cohort



(B) HBeAg-negative patients with ALT < 40 U/L as the study population

Tseng et al. Gastroenterology 2019;157:1518–1529

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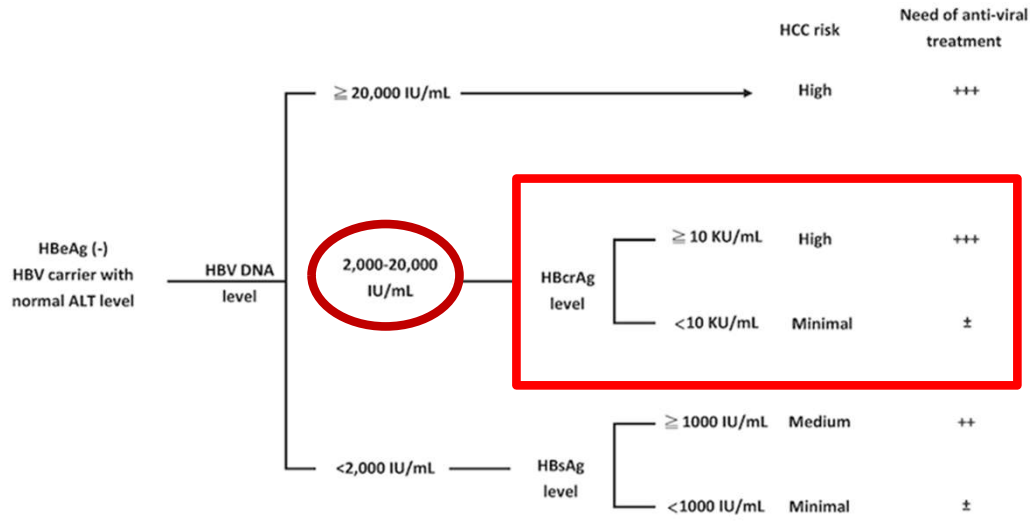
Đề xuất lưu đồ quản lý BN viêm gan B mạn tính kết hợp với HBcrAg phân tầng nguy cơ HCC



Tseng et al. Gastroenterology 2019;157:1518–1529

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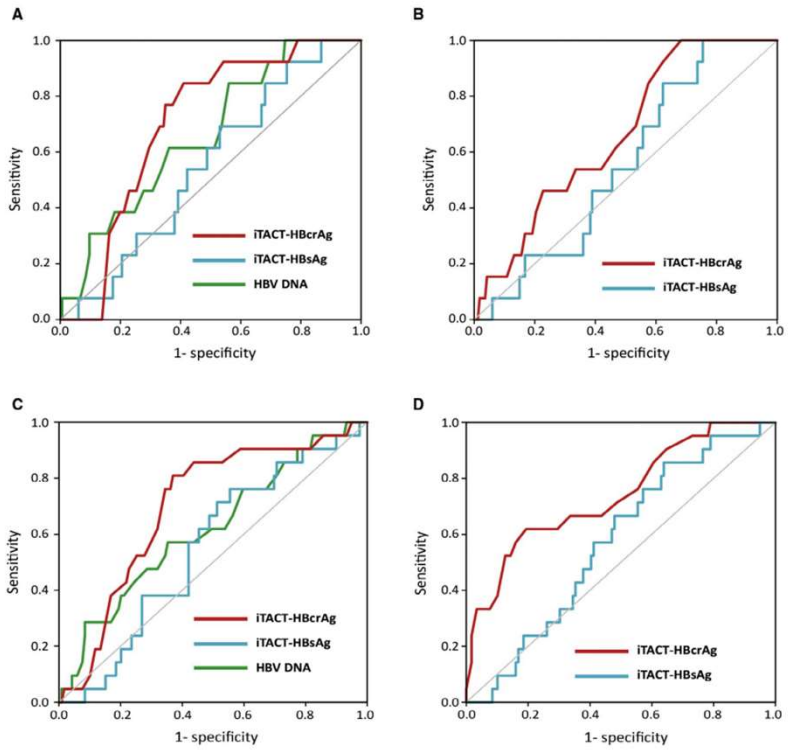

ROC curves for predicting HCC incidence

(A) ROC curves of baseline values for predicting HCC incidence in 5 years.

(B) ROC curves of baseline values for predicting HCC incidence in 10 years.

(C) ROC curves of values at year 1 for predicting HCC incidence in 5 years.

(D) ROC curves of values at year 1 for predicting HCC incidence in 10 years.

iTACT: total antigen including complex by pretreatment technology.

HOSAKA ET AL. Hepatology Communications, VOL. 0, NO. 0, 2021

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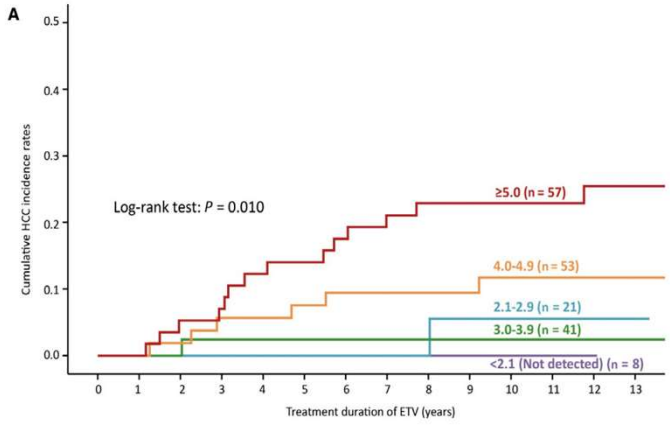
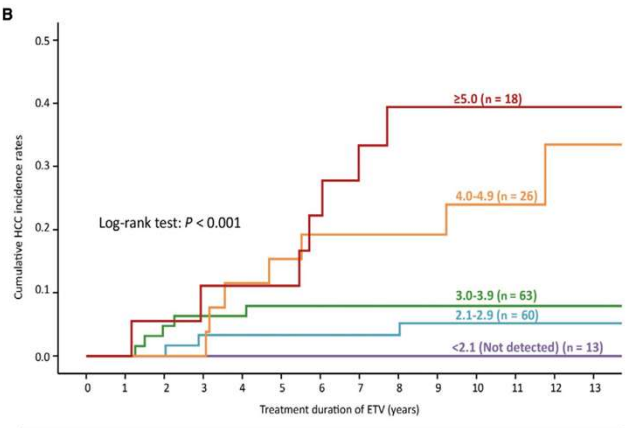
Cumulative HCC incidence rates using Kaplan-Meier curves



No. at risk	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10	Year 11	Year 12	Year 13
≥5.0	57	57	54	53	50	49	47	45	42	40	38	35	24	16
4.0-4.9	53	53	52	50	50	49	48	48	44	41	38	28	14	6
3.0-3.9	41	41	41	40	40	40	40	39	38	36	31	21	15	9
2.1-2.9	21	21	21	21	21	21	21	21	18	12	9	5	2	1
<2.1 (Not detected)	8	8	8	8	8	8	8	8	5	5	3	1	1	0

(A) HCC incidence rates by baseline iTACT-HBcrAg levels.



No. at risk	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10	Year 11	Year 12	Year 13
≥5.0	18	17	16	16	16	14	12	10	9	8	7	4	2
4.0-4.9	26	26	26	23	22	21	21	19	17	15	13	6	5
3.0-3.9	63	60	59	59	58	58	58	53	52	49	37	23	11
2.1-2.9	60	60	58	58	58	58	57	52	44	37	26	17	12
<2.1 (Not detected)	13	13	13	13	13	13	13	13	12	10	7	6	1

(B) HCC incidence rates by iTACT-HBcrAg levels at year 1.

iTACT: total antigen including complex by pretreatment technology.

HOSAKA ET AL. Hepatology Communications, VOL. 0, NO. 0, 2021

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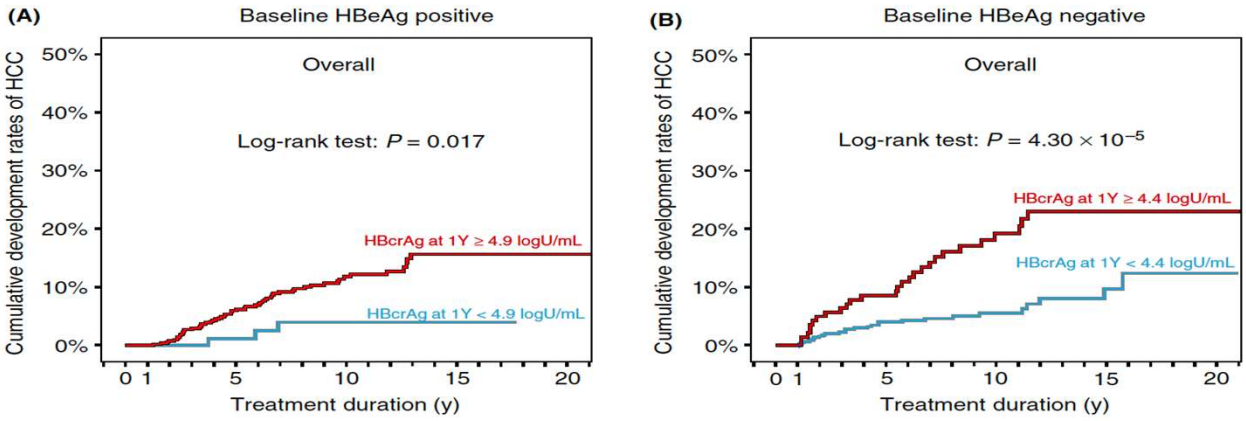
HBcrAg và Nguy cơ HCC sau 1 năm điều trị NUC

Study population: 1,268 patients on NUCs (667 HBeAg +ve; 601 HBeAg –ve)



Hosaka et al., Aliment Pharmacol Ther 2019;49:457-71

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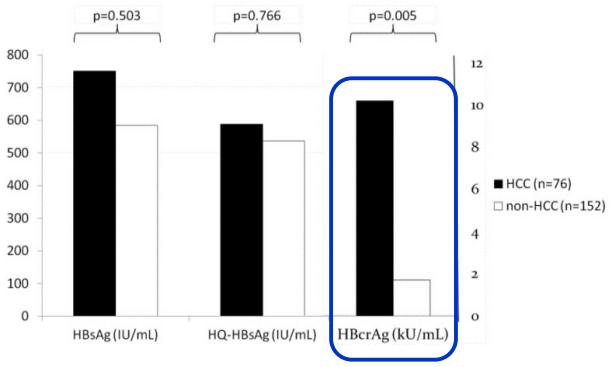
HBcrAg and HCC in NUC-treated patients with undetectable HBV DNA

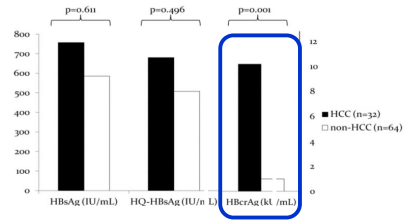
Study population: 228 patients on Nucs

- 76 patients with HCC vs. 152 without HCC

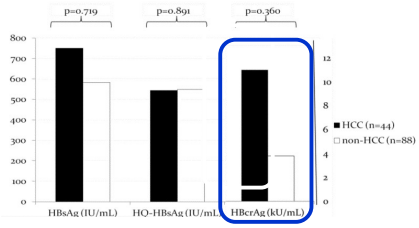
Whole cohort



Patients without cirrhosis



Patients with cirrhosis



Cheung KS, Yuen MF J Viral Hepat 2017:24(8):654-61

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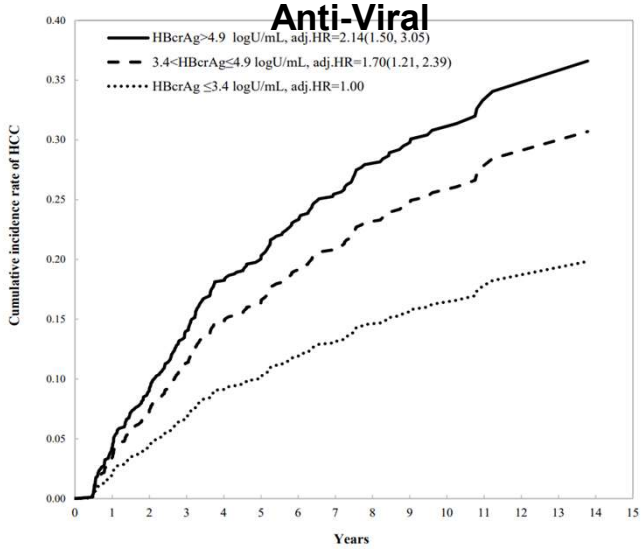
HBcrAg Predicts Hepatocellular Carcinoma Development in Chronic B Hepatitis Related Liver Cirrhosis Patients Undergoing Long-Term Effective Anti-Viral



Cumulative incidence rate of HCC by HBcrAg level.

Chang, K.-C et al. Viruses 2022, 14, 2671. https://doi.org/10.3390/v14122671

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Relationship between HBcrAg level and HCC development in treatment-naïve cohort studies

Study	Country	Study design	Disease status	Number of subjects	Number of HCC cases	Finding	Median follow-up time	Note
Tada et al.[6] (2016)	Japan	Retrospective	All HBV carriers with or without cirrhosis	1,031 (only 711 patients had HBcrAg level)	78	Higher HBcrAg level (>2.9 log U/mL vs. ≤2.9 log U/mL) was independently associated with the incidence of HCC (adjusted HR, 5.05; 95% CI, 2.40–10.63).	10.7 years	Remaining treatment-naïve during the whole follow-up
To et al.[7] (2019)	Hong Kong	Retrospective	HBeAg seroconverters with or without cirrhosis	207	14	Higher HBcrAg level (>5.21 log U/mL vs. <5.21 log U/mL) at HBeAg seroconversion was associated with HCC development (adjusted HR, 1.75; 95% CI, 1.06–2.90).	13.1 years	Treatment-naïve at enrolment but nearly half of the patients started to receive treatment at a median of 5.5 years after HBeAg seroconversion
Tseng et al.[8] (2019)	Taiwan	Retrospective	All HBV carriers without cirrhosis	2,666	209	1. For the overall patients, HBcrAg was positively associated with HCC with dose-response relationship. 2. Among the HBeAg-negative patients with HBV between 2,000–20,000 IU/mL and normal baseline ALT level, a higher HBcrAg level (≥4 log U/mL vs. <4 log U/mL) was associated with an increased HCC risk (adjusted HR, 6.29; 95% CI, 2.27–17.48).	16.0 years	Remaining treatment-naïve during the whole follow-up

HBcrAg, hepatitis B core-related antigen; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HR, hazard ratio; CI, confidence interval; HBeAg, hepatitis B e antigen; ALT, alanine aminotransferase.

Jer-Wei Wu, et al. Clinical and Molecular Hepatology 2021;27:524-534

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Relationship between HBcrAg level and HCC development in cohort studies of patients with oral antiviral treatment

Study	Country	Study design	HBcrAg measurement time points	Number of subjects	Number of HCC cases	Finding	Median follow-up time	Treatment drugs
Honda et al.[29] (2016)	Japan	Retrospective	Before treatment and at the end of follow-up	109	36	1. The HBcrAg positivity (≥3.0 log U/mL vs. <3.0 log U/mL) before treatment was not associated with HCC development. 2. At the end of follow-up, the patients with HCC development had higher detectable rates of HBcrAg than those without HCC development.	6.5 years	Patients with NA therapy for >2 years were enrolled; LAM: 12, LAM to LAM+ADV: 25, LAM to ETV: 17, ETV: 55
Ando et al.[30] (2018)	Japan	Retrospective	At the time of HBV DNA disappearance	133	13	Higher HBcrAg level (≥3.4 log U/mL vs. <3.4 log U/mL) at the time of HBV-DNA disappearance was associated with HCC development (adjusted HR, 13.532; 95% CI, 1.683–108.815).	4.8 years (after HBV-DNA disappearance)	Patients with NA and achieved HBV DNA disappearance were enrolled; LAM: 14, LAM+ADV: 18, ETV/ET-V+ADV/TDF: 101
Hosaka et al.[28] (2019)	Japan	Retrospective	At baseline and 1 year after receiving NA therapy	1,268	113	1. Higher HBcrAg levels at 1 year after treatment were significantly associated with HCC development, for both HBeAg-positive (≥4.9 log U/mL vs. <4.9 log U/mL; adjusted HR, 6.15; 95% CI, 1.89–20.0), and HBeAg-negative patients (≥4.4 log U/mL vs. <4.4 log U/mL; adjusted HR, 2.54; 95% CI, 1.40–4.60). 2. Pre-treatment HBcrAg levels could not predict the development of HCC in HBeAg-negative patients. They could not analyze the role of HBcrAg in HBeAg-positive patients as most of the HBcrAg data are greater than upper limit of quantification.	8.9 and 8.4 years for HBeAg-positive and -negative patients, respectively	Patients with NA therapy for >1 year were enrolled; LAM: 683, ETV: 585
Liang et al.[31] (2020)	Hong Kong	Retrospective	Baseline, defined as the earliest serum samples available for HBcrAg	1,400	85	Higher baseline HBcrAg level (>2.9 log U/mL vs. ≤2.9 log U/mL) was an independent factor for HCC in HBeAg-negative patients (adjusted HR, 2.13; 95% CI, 1.10–4.14).	45 months	Patients with NA therapy were enrolled; ETV: 77%, TDF: 24%

HBcrAg, hepatitis B core-related antigen; HCC, hepatocellular carcinoma; NA, nucleos(t)ide analogue; LAM, lamivudine; ADV, adefovir; ETV, entecavir; HBV, hepatitis B virus; HR, hazard ratio; CI, confidence interval; TDF, tenofovir disoproxil fumarate; HBeAg, hepatitis B e antigen.

Jer-Wei Wu, et al. Clinical and Molecular Hepatology 2021;27:524-534

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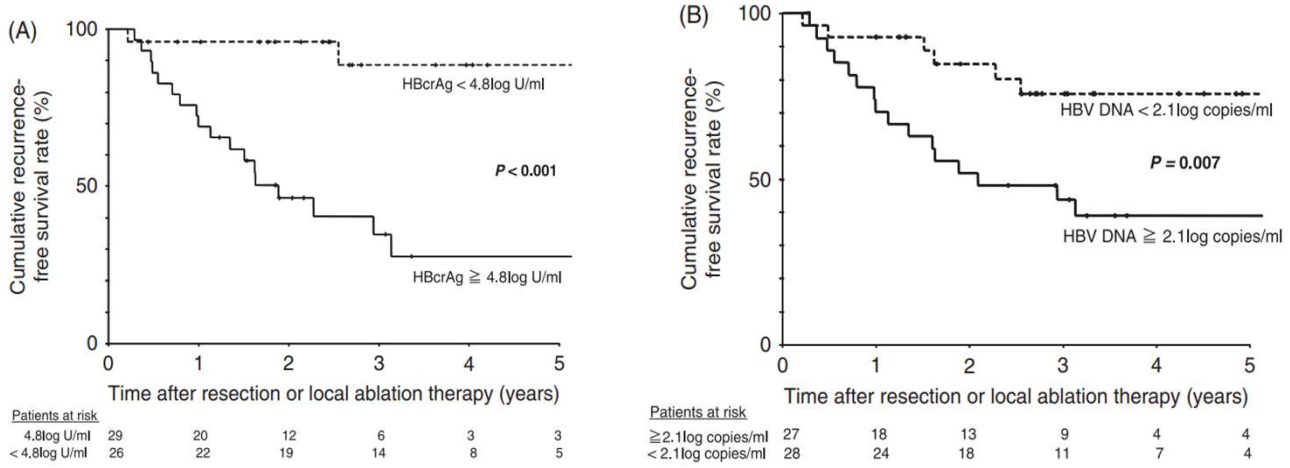
HBcrAg is a predictor of post-treatment recurrence of hepatocellular carcinoma during antiviral therapy.



(A) Kaplan–Meier life table for the cumulative recurrence□free survival rates by the serum HBcrAg levels and comparison by the log-rank test. (B) Kaplan–Meier life table for the cumulative recurrence-free survival rates by the serum hepatitis B virus DNA (HBV DNA) levels at the time of hepatocellular carcinoma (HCC) diagnosis for each patient and comparison by the log-rank test.

Hosaka et al. Liver International (2010) -1461-70

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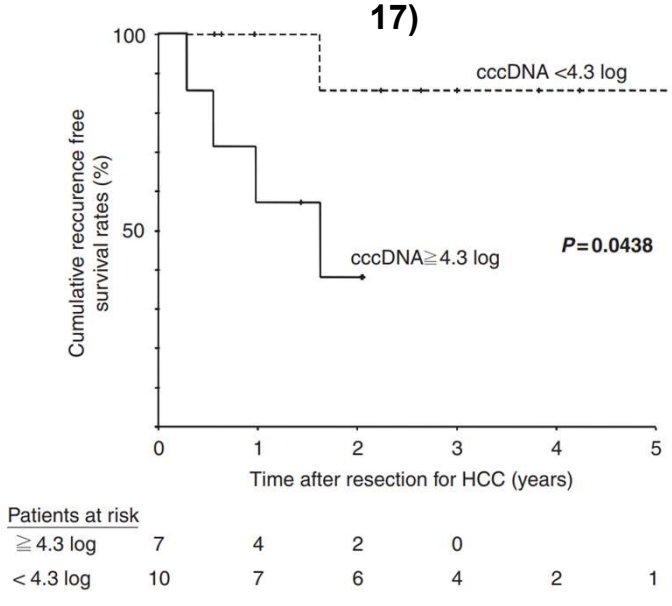
Kaplan–Meier life table for the cumulative recurrence-free survival rates by the intrahepatic cccDNA levels in patients with early- or intermediate-stage HCC (n = 17)



Hosaka et al. Liver International (2010) -1461-70

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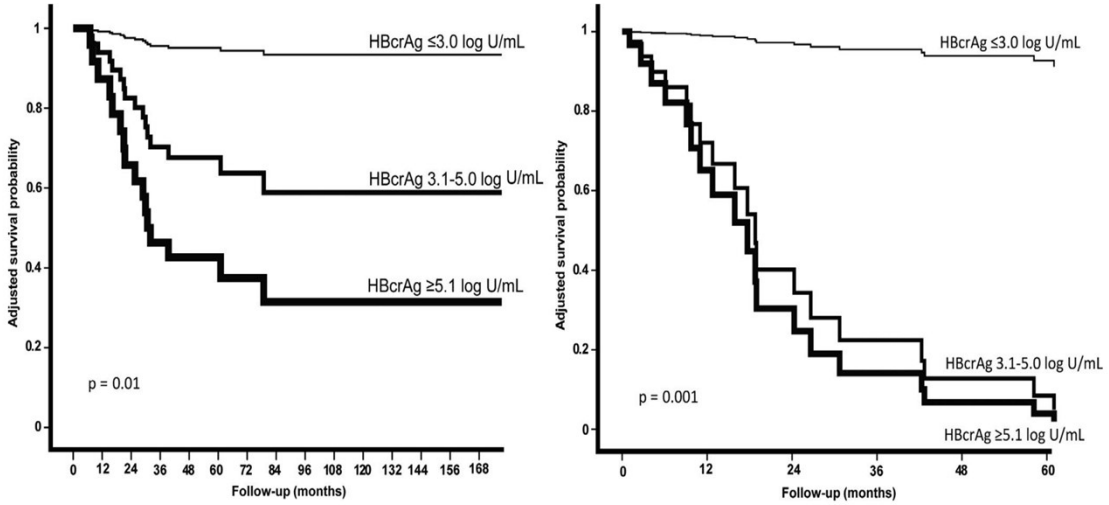
Hepatitis B core-related antigen levels predict recurrence free survival in patients with HBV-associated early-stage hepatocellular carcinoma



Univariate analysis identified no predictors of survival, but in multivariate analysis, higher HBcrAg levels at the time of HCC diagnosis were independently associated with poorer overall survival (P = .01).

In univariate analysis, HBcrAg levels were not associated with the risk of recurrence (P = .91). In multivariate analysis HBcrAg levels (P = .001), RFA (P = .001) and age (P = .030) were associated with reduced recurrence-free survival.

BEUDEKER et al. J Viral Hepat. 2021;28:205–208

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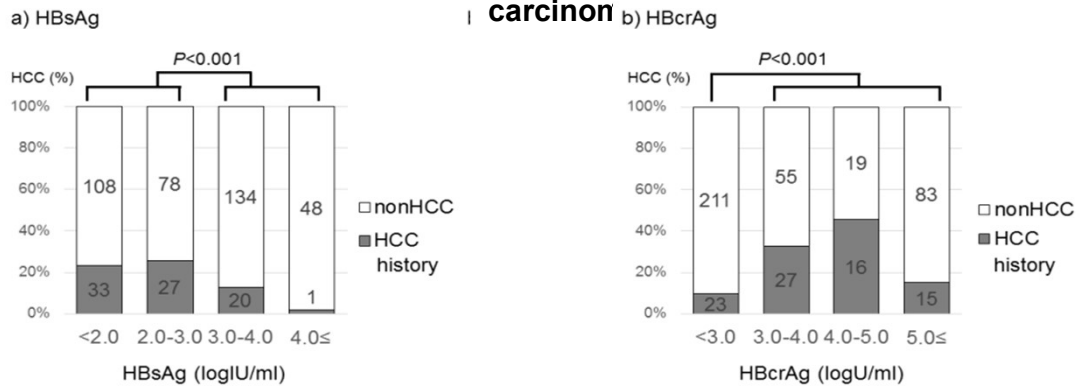
Hepatitis B virus (HBV)-infected patients with low hepatitis B surface antigen and high hepatitis B core-related antigen titers have a high risk of HBV-related hepatocellular carcinon



a) HCC history was significantly frequent in the low HBsAg group. When the patients were divided into two groups according to the HBsAg cut off of 3.0 log IU/ml, those with an HCC history were significantly frequent in the low HBsAg group (p <0.001).

b) HCC history was significantly frequent in high HBcrAg group. When the patients were divided into two groups according to the HBcrAg cut off of 3.0 log U/ml, those with an HCC history were significantly frequent in the high HBcrAg group (p <0.001)

<u>Conclusions:</u> Patients with low HBsAg/high HBcrAg values are at high risk of developing HBV-related HCC, according to this cross-sectional and longitudinal analysis, indicating that the combination of HBsAg and HBcrAg values is an excellent biomarker for assessing HCC risk.

Y Suzuki et al. Hepatology Research. Volume 49, Issue 1 January 2019 Pages 51-63

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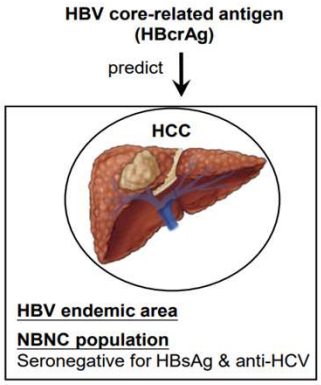
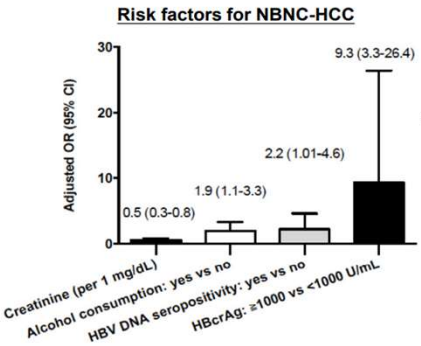
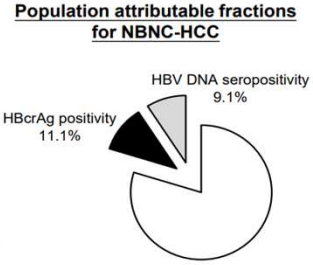
Serum HBcrAg and Hepatocellular Carcinoma in a Taiwanese Population Seronegative for HBsAg and Anti-HCV



A nested case-control study from the REVEAL-NBNC cohort
129 cases (HCC) vs 520 controls (non-HCC)





RESULTS: The proportion of baseline HBcrAg positivity (≥1000 U/mL) was significantly higher in HCC cases than in controls (12.4% vs 1.4%, $P < .001$). In multivariate analysis, HBcrAg positivity was associated with significantly higher risk of HCC (adjusted OR [95% CI]: 9.3 [3.3–26.4]; $P < .001$]. The HCC population attributable to HBcrAg positivity was 11.1% (95% CI: 9.7%–12.5%).

CONCLUSIONS: Seropositivity of HBcrAg might identify a subset of the NBNC population at higher risk of HCC in hepatitis B virus endemic areas.

Hsieh et al . Clinical Gastroenterology and Hepatology 2023;21:1303–1313

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Novel HBV biomarkers in risk prediction for HCC

HBV Biomarkers in Risk Prediction for HCC

	Treatment-Naive			On Treatment		
	HBsAg	HBcrAg	HBV RNA	HBsAg	HBcrAg	HBV RNA
HBeAg Positive	Less predictive than HBV DNA	Poorly predictive	No data	Not predictive based on small study	Persistently high (>4.9 log U/mL) = 6.2-fold ↑ risk*	Detectable = 2.2-fold ↑ risk Highest risk if ≥100,000 copies/mL^
HBeAg Negative	≥1000 IU/mL = 13.7-fold ↑ risk if HBV DNA <2000*	Levels >2.9 log U/mL = 5.1-fold ↑ risk*	No data	Not predictive based on small study	Persistently high (>4.4 log U/mL) = 2.5-fold ↑ risk	Detectable = 2.2-fold ↑ risk Highest risk if ≥100,000 copies/mL^
Comments	Addition to REACH-B ≠ improve accuracy	50% with undetectable baseline levels	More data needed	More data needed	Levels impacted by treatment duration	Detectable in up to 80% with no HBV DNA

*Both HBsAg and HBcrAg appear useful in stratifying risk in patients with intermediate viral load (2000-20000 IU/mL)

*Other studies have found no relationship between HBcrAg and HCC risk among treated HBeAg-positive patients
^Adjusted for but did not stratify on HBeAg status

Zhou et al. Hepatoma Res 2022;8:15

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CLINICAL and MOLECULAR HEPATOLOGY
Volume_28 Number_2 April 2022

KASL clinical practice guidelines for management of chronic hepatitis B

The Korean Association for the Study of the Liver (KASL)

Role of emerging HBV markers

Category	Potential role	HBV marker
Natural history	HBeAg seroconversion	Quantification of HBsAg, HBcrAg
	Diagnostic tool for differentiating disease states	Quantification of HBsAg, HBcrAg
cccDNA activity	Amounts of intrahepatic cccDNA and cccDNA activities	Quantification of HBsAg, HBcrAg, HBV RNA
	Endpoint for testing therapeutic agents that target cccDNA	Quantification of HBsAg, HBV RNA, HBcrAg
HBV treatment	Predictors of successful withdrawal of therapy	Quantification of HBsAg, HBcrAg, HBV RNA, cccDNA
	Risk of reactivation during therapy or after therapy withdrawal	Quantification of HBsAg, HBcrAg, HBV RNA, cccDNA
HCC occurrence/recurrence	Evaluation of HCC occurrence	HBcrAg, HBV RNA, HBV integration
	HCC recurrence	HBcrAg, HBV RNA, HBV integration
HBV reactivation	HBV reactivation by immune-related therapy	HBcrAg, cccDNA

HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBcrAg, hepatitis B core-related antigen; cccDNA, covalently closed circular DNA; HCC, hepatocellular carcinoma.

the possibility of achieving partial cure in patients on antiviral treatment, as defined by a sustained off-therapy virological control. In the study of 130 Hong Kong patients with undetectable serum HBV DNA during NA, HBcrAg was detectable in 101 (78%) samples.[115] After eight years of NA treatment, 21.3% of patients achieved serum HBcrAg <3 log10 U/mL.[116] Based on these findings, monitoring of HBcrAg and HBsAg quantification is recommended by the Japan Society of Hepatology guidelines to identify patients who can discontinue NA.[117] Furthermore, HBcrAg can be an aid for clinicians in identifying patients with a higher risk of HCC development or post-treatment recurrence.[118,119] Recently, the HBcrAg level has been the most emerging noninvasive predictor

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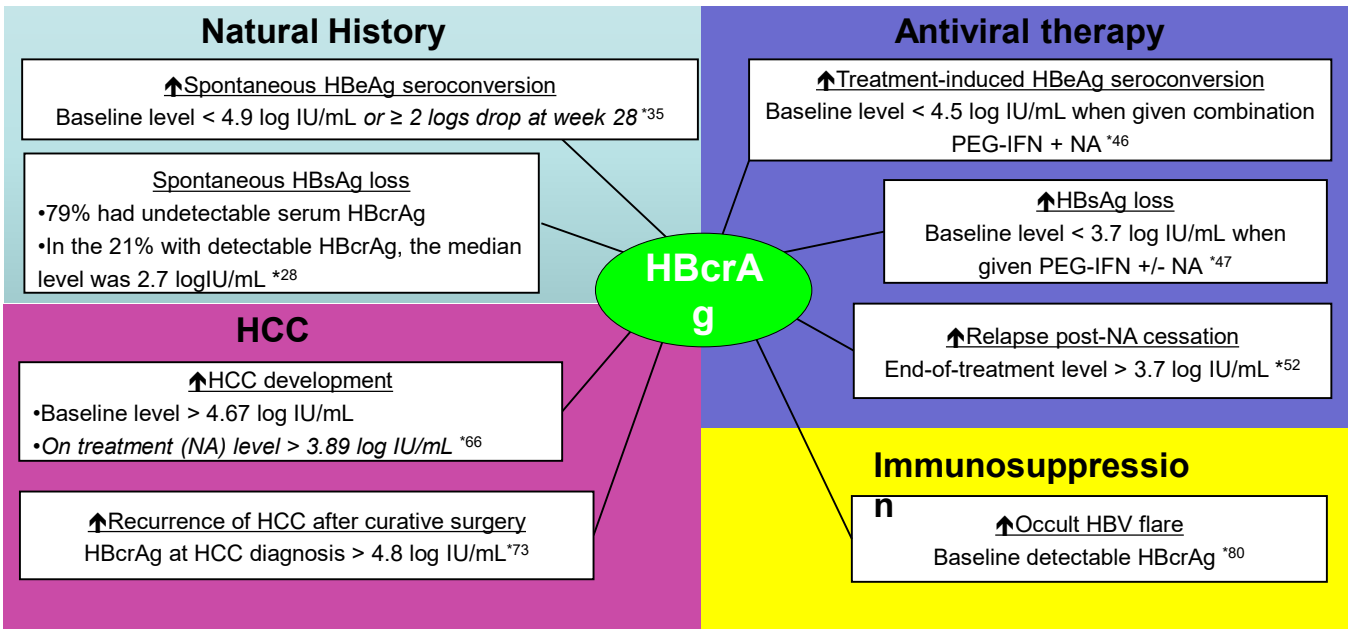
Tóm tắt giá trị lâm sàng của xét nghiệm HBcrAg



MAK ET AL. Aliment Pharmacol Ther 2018;47(1):43-54

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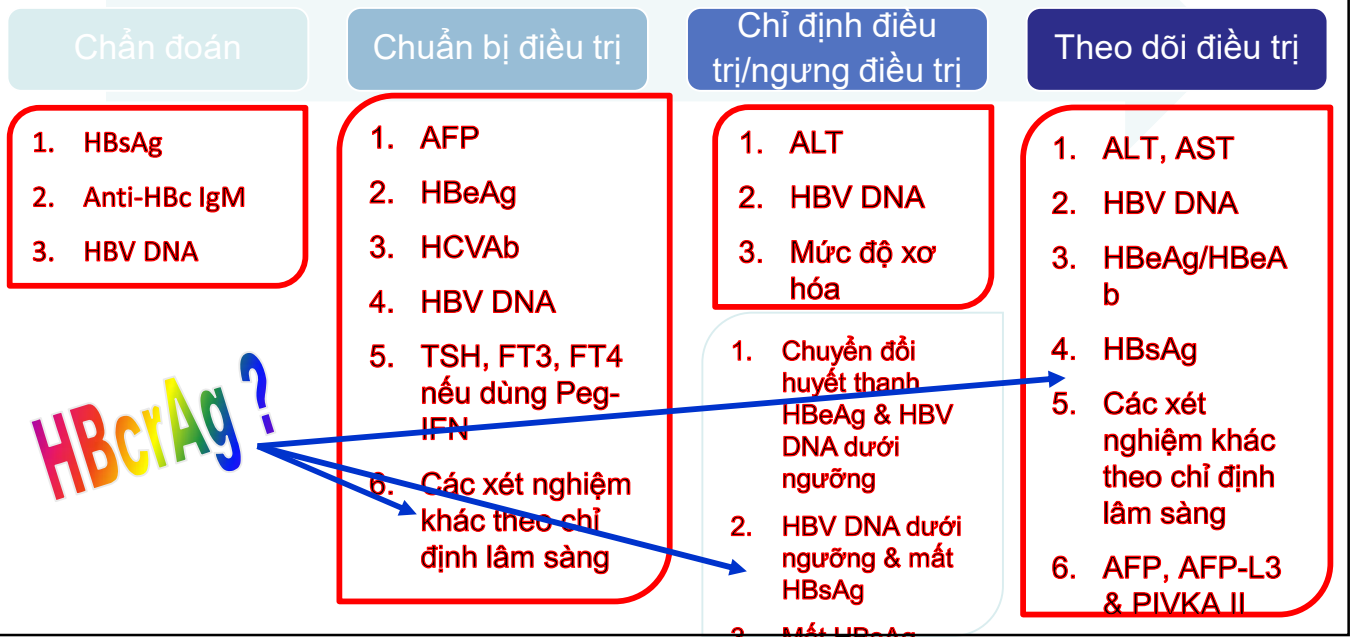
Hướng dẫn chẩn đoán & điều trị VGSV B mạn tính
Theo hướng dẫn BYT 2019



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IV, Các trường hợp lâm sàng.

Trường hợp lâm sàng 1 : Dự đoán HCC

- Bệnh nhân nam , 57 tuổi, Bến Tre.
- Uống rượu rất nhiều.
- Mẹ: HBVI.
- Nhiễm HBV từ nhỏ, không điều trị.
- Không đồng nhiễm HCV.
- Không tiền căn phẫu thuật hay truyền máu.
- Mệt, chán ăn ---→ Khám Khoa Gan-Medic.

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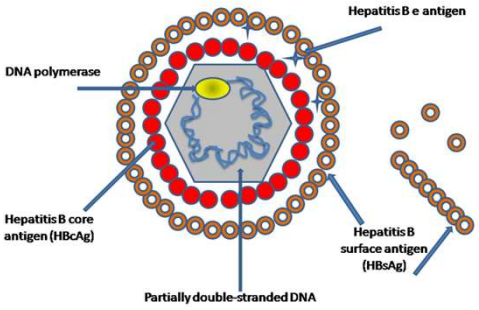
Trường hợp lâm sàng 1 : Dự đoán HCC

- HBsAg : dương tính.
- HBeAg : âm tính.
- AntiHBcIgM: âm tính.
- AntiHCV: Negative.
- HBV DNA: 7.250.000 IU/mL.



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Trường hợp lâm sàng 1 : Dự đoán HCC

Các thông số CLS	Tháng 2/2020	Tháng 4/ 2020	Ghi chú
AST(U/L)	61	25	
ALT (U/L)	35	15	
GGT (U/L)	350	220	
AFP (ng/mL)	8	7	
Tiểu cầu (10^9/L)	88	101	
Bilirubin (mg/dL)	1.07	0.9	
Prothrombin time (%)	67	72	HBV DNA: 1200 IU/mL
Albumin (g/dL)	3.2	3,5	
HBcrAg	4.5	5.9	
Ultrasound : Doppler	Xơ gan, lách to	Xơ gan, lách to	
Elastography: FibroScan(kPa)	19,5	18,5	

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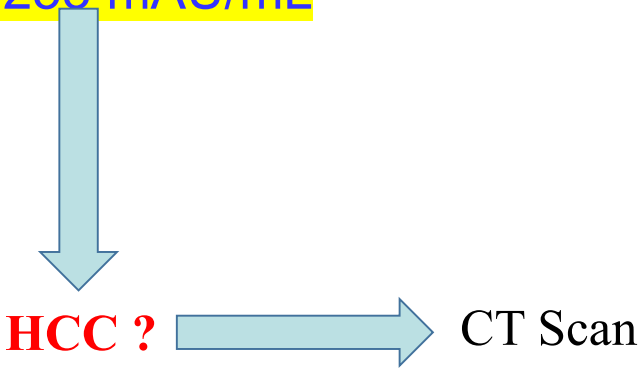
Trường hợp lâm sàng 1 : Dự đoán HCC

- AFP-L3: 37.2%
- PIVKAII: 1253 mAU/mL



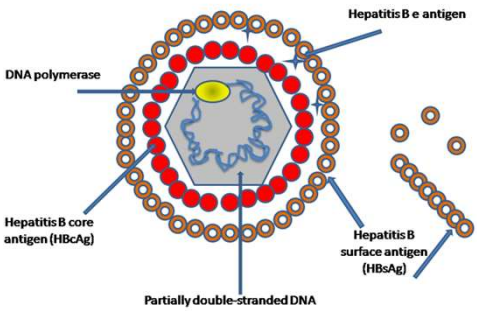
U hạ phân thùy VI , kích thước =1,1 cm nghĩ HCC

Trường hợp lâm sàng 2 : Dự đoán HCC

- Bệnh nhân nam , 56 tuổi, Bình Định
- Không thuốc lá, không uống rượu
- Mẹ, anh em: HBVI.
- Biết nhiễm HBV đã lâu, không điều trị.
- Khoảng 10 năm nay điều trị TDF
- Không đồng nhiễm HCV.
- Cao huyết áp
- Không tiền căn phẫu thuật hay truyền máu.
- Mệt, chán ăn ---→ Khám Khoa Gan-Medic.(2019)

Trường hợp lâm sàng 2 : Dự đoán HCC

- HBsAg : âm tính---→ Định lượng siêu nhạy: 10 IU/ml
- HBeAg : âm tính.
- AntiHBcIgM: âm tính.
- AntiHCV: Negative.
- HBV DNA: âm tính



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Trường hợp lâm sàng 2 : Dự đoán HCC

- Creatinin: 0,7 mg%.
- eGFR: 96mL/phút/1,73 m^2.
- Bilirubin: 1,01 mg%.
- AST: 98 U/L.
- ALT: 34 U/L.
- GGT: 99 U/L.
- Albumin: 3,1 g/dL
- Tiểu cầu: 91 x 10^9/L. PT: 65%

AFP= 9 ng/mL

HBcrAg= 7,9 Log U/mL

Siêu Âm Bụng: xơ gan, ascites(-)

FibroScan: 18 kPa

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Trường hợp lâm sàng 2 : Dự đoán HCC

- AFP-L3: 18,8 %
- PIVKAII: 2948 mAU/mL

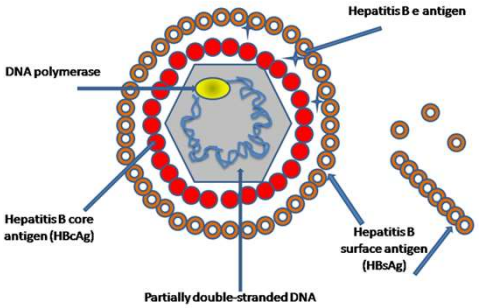
U hạ phân thùy VII , kích thước =1,2 cm nghĩ HCC

Trường hợp lâm sàng 3 : Dự đoán tái phát HCC

- Bệnh nhân nam sinh 1947, Cần Thơ.
- Không hút thuốc, uống rượu --- ngưng khi biết nhiễm HBV.
- Không tiền căn phẫu thuật hay truyền máu.
- Trong gia đình không ai bệnh gan.
- Cao huyết áp > 20 năm.
- Phát hiện và điều trị viêm gan B mạn 30 năm , hiện tại: TDF .
- 2019: Phát hiện HCC-----RFA
- Sau RFA-----Khoa Gan, Medic.

Trường hợp lâm sàng 3 : Dự đoán tái phát HCC

- HBsAg : Định lượng siêu nhạy: 18 IU/ml
- HBeAg : âm tính.
- AntiHBcIgM: âm tính.
- AntiHCV: Negative.
- HBV DNA: âm tính



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Trường hợp lâm sàng 3 : Dự đoán tái phát HCC

Các thông số CLS	2019	6 tháng sau (2020)	Ghi chú
AST(U/L)	32	25	
ALT (U/L)	35	38	
GGT (U/L)	31	41	
AFP (ng/mL)	6	7	
Tiểu cầu (10^9/L)	220	210	
Bilirubin (mg/dL)	0.8	0.9	
Prothrombin time (%)	91	95	
Albumin (g/dL)	3.3	3,5	
HBcrAg	4.2	4.9	
Ultrasound : Doppler	Viêm gan (Sẹo RFA)	Viêm gan, sẹo RFA, nốt 1,2cm nghi ngờ HCC	
Elastography: FibroScan(kPa)	6,9	6,5	

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Trường hợp lâm sàng 3 : Dự đoán tái phát HCC

- MRI Primovist: Nhân HCC hạ phân thùy IV 10x11 mm
- Xử trí: RFA
- HBcrAg: 3,5 Log U/mL

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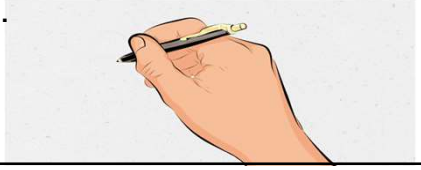
V, KẾT LUẬN.

- ☞ Viêm gan siêu vi B: Còn nhiều thách thức trong kiểm soát bệnh: Nguy cơ biến chứng vẫn còn dù bệnh đã được kiểm soát.
- ☞ Vai trò quan trọng của xét nghiệm trong bệnh viêm gan siêu vi B: Từ chẩn đoán, theo dõi điều trị, tiên lượng bệnh đến phòng ngừa.
- ☞ Nhiều tiến bộ của xét nghiệm đã góp phần trong cuộc chiến chống lại HBV.

HBcrAg là 1 dấu ấn mới giữ vai trò quan trọng trong đánh giá hiệu quả điều trị có hết không, đặc biệt với các thuốc mới – "DAA", tiên lượng diễn tiến bệnh cũng như nguy cơ biến chứng HCC của bệnh.

- ☞ Người thầy thuốc: Phải hiểu được ý nghĩa các xét nghiệm dấu ấn của HBV.
- ☞ Phòng ngừa vẫn giữ 1 vị trí cực kỳ quan trọng.



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Thank
you