Review Article

Evolution of viral biomarkers in predicting outcomes of chronic hepatitis B patients: From DNA to surface antigen

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ABSTRACT

Quantification of hepatitis B virus (HBV) DNA and quantitative hepatitis B surface antigen (HBsAg) have improved our understanding and management of chronic hepatitis B (CHB). Both HBV DNA and HBsAg levels are highest in the immune tolerance phase, start to decline during the immune clearance phase, and further decline after hepatitis B e antigen (HBeAg) seroconversion. These levels are lowest in the inactive carrier state but rise again in patients who develop HBeAg-negative hepatitis. Previous studies have shown that an HBV DNA level \( \leq 2000 \) IU/mL is associated with high risks of hepatocellular carcinoma, liver cirrhosis, and hepatitis activity, whereas a lower HBV DNA level is associated with a better chance of HBsAg loss, which is very close to a clinical cure for HBV infection. Recent studies further suggested that HBsAg level is not only a better predictor of HBsAg loss compared with the HBV DNA level, but also can complement the HBV DNA level in predicting HBV-related adverse events in patients with an HBV DNA level \( < 2000 \) IU/mL. In the Asia Pacific region, where HBV genotypes B and C prevail, an HBsAg level \( \leq 100 \) IU/mL has been shown to serve as a predictor of HBsAg loss over time. In HBeAg-negative patients with an HBV DNA level \( < 2000 \) IU/mL, an HBsAg level \( > 1000 \) IU/mL is associated with higher risks of hepatocellular carcinoma, cirrhosis, and HBeAg-negative hepatitis. European studies also indicated that combining levels of HBsAg \( < 1000 \) IU/mL and HBV-DNA \( < 2000 \) IU/mL aids in identifying true inactive carriers in genotype D HBeAg-negative carriers. All this evidence highlights the evolution of viral biomarkers in predicting the prognosis of CHB. Quantitative HBsAg can complement HBV DNA in optimizing the management of CHB patients in clinical practice.

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1. Introduction

Although safe and effective vaccines have been available for three decades, hepatitis B virus (HBV) infection remains a major public health problem across the world. The clinical manifestations of HBV infection range from acute or fulminant hepatitis to various forms of chronic infection, including the inactive carrier state, chronic hepatitis, cirrhosis, and even hepatocellular carcinoma (HCC) [1,2].

Hepatitis B surface antigen (HBsAg) is the hallmark of HBV infection and was first discovered by Blumberg et al in 1965 [3]. Since then, the qualitative status of HBsAg has been used to define the HBV infection status. Initially, this marker was not widely used to monitor disease progression in patients with chronic HBV infection. In short, clinical practice has generally relied on qualitative or semiquantitative serological markers, such as HBsAg and the hepatitis B e antigen (HBeAg), to determine HBV disease stages. HBsAg is a marker of chronic HBV infection. HBeAg is a circulating peptide derived from the core gene, then modified and secreted from liver cells. It usually serves as a marker of active viral replication. In addition, liver biochemical markers, such as the alanine aminotransferase (ALT) level, are checked repeatedly to evaluate the severity of liver cell necrosis and to estimate viral activity.
This practice has evolved since 2006, when quantification of the serum HBV DNA level was found to be useful in predicting long-term adverse outcomes [4,5]. Since then, the HBV DNA level has been widely used to evaluate viral activity and the risk of disease progression. The HBV DNA is a more precise predictor of viral activity than the ALT level, but both share the same flaw—they vary with time [6]. Therefore, both require repeated testing to determine viral activity.

Recently, HBsAg quantification has gained much attention because it stratifies the risk of disease progression more accurately than HBV DNA level and may serve as a marker reflecting host immune control over HBV infection [7].

In this review article, the evolutionary role of the HBV DNA and HBsAg levels in predicting the prognosis of chronic hepatitis B (CHB) is summarized and discussed.

2. Life cycle of HBV and synthesis of HBV DNA and HBsAg

With only 3200 bp in its genome, HBV is the smallest DNA virus. Fig. 1 illustrates the pathway of HBV DNA and HBsAg production in the HBV life cycle. The replication template of HBV is the covalently closed circular DNA (cccDNA), which exists in the liver and encodes four overlapping open reading frames (ORF).

S stands for the surface or envelope gene, C for the core gene, P for the polymerase gene, and X for the X gene [2]. The S and C genes have upstream regions designated pre-S and pre-C. The complete infectious virion, or Dane particle, is a 42-nm sphere containing the nucleocapsid and partially double-stranded circular HBV DNA. HBV DNA is synthesized via reverse transcription of the pregenomic RNA, which is also derived from cccDNA. Therefore, cccDNA is the template for both HBV DNA and HBsAg synthesis, although both products are derived from different ORFs of cccDNA (Fig. 1).

HBsAg is a glycosylated envelope protein of the HBV virion. There are three HBsAg proteins—small, medium, and large—and these are produced from three ORFs, called the pre-S1, pre-S2, and S ORF, of cccDNA. In addition to being on the mature virion, there are large numbers of two types of noninfectious HBsAg particles in the sera of HBV carriers, spherical particles and filamentous forms (Fig. 1). These subviral particles do not contain the HBV genome but are secreted at levels in excess (100- to 100,000-fold) of mature virions. In addition, HBsAg can also be derived from viral sequences that are randomly integrated into the host genome. Therefore, whereas serum HBV DNA levels merely reflect viral replication activity, serum HBsAg levels reflect activity from translated messenger RNAs of transcriptionally active cccDNA and from integrated HBV DNA sequences. Thus, the HBsAg level provides complementary information that may improve our understanding of the infection status of patients.

3. Natural history of CHB

In Asia, where HBV infection is hyperendemic, HBV carriers usually acquire the virus perinatally or in early childhood (by the age of 2 years) [8]. Therefore, the age of a given patient can be considered the duration of HBV infection.

Considering virus and host interaction, the natural course of chronic HBV infection in Asian patients can be divided into four chronological phases [9,10] (Fig. 2). The first is the “immune tolerance phase”, where there is active replication of HBV. Hence, this is characterized by positive HBeAg and normal-to-low ALT levels. The second is the “immune clearance phase”, where HBeAg-positive patients have raised ALT and declining HBV DNA levels. In the third “low replication or residual phase”, where HBeAg is lost, anti-HBe is gained, and remission of liver disease occurs, and thus patients are said to be in an “inactive carrier state”. Taken together, HBeAg seroconversion is regarded as a pivotal event in the natural history of HBV infection because it usually confers a favorable clinical outcome [11]. About 20–30% of inactive carriers enter the “reactivation or HBeAg-negative hepatitis phase”, which is a variant form of the immune clearance phase [12–14]. Previous longitudinal studies indicated that HBeAg-negative hepatitis (EHN) is an important risk factor for subsequent cirrhosis and HCC.
development [12,15–17]. Therefore, early identification of patients at risk of ENH and prompt antiviral treatment are mandatory in preventing or hindering disease progression. However, ENH also provides the opportunity for HBsAg seroclearance or seroconversion, which is a favorable clinical outcome [18].

4. HBsAg and HBV DNA levels in different phases of CHB

Several cross-sectional studies have explored HBV DNA and HBsAg levels in different phases of CHB (Fig. 2) [19–21]. Comparable results have been found irrespective of study population and HBV genotype. Both HBsAg and HBV DNA levels vary in different phases of HBV infection but generally decrease as HBV carriers age. The levels are highest in the initial immune tolerance phase when there is no or only minimal hepatitis activity and hence, serum ALT levels are normal. The levels decline during the immune clearance phase and further decrease in those who maintain normal ALT levels after HBeAg seroconversion. It has been consistently shown that the lowest HBsAg and HBV DNA levels occur in the immune control phase or inactive carrier state but rise again in the reactivation phase or in ENH.

5. Predictive value of HBsAg and HBV DNA in the outcome of CHB

Several previous studies indicated that in HBV carriers, cirrhosis is a consequence of extracellular matrix accumulation from liver cell injury, and HCC may subsequently emerge under this setting [15,16]. Therefore, HBV-related hepatitis, cirrhosis, and HCC are regarded as sequential adverse outcomes. By contrast, HBsAg loss occurs at an annual rate of 0.5–2.3%, which is a marker for disease cure [6,22–27]. Fortunately, in the absence of confounding factors, such as liver cirrhosis, hepatitis C or hepatitis D virus, superinfection or age >50 years at the time of HBsAg loss, the risk for HCC development is minimal [28].

Cohort studies are preferred over cross-sectional studies to investigate the impact of dynamic factors on disease progression, so we will review the role of HBV DNA and HBsAg levels in predicting favorable and unfavorable outcomes by referring to three cohort studies (Table 1). The first was a community-based cohort study known as the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV), which followed 3653 adult Taiwanese HBsAg seropositive patients over a mean follow-up period of 11.4 years. The second study was a hospital-based cohort study, the Study of E Antigen seroClearance of Hepatitis B (SEARCH-B). It enrolled 390 Taiwanese spontaneous HBeAg seroconverters without liver cirrhosis at enrollment and followed them for an average of 7.4 years. This study is unique in that it enabled investigation of the early HBeAg-negative stage because follow-up started at 1 year after HBeAg seroconversion. The third study was a hospital-based cohort study, the Elucidation of Risk fActors for DIsease Control or Advancement in Taiwanese Hepatitis B Carriers (ERADICATE-B), which enrolled 2688 Taiwanese HBV carriers who did not have evidence of cirrhosis at baseline and were not treated during the follow-up period. The mean follow-up period was 14.7 years.

| Table 1 Summary of three Taiwanese HBV cohort studies. |
|---|---|---|---|---|---|
| Cohort | Study design | Disease stage | Number of participants | Follow-up (y) | References |
| REVEAL-HBV | Community based cohort | Including HBeAg-positive and -negative phases | 3653 | 11.4 | [4,5,26,36,48–50,53,54] |
| SEARCH-B | Hospital based cohort | Early HBeAg negative phase | 390 | 7.4 | [6,14] |
| ERADICATE-B | Hospital based cohort | Including HBeAg-positive and -negative phases | 2688 | 14.7 | [27,47,51] |

ERADICATE-B = Elucidation of Risk Factors for Disease Control or Advancement in Taiwanese Hepatitis B Carriers; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; REVEAL-HBV = Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus; SEARCH-B = Study of E Antigen seroClearance of Hepatitis B.
6. Role of HBV DNA and HBsAg levels in predicting HBsAg loss

Spontaneous clearance of HBsAg has been widely accepted as an indicator of disease remission [18,28–31]. Earlier studies suggested that the rate of HBsAg loss is lowest in HBeAg-positive patients, followed by patients with ENH, and is highest in inactive carriers [18]. A Taiwanese longitudinal study of 1965 HBeAg-negative patients with normal ALT levels reported an annual HBsAg loss rate of 1.15% [23]. The authors noted that HBeAg-negative patients with sustained normal ALT levels were more likely to clear HBsAg than those with hepatitis relapse. Later, the REVEAL-HBV study found that a low HBV DNA level could predict HBsAg loss [26], where sustained normal ALT levels were more likely to clear HBsAg than patients with an undetectable viral load (<60 IU/mL) had an annual HBsAg loss rate of 5.76%. Compared with patients with HBV DNA levels ≥200,000 IU/mL, the hazard ratio (HR) for HBsAg loss was 15.9 (95% confidence interval [CI], 9.3–27.2). The positive association between limited viral replication and a higher chance of HBsAg loss as well as a low viral load linked to a low risk of hepatitis relapse can explain why HBsAg clearance occurs more frequently in patients with persistently normal ALT levels. In addition, the fact that an undetectable HBV DNA level usually precedes HBsAg loss also stresses the importance of the HBV DNA level in predicting HBsAg loss [26].

The SEARCH-B study revealed another predictor for HBsAg loss, the HBsAg level [6]. In this study, 18 patients cleared HBsAg at an annual rate of 0.6% during a mean follow-up period of 7.4 years. It was noted that both lower HBV DNA and HBsAg levels were associated with a higher likelihood of HBsAg clearance. Evaluation of 6-year HBsAg loss via receiver operating characteristic (ROC) curve analysis showed the HBsAg level was a better predictor than the HBV DNA level (area under the ROC curve: 0.90 vs. 0.69, p = 0.012). Even in patients with limited viral replication (HBV DNA level <200 IU/mL), an HBsAg level <100 IU/mL remained an independent predictor for HBsAg loss. Although this study shed much light on the importance of HBsAg levels, it lacked the statistical power to fully establish a relationship between HBsAg levels and HBsAg loss.

The subsequent ERADICATE-B cohort study investigating the relationship between HBsAg loss and both HBV DNA and HBsAg levels in 688 HBeAg-negative patients with HBV DNA levels <2000 IU/mL at baseline showed similar findings [27]. This study had adequate statistical power with 130 patients clearing HBsAg at an annual rate of 1.6% during a mean follow-up of 11.6 years. It also found that the HBsAg level served as a better predictor for HBsAg loss than the HBV DNA level. For example, the HBsAg annual clearance rate was 7% in patients with an HBsAg level <10 IU/mL, and its HR for HBsAg loss was 13.2 (95% CI, 8.1–21.5) compared with an HBsAg level ≥1000 IU/mL. This large-scale study firmly established the importance of HBsAg levels at baseline for subsequent HBsAg loss.

Several additional studies reaffirmed the relationship between the HBsAg level and HBsAg loss (Table 2). [4,27,32–36] A cohort study and a case-control study from Hong Kong showed that a lower HBsAg level was associated with a higher chance of HBsAg loss, and HBsAg levels of 100 and 200 IU/mL were the recommended cutoffs, respectively [32,33]. Other studies from Taiwan, including the REVEAL-HBV cohort study, a pediatric cohort study, and a case-control study, all had similar data [34–36]. In the recent REVEAL-HBV study, the authors proposed a 5- and 10-year HBsAg loss prediction model by combining the HBV DNA and HBsAg levels, and this combination indeed improved the prediction power compared with HBV DNA alone [36]. In summary, multiple lines of evidence support the notion that the HBsAg level serves as a very important predictor for HBsAg loss.

7. Role of HBV DNA and HBsAg levels in predicting HCC risk

Although most longitudinal cohort studies consider chronic hepatitis, cirrhosis, and HCC as sequential complications [12,15–17], HCC is still regarded as the most definitive end point for complications owing to its disastrous prognosis. In 2006, the REVEAL-HBV study reported that the serum HBV DNA level was a major determinant for HCC development [4]. They found that in adult HBV carriers, a higher HBV DNA level was associated with HCC development in a dose response manner [4]. In addition, the risk increased at HBV DNA levels >2000 IU/mL and further increased when the HBV DNA level was ≥20,000 IU/mL. These findings assisted in establishing 2000 IU/mL as the HBV DNA threshold required for treatment and defining patients with levels <2000 IU/mL as inactive HBV carriers [37–39]. Several cross-sectional and longitudinal studies in Taiwan, Hong Kong, and China reiterated the impact of the HBV DNA level on HCC development [40–46].

As HBsAg quantification became available, the association between the HBsAg level and HCC was first addressed by the ERADICATE-B cohort [47]. Initially, it demonstrated that elevated HBV DNA and HBsAg levels were both positively correlated with HCC development. When these two biomarkers were compared, the HBV DNA level was found to be a better predictor of 10- and 15-year HCC risk in the overall cohort. However, once the study population was restricted to HBeAg-negative patients with HBV DNA levels <2000 IU/mL, the HBV DNA level had a minimal role in predicting HCC, whereas HBsAg retained its predictive value. More specifically, in HBeAg-negative patients with HBV DNA levels <2000 IU/mL, the HCC risk increased in patients with an HBsAg level >1000 IU/mL compared with those with a level <1000 IU/mL (HR of 5.4; 95% CI, 2.1–14.2). The 10-year cumulative incidence rate of HCC was 0.2% for HBeAg-negative patients with an HBV DNA level <2000 IU/mL and an HBsAg level <1000 IU/mL similar to the rate of non-HBV and non-HCV infected individuals [48].

### Table 2

<table>
<thead>
<tr>
<th>Country</th>
<th>Study design</th>
<th>Disease stage</th>
<th>Number of participants</th>
<th>HBsAg cutoff (IU/mL)</th>
<th>Note</th>
<th>References</th>
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<td>SEARCH-B</td>
<td>[4]</td>
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<td>ERADICATE-B (partial)</td>
<td>[27]</td>
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<td>200</td>
<td></td>
<td>[35]</td>
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<td>[33]</td>
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<td>100</td>
<td>REVEAL-HBV</td>
<td>[36]</td>
</tr>
</tbody>
</table>

ERADICATE-B = Elucidation of Risk Factors for Disease Control or Advancement in Taiwanese Hepatitis B Carriers; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; REVEAL-HBV = Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus; SEARCH-B = Study of E Antigen seRoClearance of Hepatitis B.
REVEAL-HBV study similarly found that the HBsAg, but not the HBV DNA level, could further stratify HCC risk in HBeAg-negative patients with an HBV DNA level <2000 IU/mL [49]. This strengthened the role of the HBsAg level in predicting HCC in HBV carriers with low viral loads.

8. Role of HBV DNA and HBsAg levels in predicting liver cirrhosis

It is generally believed that cirrhosis develops with the accumulation of extracellular matrix consequent to liver cell injury, and HCC may subsequently emerge in the setting of cirrhosis [10,12,14–17]. Therefore, it was postulated that if a correlation exists between HCC and HBV DNA as well as HBsAg levels, the relationship between these two biomarkers and cirrhosis development should also hold. In the REVEAL-HBV study, a dose–response relationship between the HBV DNA level and cirrhosis development was indeed noted [50], and the risk started to rise when the HBV DNA level >2000 IU/mL. The SEARCH-B study subsequently reaffirmed the HBV DNA level as a major stimulant of cirrhosis development [14].

Based on previous findings, it is logical to extrapolate that a similar relationship should exist between the HBsAg level and cirrhosis development in HBV carriers with low viral loads. The ERADCIATE-B cohort study moved on to investigate this issue by analyzing 1068 HBeAg-negative patients with low viral loads. The results showed that an HBsAg level >1000 IU/mL was consistently associated with a higher cirrhosis risk compared with an HBsAg level <1000 IU/mL (HR 2.2: 95% CI, 1.1–4.2), suggesting that HBsAg could assist in predicting cirrhosis development [51].

9. Role of HBV DNA and HBsAg levels in predicting HBeAg-negative hepatitis

Hepatitis activity is regarded as the first step in many HBV-related complications. However, unlike cirrhosis and HCC, various definitions exist and it can spontaneously resolve. Therefore, a convincing detection of hepatitis occurrence warrants a cohort study with regular follow-ups and repeated testing of ALT levels. [12,14,27] This issue can only be adequately addressed by hospital-based cohorts that use the following criteria for HBeAg-negative hepatitis: an ALT level ≥2 of the upper limit of normal plus an HBV DNA level ≥2000 IU/mL. These criteria are consistent with the definition of clinical relapse in the guidelines of the Asia Pacific Association for the Study of the Liver [38].

The relationship between the HBV DNA level and ENH was first publicized in the SEARCH-B study [14]. It found that the risk of ENH increased if the HBV DNA level at 1 year after HBeAg seroconversion was >200 IU/mL. Compared with patients with an HBV DNA level <200 IU/mL, the HRS were 2.5 (95% CI, 1.4–4.4) for an HBV DNA level 200–20,000 IU/mL, 3.8 (95% CI, 2.0–7.3) for a level 20,000–200,000 IU/mL, and 6.7 (95% CI, 4.0–11.2) for a level ≥200,000 IU/mL.

The ERADCIATE-B study also explored the role of the HBsAg level in predicting ENH in HBeAg-negative patients with low viral loads. Again, this study used an HBsAg level of 1000 IU/mL as the cutoff and showed that a higher HBsAg level was associated with a higher risk of ENH. Compared with patients with an HBsAg level <1000 IU/mL, an HBsAg level ≥1000 IU/mL had an HR of 1.4 (95% CI, 1.1–1.8) [51]. Furthermore, the low viral load subcohort of the SEARCH-B study yielded consistent findings where the risk of ENH was higher for an HBsAg level ≥1000 IU/mL compared with an HBsAg level <1000 IU/mL (unpublished data).

10. Role of HBsAg in predicting HBV reactivation

Chronic hepatitis, cirrhosis, and HCC are sequential complications of CHB. For patients with low viral loads at baseline, the instigator of these sequential complications is the reactivation of HBV replication. Brunetto et al [51] first investigated whether serum HBsAg levels contribute to define inactive carriers in HBeAg-negative HBV carriers with genotype D infection. They analyzed 209 treatment-naïve and asymptomatic carriers in Italy. Defining “inactive carrier state” as an HBV DNA level <2000 IU/mL plus a normal ALT, they found that an HBsAg level <1000 IU/mL at baseline could identify a 3-year inactive state with 94.3% diagnostic accuracy, 91.1% sensitivity, 95.4% specificity, an 87.9% positive predictive value, and 96.7% negative predictive value. In other words, a lower HBsAg level at baseline can predict 3-year sustained viral suppression.

The ERADCIATE-B study, which included mostly genotype B and C patients, reported similar findings. We analyzed the HBV DNA level in the 3rd year of follow-up in patients with low viral loads and found that an HBsAg level <1000 IU/mL was associated with a lower rate of HBV DNA reactivation [51].

11. Conclusions and perspectives

Ample evidence confirms that a combination of HBV DNA and HBsAg levels can identify HBV carriers with “minimal viral activity.” These specific Asian HBV carriers can thus be regarded as “minimal risk” for cirrhosis and HCC after long-term follow-up if they have minimal liver fibrosis at enrollment. Whether this definition could be extrapolated to HBV carriers with genotypes other than B or C requires further validation in different populations.

Limited disease activity in HBV carriers has long been described as an “inactive carrier state” [37,38]. This relies on patients maintaining low levels of ALT and HBV DNA indefinitely, and hence, repeated testing of these levels, which is very unlikely in routine daily practice. Snapshot levels of HBV DNA and HBsAg, by contrast, enable the identification of “minimal viral activity,” in which multiple Asian and European studies have reported to yield outcomes comparable to “inactive carriers” [47,52]. Physicians may stratify patients into risk levels based on viral activity, providing them with personalized treatment strategies.

From bench to bedside, several issues need to be addressed. First, the appropriate cutoffs of the HBsAg level need further examination. Second, most existing data are from Asian studies examining patients with genotype B or C, and the validity in European populations—where different genotypes predominate and the infection is acquired later in life—needs to be investigated. We hope that, as more lines of evidence accumulate, the HBsAg level can be integrated to improve the risk calculator or nomogram for HBV carriers and treatment guidelines for CHB [53,54]. Third, prospective clinical studies are mandatory to confirm the combined role of HBV DNA and HBsAg for a “minimal viral activity” cutoff and to predict disease progression.

In HBV carriers, HBsAg loss is the treatment goal. However, this is very rarely achieved in patients who acquire the infection perinatally. Therefore, the antiviral treatment response has been defined as an HBV DNA level <2000 IU/mL plus HBeAg seroconversion at 6 months after therapy for HBeAg-positive patients and an HBV DNA level <2000 IU/mL at 6 months after therapy for HBeAg-negative patients. In interferon-based therapy, the HBsAg level during the treatment seems to predict the treatment response [55–58]. However, surging evidence has shown that clinical relapse may occur even if the treatment endpoint is achieved [59]. Similarly, several studies have found a high rate of clinical relapse after achieving treatment endpoints in patients receiving nucleos(t)ide
analogue therapy [60,61]. This is compounded by the fact that the time point of nucleos(t)ide analogue therapy cessation is difficult to determine because most patients achieve undetectable viral loads regardless of future outcome. Because the criteria for "minimal viral activity" has been established in the natural history of HBV, a combination of the HBV DNA and HBsAg levels may be adopted to define new criteria for treatment response.

References