Application of Risk Scores for Hepatocellular Carcinoma in Patients with Chronic Hepatitis B: Current Status and Future Perspective

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Abstract

Accurate risk prediction for hepatocellular carcinoma (HCC) among patients with chronic hepatitis B (CHB) may guide treatment strategies including initiation of antiviral therapy and also inform implementation of HCC surveillance. There have been 26 risk scores developed to predict HCC in CHB patients with ($n = 14$) or without ($n = 12$) receiving antiviral treatment; all of them invariably include age in the scoring formula. Virological biomarkers of replicative activities (i.e., hepatitis B virus DNA level or hepatitis B envelope antigen status) are frequently included in the scores derived from patients with untreated CHB, whereas measurements that gauge severity of liver fibrosis and/or reserve of hepatic function (i.e., cirrhosis diagnosis, liver stiffness measurement, platelet count, or albumin) are essential components in the scores developed from treated patients. External validation is a prerequisite for clinical application but not yet performed for all scores. For the future, higher predictive accuracy may be achieved with machine learning based on more comprehensive data.

Keywords
- chronic hepatitis B
- hepatocellular carcinoma
- risk prediction
- precision medicine

Hepatitis B virus (HBV) infection chronically affects more than 250 million people worldwide with a higher prevalence in sub-Saharan Africa, Western Pacific, and South-East Asia.[1] Globally and particularly in the endemic regions, it is the leading etiology of liver-related morbidity and mortality.[1,2] The causal effect of chronic HBV infection on hepatocellular carcinogenesis is indisputably supported by a large body of evidence from observational studies, interventional trials, and animal models.[3–5] The viral infection is believed to be indirectly carcinogenic through chronic inflammation of the

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liver tissue in most cases of HBV-associated hepatocellular carcinoma (HCC)[6–8]; however, this deoxyribonucleic acid (DNA) virus may also directly transform the infected hepatocytes by inserting viral genetic fragments into the host genome and producing viral proteins that could promote carcinogenesis.[9,10] On the basis of longitudinally observing the natural history of a community-based cohort comprising chronic hepatitis B (CHB) patients from Taiwan (the REVEAL-HBV cohort), Huang et al estimated the lifetime (age: 30–75 years) incidences of developing HCC to be 27.38 and 7.99% in male and female patients, respectively.[11] Conceivably, the risks of HCC are not the same among all patients with CHB.

Potential Utilities of a Risk Score to Predict HCC in Patients with CHB

Accurate risk stratification for a major clinical outcome is fundamental for the practice of precision medicine, in which healthcare is tailored to meet the needs of individual patients.[12] An accurate risk estimation is not only essential for the communication with individual patients to optimize the clinical care but also indispensable for cost-effective allocation of healthcare resources at a population level.[13] Therefore, the knowledge with regard to risk prediction of HCC is imperative in the management of patients with CHB. For example, patients who are predicted to carry a high risk of developing HCC should receive interventions that can effectively reduce such a risk. On the other hand, those whose HCC risks are confirmed to be negligible can be reassured and spared from undue anxiety along with unnecessary and potentially harmful interventions.

Risk Prediction to Guide Treatment Strategies

Approved antiviral therapies for the treatment of CHB, which include nucleos(t)ide analogs (NAs) and interferon α-based regimens, have been shown to decrease the risk of HCC in treated patients as compared with untreated controls.[14] Although direct evidence from the setting of randomized placebo-controlled trial is limited, the pool of available data has consistently attested the effectiveness of antiviral treatment in reducing HBV-related HCCs.[15] As a result, identification of patients to whom antiviral treatment is indicated is one of the major applications of risk prediction for CHB. Other interventions to attenuate the HCC risk, such as chemopreventive agents like aspirin, statin, and metformin, have been suggested with encouraging findings from observational studies,[16–19] although adoption into daily practice awaits further evidence.[20] Lifestyle interventions, such as changes in dietary contents and/or habitual intakes (e.g., coffee consumption),[21–24] are additional factors that are modifiable to lower the risk of HCC. These lifestyle modifications are thought to be healthy overall with a beneficial effect on primary prevention of HCC,[25] despite the fact that data are mainly accrued from epidemiological surveys and careful interpretation is advised. Regardless, accurate risk prediction is the basis to identify among CHB patients the candidates who are more likely to benefit from such an additional intervention, particularly for patients who continue to carry a substantially high risk of HCC even after taking effective antiviral therapies.

Risk Prediction to Inform Implementation of HCC Surveillance

Furthermore, accurate estimation of an individual's risk of developing HCC within a certain period of time may also inform the practice of surveillance for this lethal cancer. In general, it has been accepted with supportive data predominantly from observational studies that HCC surveillance is associated with an earlier diagnosis of the cancer and prolongation in overall survival among at-risk populations including patients with CHB.[26–30] To be cost-effective, HCC surveillance is recommended to CHB patients whose HCC risks exceed a certain threshold, for example, an annual incidence rate of 0.2% as endorsed by the American Association for the Study of Liver Diseases.[28] Obviously, a reliable risk predictive tool is essential to implement such a surveillance program. Besides, it is generally recommended to carry out the surveillance using ultrasound with or without circulatory biomarkers (mainly α-fetoprotein) at the interval of 6 months.[26–28] Presumably, it is dubious that a single fixed surveillance program could fit the diverse CHB population with heterogeneous characteristics and distinct HCC risks. A more personalized surveillance strategy has yet to be realized.

Uncovering Risk Determinants May Help Understand Underlying Pathogenesis

Knowledge learned from the risk scores for HCC prediction among CHB patients may also shed light on understanding the pathogenesis of HBV-associated HCCs, given that development of a risk score usually starts from examining and proceeds to validating measurement of a certain exposure as an independent variable in association with the outcome in question. For instance, the scoring formula that reflects the "dose-response" association between serum levels of HBV DNA and risks of clinical complications in patients without receiving antiviral therapy helps to establish the conceptual model that regards activity of viral replication as the driving force of disease progression in the natural history of CHB.[31–34] It follows that efficacious inhibition of viral replication may prevent disease from progression. Accordingly, an informative risk score may uncover modifiable risk factors as the targets for interventions with or without pharmacological agents, although the component predictors in a validated risk score are not necessarily causative and additional evidence from more studies are essential to verify the causal relationship. For the verified risk determinants, their relative importance can be further appreciated by comparing their respective weights in the scoring formula, which are usually derived from the regression coefficients in a statistical model.

With the explanation of potential applications and utilities for risk prediction, we will summarize below current scores that are developed to predict HCC risks in patients with CHB. Scores that were not developed for HCC prediction but later examined for this application, such as the fibrosis-4

index,[35] were not reviewed here. Because antiviral therapy effectively reduces the risk of HCC and the trajectory of HCC incidence is changed in treated patients as compared with untreated counterparts,[36,37] it is advisable to distinguish whether a risk score is developed using data from patients with or without receiving antiviral therapy. Such distinction is also important for applying the scores appropriately in each clinical scenario. Therefore, the risk scores are summarized according to the patient populations which the scores are derived from and divided into scores developed from patients with treatment-naïve CHB or those from patients treated with antiviral therapy. The risk scores reviewed herein were those published in academic journals indexed in PubMed, with the latest update on January 20, 2021. We have been attentive to relevant articles because of our previous work that included two systematic reviews and also ongoing research in this field.[38,39] For this narrative review, however, we did not particularly adhere to any specific Mesh term or keyword.

Risk Scores Developed from Patients without Receiving Antiviral Therapy

Summaries of the Scores and Their Derivation Cohorts

As of January 20, 2021, we identified the following seven risk scores that were developed exclusively using data from CHB patients not receiving antiviral therapy (listed in an alphabetic order): D^2AS,[40] GAG-HCC,[41] NGM1-HCC,[31] NGM2-HCC,[31] NGM3-HCC,[31] REACH-B,[42] and REACH-B II.[43,44] We also found the other five risk scores built on a predominantly untreated study population mixed with a minor proportion (15.1–38%) of treated patients: CU-HCC,[45] HCC-ESC,[46] LS Model,[47] LSM-HCC,[48] and RWS-HCC.[49] Features of these 12 scores and their derivation cohorts are summarized in ►**Table 1**. Among them, the sample size ranged from 538 to 3,584 patients with a mean or median age from 36.0 to 56.4 years. The distribution of biological sex was consistently male-predominant (58.1–70.0%). The proportion of liver cirrhosis varied from 0 to 38.1%. D^2AS was built with a restrictive eligibility requiring serum HBV DNA $>$ 2,000 IU/mL and alanine aminotransferase concentration (ALT) $<$ 80 U/L, and HCC-ESC was developed with the baseline status explicitly set at hepatitis B envelope antigen (HBeAg) seroclearance. NGM1-HCC, NGM2-HCC, NGM3-HCC, REACH-B, and REACH-B II were derived from the same REVEAL-HBV cohort composed of participants recruited from the community, whereas the rest were all developed from hospital-based cohorts. All these scores were developed from Asian populations.

The number of component variables ranged from 3 to 8 across the risk scores. Age is the only predictor invariably included. Indicators of viral activity, either in the form of serum viral load (HBV DNA) or HBeAg seropositivity, are included in 10 scores, and actually were replaced by less expensive measurements by intention in the development of RWS-HCC.[49] Biological sex is also included in 10 scores except for CU-HCC and LSM-HCC, of which derivation cohorts probably overlapped substantially.[45,48] Notably, all the risk scores built on the REVEAL-HBV cohort contain measurement of serum ALT but do not include indicators that gauge liver fibrosis or hepatic function. On the contrary, the other scores, with the only exception of D^2AS, include variables that assess the status of liver fibrosis (e.g., a diagnosis of cirrhosis or liver stiffness measurement [LSM]) or functional reserve (e.g., serum levels of albumin or bilirubin). Common and major features of the risk scores are illustrated (►**Fig. 1**).

Predictive performances of these scores are reasonably good in the derivation cohorts. The discriminative capability, usually evaluated in the form of the area under the receiving operating characteristic (AUROC) or Harrell's C (concordance)-index, was reported in almost all derivation cohorts, except for the study by Wong et al, in which it was reported only in the derivation cohort.[45] Besides, the confidence intervals (CIs) for estimation of the discriminative performance were generally narrow. For instance, the 5-year AUROC reported form the GAG-HCC development cohort was 0.87, with a 95% CI of 0.82 to 0.93. Nonetheless, calibration performance, usually appraised by the correlation between expected events predicted by the score and observed events that actually occurred, was not reported in every study.

External Validation and Comparative Performance Outside the Development Cohorts

Eight of the 12 scores have been validated in subsequent studies using independent patient populations, but NGM3-HCC, LS Model, D^2AS, and HCC-ESC have not been externally examined, according to the best of our knowledge. Notably, most of the validation studies were based on patients treated with antiviral therapy, instead of an untreated population which the scores were derived from. The results of external validation were variable. In general, the performance was similar with that of the original report if the validation cohorts were also composed of patients with untreated CHB. For example, the REACH-B score performed well in the independent cohorts of untreated patients from the Chinese University of Hong Kong, Hong Kong University, and Yonsei University (South Korea), with the 5-year AUROCs of 0.83 (95% CI, 0.79–0.87), 0.86 (95% CI, 083–0.88), and 0.71 (95% CI, 0.65–0.76), respectively.[42] On the other hand, the validation results were mixed in patients who received antiviral therapy. For instance, predictive performance of the REACH-B score was unsatisfactory with a AUROC of 0.61 (95% CI, 0.54–0.68) at 5 years in the study by Kim et al,[50] and 0.64 (95% CI, 0.56–0.72) at 10 years in the study by Yu et al.[51]

There is a paucity of literature concerning direct comparison of these risk scores in untreated CHB patients. Such a study is understandably difficult to conduct following the approval and rapid uptake of antiviral therapy; patients deemed at risk of HCC would not be kept untreated after all. We could only find comparative data in a Korean study by Jeon et al, in which the 5-year AUROCs of CU-HCC, LSM-HCC, and REACH-B in 922 untreated patients were 0.74 (95% CI, 0.68–0.80), 0.71 (95% CI, 0.64–0.78), and 0.68 (95% CI, 0.60–0.77), respectively.[52] Formal statistical comparison

Table 1 Summary of HCC risk scores developed (mainly) from patients with untreated CHB

	Race	Setting	Sample size	Age, years	Male sex	Cirrhosis	Antiviral exposure		Component variables	Maximal length	Discrimination[h]	Calibration	Independent validation[i]	NPV[j] at 5 years
							Initial	Follow-up						
GAG-HCC Yuen et al, 2009[41]	Asian	Hospital-based	820	40.6[f]	70.0%	15.1%	0%	10.7%	Age, sex, cirrhosis, HBV DNA +/− core promoter mutation	10 years	0.88 (95% CI, 0.82–0.92)	NA	Yes	98.3%
CU-HCC Wong et al, 2010[45]	Asian	Hospital-based	1005	48[e]	67.8%	38.1%	15.1%	NA	Age, HBV DNA, cirrhosis, bilirubin, albumin	10 years	NA	NA	Yes	98.3%[j]
NGM1-HCC[a] Yang et al, 2010[31]	Asian	Community-based	2435	45.8[e]	62.6%	1.9%	0%	0%	Age, sex, ALT, alcohol, HBeAg, family history	10 years	0.83	Yes	Yes	NA
NGM2-HCC[a] Yang et al, 2010[31]	Asian	Community-based	2435	45.8[e]	62.6%	1.9%	0%	0%	Age, sex, ALT, alcohol, HBeAg, HBV DNA, family history	10 years	0.85	Yes	Yes	NA
NGM3-HCC[a] Yang et al, 2010[31]	Asian	Community-based	2435	45.8[e]	62.6%	1.9%	0%	0%	Age, sex, ALT, alcohol, HBeAg, HBV DNA, family history, HBV genotype	10 years	0.87	Yes	No	NA
REACH-B Yang et al, 2011[42]	Asian	Community-based	3584	45.7[e]	61.3%	0%	0%	0%	Age, sex, HBV DNA, HBeAg, ALT	10 years	0.77 (95% CI, 0.75–0.79)	Yes	Yes	NA
REACH-B II Lee et al, 2013[43]	Asian	Community-based	2227	45.5[e]	60.8%	9.7%	0%	0%	Age, sex, HBV DNA, ALT, HBeAg, HBsAg, HBV genotype, family history	10 years	0.86	NA	Yes	NA
LS Model Kim et al, 2013[47]	Asian	Hospital-based	1110	50.0[f]	68.5%	16.3%	37.8%[g]	NA	Age, sex, HBV DNA, LSM	3 years	0.81 (95% CI, 0.74–0.87)	Yes	No	NA
LSM-HCC Wong et al, 2014[48]	Asian	Hospital-based	1035	46[e]	64.0%	32.0%	38%	NA	Age, HBV DNA, albumin, LSM	5 years	0.83 (95% CI, 0.77–0.90)	NA	Yes	99.4%
RWS-HCC[b] Poh et al, 2016	Asian	Hospital-based	538	56.4[e]	62.6%	14.9%	16.7%	NA	Age, sex, cirrhosis, AFP	10 years	0.92 (95% CI, 0.88–0.95)	NA	Yes	98.8%[k]
D^2AS[c] Sinn et al, 2017	Asian	Hospital-based	971	42.6[e]	58.1%	0.0%	0%	0%	Age, sex, HBV DNA	5 years	0.88 (95% CI, 0.81–0.96)	NA	No	NA
HCC-ESC[d] Fung et al, 2018	Asian	Hospital-based	723	36.0[f]	60.6%	NA	30.3%	32.0%	Age, sex, cirrhosis, ALT, albumin	20 years	0.92 (95% CI, 0.88–0.96)	NA	No	99.97%

Abbreviations: AFP, α-fetoprotein; ALT, alanine aminotransferase concentration; anti-HBeAb, anti-hepatitis B envelope antibody; AST, aspartate aminotransferase to platelet ratio index; CHB, chronic hepatitis B; CI, confidence interval; DNA, deoxyribonucleic acid; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LSM, liver stiffness measurement; NA, not available; NPV, negative predictive value.

[a]Derived from the same study.

[b]Published as a letter with limited data.

[c]Enrollment restricted to patients with serum HBV DNA > 2,000 IU/mL and ALT < 80 U/L.

[d]The baseline status explicitly set at HBeAg seroclearance.

[e]Mean.

[f]Median.

[g]Prior or ongoing antiviral therapy.

[h]Area under the receiver operating characteristic curve for HCC at the longest follow-up, reported along with 95% CI if available.

[i]Validated by subsequent studies using independent patient populations outside the derivation cohorts.

[j]For the reported cutoff to identify patients at low risk.

[k]10-year prediction.

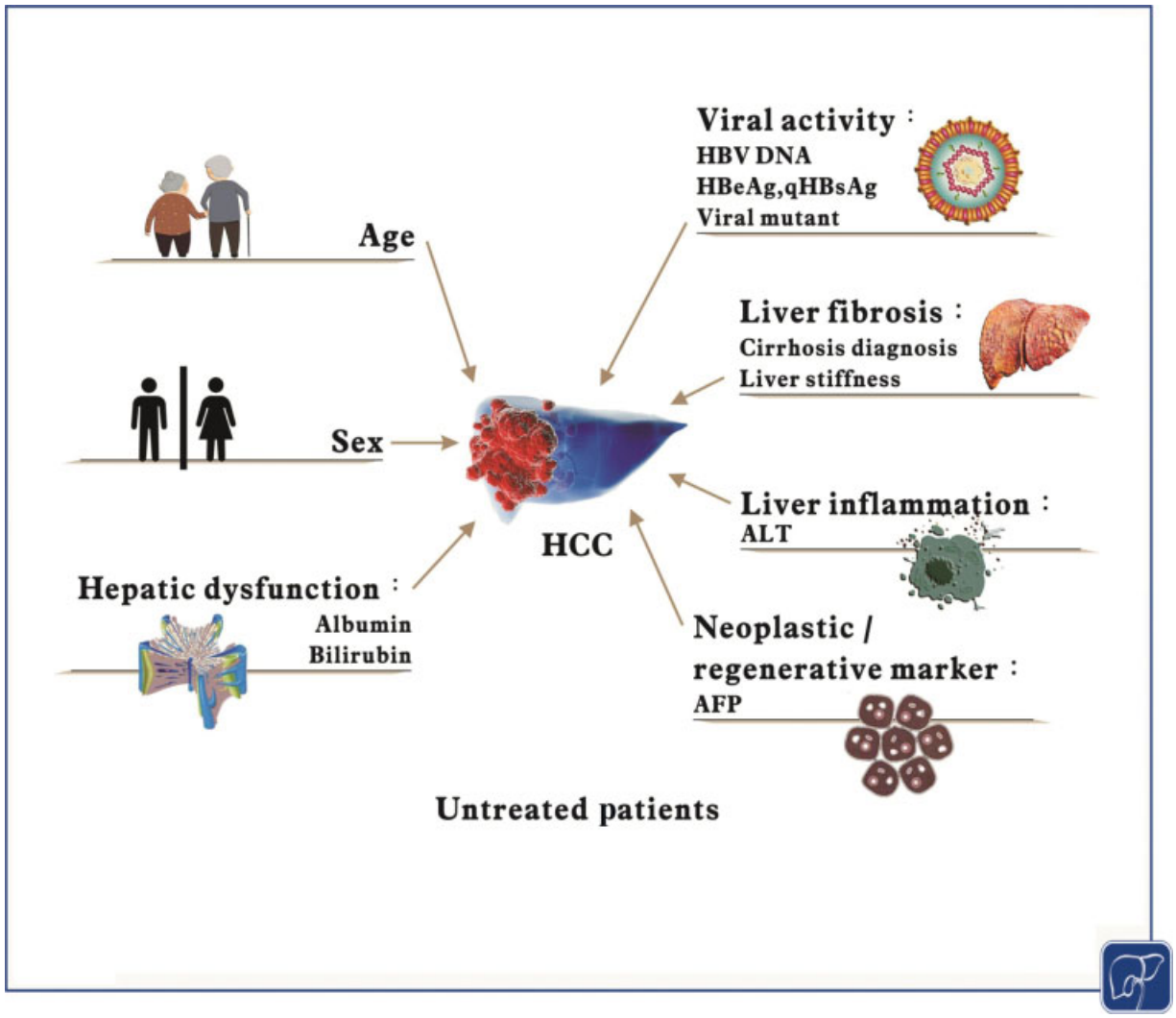

Fig. 1 Major risk predictors of hepatocellular carcinoma (HCC) commonly seen in predictive scores developed from patients without receiving antiviral therapy for chronic hepatitis B. AFP, α-fetoprotein; ALT, alanine aminotransferase concentration; HBeAg, hepatitis B envelope antigen; HBV, hepatitis B virus.

was not reported but the results were likely nonsignificant in view of the overlapping point estimates and 95% CIs.

Conversely, relatively abundant data are available for comparing these scores in treated populations, particularly for CU-HCC, GAG-HCC, and REACH-B. Overall, CU-HCC and GAG-HCC appeared to outperform REACH-B in treated patients. For example, Abu-Amara et al reported that the AUROCs of CU-HCC (0.86; 95% CI, 0.82–0.89) and the continuous model of GAG-HCC (0.87; 95% CI, 0.82–0.89) was significantly higher than that of REACH-B (0.78; 95% CI, 0.73—0.83) as well as other two REVEAL-HBV-derived scores, that is, NGM1-HCC (0.81; 95% CI, 0.77–0.85) and NGM2-HCC (0.79; 95% CI, 0.74–0.83).[53] Similarly, Kim et al found that both CU-HCC (5-year AUROC, 0.74; 95% CI, 0.68–0.81) and GAG-HCC (0.80; 95% CI, 0.75–0.86) were significantly more accurate than REACH-B (0.57; 95% CI, 0.47–0.68) to predict the occurrence of HCC in patients on antiviral therapy.[54]

Comments and Caveats for Clinical Application

Among the risk scores developed mainly from patients with untreated CHB, REACH-B is likely the one most often cited and widely tested in independent studies (cited 428 times according to the Google Scholar Citations as of January 16, 2021). The rich data accrued from all these studies helped to illustrate why one size may not fit all. The discrepant results in external validation studies exemplified the importance of fitting a "right" score to a "right" target population. In view of the unsatisfactory performance (AUROC < 0.7) in treated patients, REACH-B may not be the predictive tool of choice for patients already on antiviral therapy. In addition to therapeutic effects on the modification of HCC risk, differences in baseline compositions between the derivation and validation cohorts presumably also account for the results observed in external validation studies. In fact, the REVEAL-HBV cohort is composed of volunteers recruited from the communities and thus less vulnerable to biases that may result from a hospital-based setting.[55] In addition, those with liver cirrhosis were also deliberately excluded. Dismissing the risk of HCC is improbable for a patient with a diagnosis of liver cirrhosis even if the diagnosis is made clinically without pathological confirmation. Therefore, the REVEAL-HBV cohort is conceivably more representative of

patients with a milder disease severity and/or at an earlier stage of the natural history. As a result, it is reasonable to apply the REACH-B score to identify patients who are more likely to progress and thus require antiviral treatment. The same score, however, may not serve to stratify the risks among patients with a more advanced disease status who have initiated antiviral treatment.

Intriguingly, CU-HCC and GAG-HCC also performed fairly well in treated patients regardless of their development from a (predominantly) untreated population. It has been shown that CU-HCC and GAG-HCC could predict HCC occurrence in CHB patients on antiviral therapy as accurately as the PAGE-B score, which was specifically developed to be applied in the treated populations.[54,56] Their superior performance over the REACH-B score in treated patients may be explained by the inclusion of risk predictors that indicate severity of liver fibrosis and reserve of hepatic function. Indeed, fibrosis status and hepatic dysfunction appear to be the major risk predictor in patients on antiviral treatment (elaborated below). Nevertheless, risk determinants are likely to be changed or modified after antiviral treatment and thus caution is advisable for applying CU-HCC or GAG-HCC as the predictive tool of choice in the era of antiviral therapy.[57,58]

Risk Scores Developed from Patients on Antiviral Therapy

Summaries of the Scores and Their Derivation Cohorts

Risk scores that were developed from CHB patients treated with antiviral therapy have proliferated within a decade. As of January 20, 2021, we were able to find 14 published scores (listed in an alphabetic order): AASL-HCC,[51] aMAP,[59] APA-B,[60] CAGE-B,[61] CAMD,[62] CAMPAS,[63] HCC-RESCUE,[64] mPAGE-B,[50] mPAGE^{LS}-B,[65] mREACH-B I,[66] mREACH-B II,[66] PAGE-B,[67] REAL-B,[68] and SAGE-B,[61] most of which were published after 2016. All these risk scores were developed from patients who received NA, as we were unaware of any score dedicated to patients treated with interferon-based regimens. Features of these scores and characteristics of the development cohorts are summarized in ►**Table 2**. The number of patients contained in the derivation cohorts ranged from 192 to 23851, and their mean or median age ranged from 38 to 52.1 years. The distribution of biological sex was invariably male-predominant (59.8∼80.7%) and the proportion of liver cirrhosis varied from 19.1 to 46.9%. The mREACH-B I and mREACH-B II scores were actually developed in a single study with identical predictors of different weighting. PAGE-B, CAGE-B, and SAGE-B were mainly derived from the same Caucasian population, with PAGE-B developed to predict HCC occurrence within 5 years of antiviral therapy and the latter two scores for the prediction beyond 5 years of treatment (up to 10 years).[61,67] REAL-B was developed using data from an international consortium encompassing sites in the United States of America and several Asian countries, but the ethnic composition was mainly Chinese (82%).[68] Most of the scores were based on hospital-based cohorts, except for CAMD,[62] which was developed on a population-based cohort from a national healthcare database.

The minimal and maximal number of component variables were 2 (SAGE-B) and 7 (REAL-B), respectively. As with the scores from untreated patients, age is the only variable included in all scores here. Biological sex is included in 11 scores except for APA-B, CAGE-B, and SAGE-B. Platelet count, LSM, and diagnosis of cirrhosis were present in 7, 6, and 5 scores, respectively. Of note, all scores included predictors that gauged severity of liver fibrosis, that is, cirrhosis diagnosis, LSM,[69] or platelet count.[70] Albumin was incorporated in four scores, whereas diabetes mellitus (DM) was included in CAMD and REAL-B. Notably, viral parameters were contained only in one score (i.e., HBeAg in mREACH-B), in contrast to common inclusion in the scores from untreated populations. Major characteristics commonly seen in these risk scores were illustrated in ►**Fig. 2**.

Most of the scores were developed to predict HCC following commencement of antiviral therapy, but CAMPAS and mREACH-B were designed for HCC prediction after attainment of viral remission on treatment (HBV DNA undetectable in the blood). In addition, the baseline for variable definition and outcome observation did not start at treatment commencement for APA-B, CAGE-B, and SAGE-B. It was 1 year after treatment for APA-B and 5 years after treatment for CAGE-B and SAGE-B. Discriminative performance in the derivation cohort was reported with reasonably good results (AUROC generally above 0.8) in all development studies. The performance in calibration was not reported in every study.

External Validation and Comparative Performance Outside the Development Cohorts

At the time of writing, we found only mREACH-B, PAGE-B, mPAGE-B, and CAMD were externally validated in independent patient populations outside the development studies. Presumably, newer scores were published too recently for external validation to be available. In independent validation studies using data from treated patients, these scores were generally shown to be more accurate than the scores developed from untreated patients. For example, Jung et al reported in a study including 848 Korean patients receiving antiviral treatment that mREACH-B was superior to LSM-HCC, GAG-HCC, REACH-B, and CU-HCC, with a significantly higher 5-year AUROC of 0.80 (95% CI, 0.76–0.84) over 0.75 (95% CI, 0.71–0.80), 0.75 (95% CI, 0.69–0.80), 0.66 (95% CI, 0.60–0.72), and 0.69 (95% CI, 0.63–0.75), respectively.[57] PAGE-B has been widely validated with acceptable results in subsequent studies and is the only score with validation reports from both Caucasian and Asian populations.[54,56] Intriguingly, none of the many scores derived from Asian patients has been externally validated using data from Caucasian populations.

Comparative data among these scores is understandably sparse and is currently available for PAGE-B, mPAGE-B, and CAMD only. The results of comparisons were mixed. By conducting a territory-wide database analysis involving 32,150 patients from Hong Kong, Yip et al found mPAGE-B was significantly though slightly more accurate than PAGE-B, with a 5-year AUROC of 0.80 (95%, 0.79–0.81) versus 0.77 (95% CI, 0.76–0.78).[71] Besides, Lee et al reported in a Korean

Table 2 Summary of HCC risk scores developed from patients with treated CHB

	Race	Setting	Number	Age, years	Male sex	Cirrhosis	Component variables	Maximal length	Discrimination[d]	Calibration	Independent validation[h]	NPV[i] at 5 years
mREACH-B I[a,g] Lee et al, 2014[66]	Asian	Hospital-based	192	49[f]	69.8%	46.9%	Age, sex, HBeAg, ALT, LSM	3 years after viral remission	0.81 (95% CI, 0.68–0.93)	NA	Yes	NA
mREACH-B II[a,g] Lee et al, 2014[66]	Asian	Hospital-based	192	49[f]	69.8%	46.9%	Age, sex, HBeAg, ALT, LSM	3 years after viral remission	0.81 (95% CI, 0.71–0.91)	NA	Yes	NA
PAGE-B[b] Papatheodoridis et al, 2016[67]	Caucasian	Hospital-based	1325	52[e]	70.0%	20%	Age, sex, platelet	5 years	0.82	Yes	Yes	100%
APA-B[c] Chen et al, 2016[60]	Asian	Hospital-based	883	50[e]	71.9%	35.9%	Age, platelet, AFP (all measured 1 year after treatment)	5 years	0.83 (95% CI, 0.77–0.88)	Yes	No	98.1%
HCC-RESCUE Sohn et al, 2017[64]	Asian	Hospital-based	990	47.4[e]	65.0%	39%	Age, sex, cirrhosis	5 years	0.82 (95% CI, 0.72–0.82)	NA	No	NA
mPAGE-B Kim et al, 2018[50]	Asian	Hospital-based	2001	50[f]	64.1%	19.1%	Age, sex, platelet, albumin	5 years	0.82 (95% CI, 0.78–0.86)	Yes	Yes	NA
CAMD Hsu & Yip et al, 2018[62]	Asian	Population-based	23,851	47.5[f]	74.0%	26.5%	Age, sex, cirrhosis, diabetes mellitus	3 years	0.82 (95% CI, 0.80–0.83)	Yes	Yes	NA
AASL-HCC Yu et al, 2019[51]	Asian	Hospital-based	944	50[f]	62.1%	39.3%	Age, sex, cirrhosis, albumin	5 years	0.80 (95% CI, 0.72–0.89)	Yes	No	99.4%
REAL-B Yang et al, 2020[68]	Asian	Hospital-based	5,365	48.4[e]	69.2%	20.2%	Age, sex, cirrhosis, platelet, AFP, diabetes mellitus, alcohol	10 years	0.80 (95% CI, 0.78–0.82)	Yes	No	NA
CAGE-B[b] Papatheodoridis et al, 2020[61]	Caucasian	Hospital-based	1,427	52.1[e]	69.5%	25.9%	Age (5 years after treatment), LSM (5 years after treatment), baseline cirrhosis	10 years	0.81	Yes	No	100%
SAGE-B[b] Papatheodoridis et al, 2020[61]	Caucasian	Hospital-based	1,427	52.1[e]	69.5%	25.9%	Age (5 years after treatment), LSM (5 years after treatment)	10 years	0.81	Yes	No	100%
CAMPAS[g] Lee et al, 2020[63]	Asian	Hospital-based	1,511	49.7[e]	65.5%	39.8%	Age, sex, cirrhosis, platelet, albumin, LSM	7 years after viral remission	0.87 (95% CI, 0.82–0.92)	Yes	No	99.4%
aMAP Fan et al, 2020[59]	Asian	Hospital-based	3,688	38[f]	80.7%	19.3%	Age, sex, platelet, albumin, bilirubin	5 years	0.82 (95% CI, 0.77–0.86)	Yes	No	99.5%
mPAGE^{LS}-B Chon et al, 2021[65]	Asian	Hospital-based	1,211	50.3[e]	59.8%	45.9%	Age, sex, platelet, LSM	5 years	0.76 (95% CI, 0.72–0.80)	NA	No	NA

Abbreviations: ALT, alanine aminotransferase concentration; AFP, α-fetal protein; CHB, chronic hepatitis B; CI, confidence interval; HCC, hepatocellular carcinoma; HBeAg, hepatitis B envelope antigen; LSM, liver stiffness measurement; NA, not available; NPV, negative predictive value.

[a]mREACH I and mREACH-B II derived from the same study sharing same variables with different weighting.

[b]PAGE-B, CAGE-B, and SAGE-B generally built on the same cohort.

[c]The baseline status set at one year after antiviral therapy.

[d]Area under the receiver operating characteristic curve for HCC at the longest follow-up, reported along with 95% confidence interval if available.

[e]Mean.

[f]Median.

[g]The baseline status set at viral remission on antiviral therapy.

[h]Validated by subsequent studies using independent patient populations outside the derivation cohorts.

[i]For the reported cutoff to identify patients at low risk.

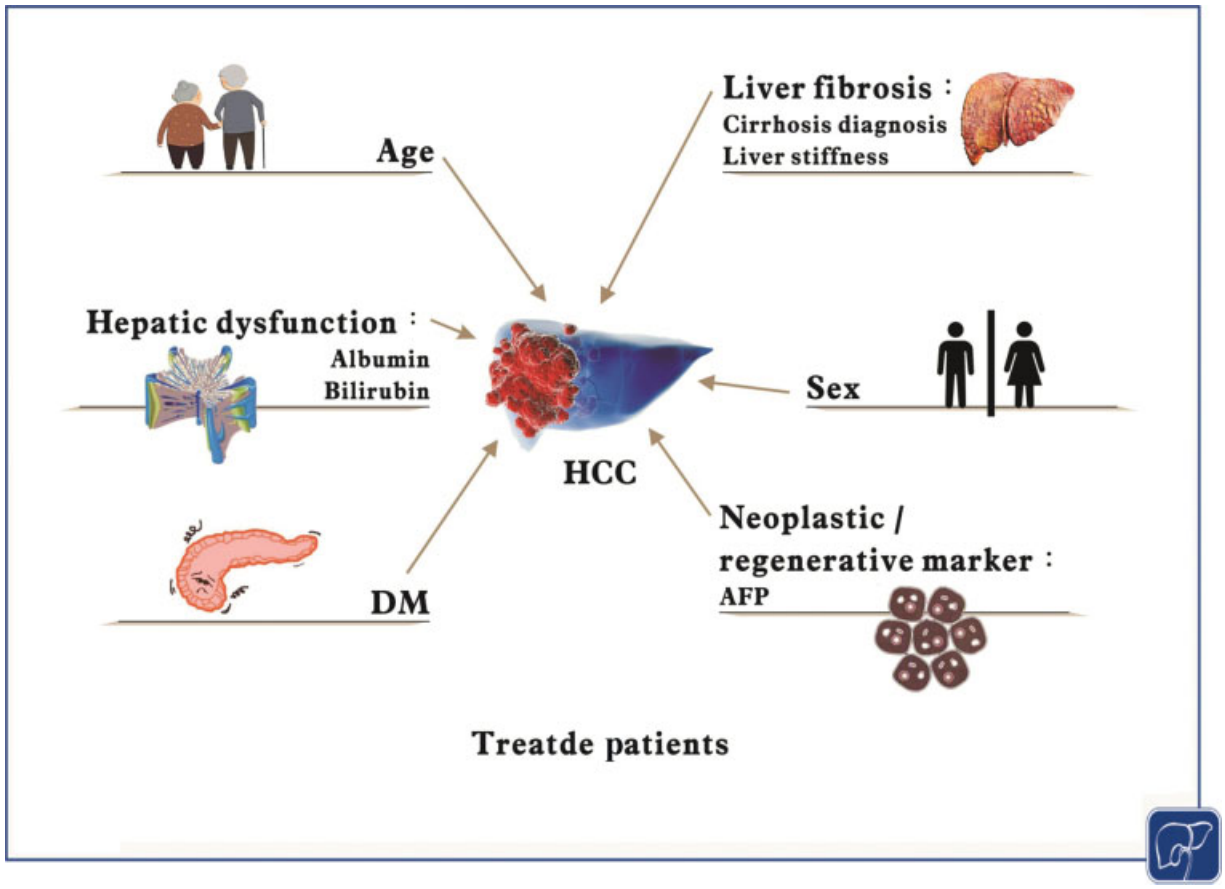

Fig. 2 Common and major features of risk scores developed from patients with chronic hepatitis B under antiviral treatment. AFP, α-fetoprotein; DM diabetes mellitus; HCC, hepatocellular carcinoma.

cohort that mPAGE-B achieved a numerically higher Harrell's C index for HCC than PAGE-B did (0.77, 95% CI, 0.74–0.80 vs. 0.74, 95% CI, 0.71–0.78) but the difference was not statistically significant.[58] On the other hand, Kirino et al reported that the 7-year AUROC for HCC occurrence was 0.74 for PAGE-B and 0.73 for mPAGE-B among 443 Japanese patients; regrettably, statistical significant was not reported and the 95% CI was not available.[72] Finally, Kim et al reported in a multicenter cohort study including 3,277 Korean patients that iAUROC for HCC was highest with CAMD (0.79, 95% CI, 0.77–0.81) than PAGE-B (0.76, 95% CI, 0.74–0.78) and mPAGE-B (0.77, 95% CI, 0.75–0.79), although the comparison with mPAGE-B was not statistically significant.[73] Comparative data have not been reported from Caucasian populations to date.

Comments and Caveats for Clinical Application

Currently, PAGE-B is the most extensively validated risk score derived from treated patients and has been examined with acceptable results in a population-based setting,[71] although it is not necessarily the most accurate one.[71,73] In light of a simple formula with three predictive variables that are usually available in daily practice, PAGE-B will probably continue to serve as a comparator in comparative studies and as the reference for development of further new scores.

Essential components are actually similar across these risk scores. In addition to age, variables that reflect severity of liver fibrosis and/or hepatic dysfunction, in the form of a diagnosis of liver cirrhosis, platelet count, and albumin level,[69,70,74,75] were present in all scores. For CAGE-B and SAGE-B that were developed from patients with sustained viral inhibition for 5 years, age and fibrosis burden (indicated by LSM with or without baseline cirrhosis) are the only risk predictors. For other scores with more variables, age and the fibrosis indicator outweigh other variables by far in the scoring formula. According to the CAMD score, for instance, either age above 50 years or presence of liver cirrhosis alone will sufficiently classify a patient at an intermediate or high risk of HCC who cannot be spared from HCC surveillance, regardless of the points scored by biological sex and DM.[62]

In our opinion, the heavy weighting of age and fibrosis burden (with or without functional assessment) suggest that severity of accumulated injury in the liver is the major HCC risk determinant in CHB patients whose viral replication is effectively controlled by antiviral therapy. Our interpretation may also hold true for patients with chronic liver diseases other than CHB. In the development study of aMAP, which was derived from patients with CHB and thus included in this review, Fan et al demonstrated that a scoring formula composed of age, sex, platelet, and albumin could stratify the risk of HCC with similar accuracy in patients with chronic liver diseases of various etiologies.[59]

We believe a few caveats warrant attention when interpreting these risk scores and before applying them in clinical

practice. First, eligibility criteria, patient compositions, and antiviral regimens were heterogeneous among the derivation cohorts. For example, patients with excessive alcohol ingestion were explicitly excluded from some studies (e.g., mPAGE-B, mREACH-B) but were eligible in others (e.g., aMAP, REAL-B). Also, some derivation studies included treatment-experienced patients (e.g., PAGE-B, REAL-B), whereas others enrolled only treatment-naïve patients who initiated entecavir or tenofovir (e.g., APA-B, CAMD). Second, prediction of HCC was not started right after antiviral therapy in all scores. For instance, it was not started until viral remission for CAMPAS and mREACH-B, and not until 1 year after antiviral treatment for APA-B. It is also advisable to keep this notion in mind when comparing these scores. Third, all scores were derived from patients who continuously received antiviral treatment. Given that it remains unclear how treatment interruption would impact the risk of HCC, current scores may not be applicable to patients who discontinue antiviral therapy. Finally, competing risk analysis would be necessary if the risk of death far exceeded the risk of HCC, a nonfatal event,[76] while the estimations with or without consideration of competing mortality would yield little difference if the incidence of death was not exceedingly higher than that of HCC.[62] Therefore, whether competing risk events need to be taken into account depends on the patient population which the model is built on and applied to.

Perspectives on Future Development of Risk Scores for HBV-Associated HCC

Although there have been dozens of risk score reported to predict occurrence of HCC in CHB patients with or without receiving antiviral treatment (►**Tables 1** and **2**), more scores are expected to be developed in the future. Thanks to increasing accessibility to the extensively digitalized healthcare data, it has become less effortful to collect pertinent information from a group of CHB patients with longitudinal observation of clinical events including incident HCC. Nonetheless, it is intelligibly very difficult in the era of antiviral therapy to follow up a cohort of untreated patients who keep withholding treatment to depict clinical risks along the natural history of CHB. Even if such a score could be built on archived data retrospectively, prospective validation without antiviral intervention would be improbable and likely unethical for patients deemed at high risks.

On the other hand, we anticipate more new scores dedicated to patients on antiviral therapy because available treatment does not eradicate the viral infection and cannot eliminate the HCC risk. The risk appears to linger during the prolonged treatment course, particularly for patients at older ages or with liver cirrhosis,[61] although the incidence rate of HCC declines over time in patients receiving antiviral treatment.[77] Several therapeutic factors, such as incomplete virological response,[78] on-treatment ALT elevation,[79] and treatment interruption,[80] may impact the risk of HCC as well, but their roles in a risk score have not been clarified. Therefore, how to optimize and apply the tools of risk prediction in treated patients remains viable in the agenda to clinical researchers.

We believe critical appraisal of the scores currently available is equally, or perhaps even more, important as compared with development of new ones. Prior to clinical application, generalizability of the score must be verified through external validation. Performance of a risk score in the derivation cohort is often overoptimistic. After all, the score is ingeniously built to fit the data, usually with an underpinning regression model (mostly Cox proportional hazard model with or without some further accounting for competing risks). This ad hoc data-driven approach usually underestimates the uncertainty in model building and could bias the predictive performance toward overestimation.[81] Therefore, no matter how promising a score may appear in the derivation dataset, it is mandatory to test the score using data from patient populations outside the derivation cohort before application to the clinics. Similarly, such an overfitting issue applies to the score comparison. It is not surprising for a newly developed score to outperform existing ones in the development study, of which data was best fitted by the sophisticatedly selected variables along with their regression coefficients of the data model for the new score. To minimize potential bias, comparative studies should ideally be performed by independent researchers using data from patient populations which none of the compared scores are based upon.

Following the enthusiasm for developing and validating risk scores, research efforts are needed to elucidate whether these scores are applicable in everyday practice and how they may improve outcomes of various sorts. The many claimed utilities of accurate risk prediction cannot be taken for granted without empirical evidence. Such evidence is indispensable to policymaking for resource allocation. Randomized controlled trial is the preferred design to examine effectiveness though difficult to be performed. So far, there is a huge gap of data from outcome research to clarify the effectiveness and/or cost-effectiveness of putting a risk score into practice.

We also believe that more comprehensive and dynamic data are crucial to improve HCC risk prediction on top of available predictive tools. The vast majority of current risk scores were based on clinical and laboratory data that were conveniently accessible to investigators when developing the scores, and thus usually limited by data availability. For instance, excessive alcohol consumption is an established risk factor for cirrhosis and HCC,[82,83] but was only included in the NGM-HCC scores and REAL-B. However, information regarding lifestyle was usually very limited, if not completely missing, in most studies. Therefore, the absence of alcohol intake as a risk predictor in most scores likely resulted from exclusion or underrepresentation of patients with habitual drinking and should not be misinterpreted as if it exerted no influence on the risk of HCC. Likewise, information about family history of HCC was usually insufficient in most studies, particularly those retrospectively designed.

Current scores are all static with risk calculation done at a single time point and do not accommodate time-varying

parameters. Patients were classified once and for all at treatment initiation (most scores), at attainment of viral remission (e.g., CAMPAS), or after a certain period of treatment (e.g., APA-B), as if the risk would be fixed thereafter. However, many risk predictors were changeable over time or even modifiable with interventions, but the effects of changes could not be captured in current scoring formula. For instance, patients scored a point for alcohol consumption according to REAL-B.[68] This point would stay there for good (or at least 10 years, the maximum duration for HCC prediction in the development study) whether or not the patient could succeed in abstinence afterwards. Also, changes in liver fibrosis actually differ among patients on antiviral therapy.[84] Patients with an identical LSM value or platelet count at baseline could end up having significantly different values after a few years of therapy.[85] Whether incorporation of these time-varying changes into risk prediction may improve accuracy of the score remains unknown but warrants investigation. To this end, data for explanatory variables should be collected at multiple time points to allow for the build-up of a time-dependent model.[86]

While current HCC risk scores are all built upon conventional regression models with assumptions of linearity and additivity within and among predictors, we expect to see new scores coming from algorithmic methods based on machine learning. As a result of advances in technology, digitalized data covering various levels of biomedical information including demographics, clinical manifestations, environmental exposure, genetic makeup, laboratory or radiographic findings, metabolomics, and microbiota has been expanding explosively and becoming more and more accessible to the researchers. These data could be integrated and used to classify health status and predict disease outcomes.[87] Nevertheless, it is difficult to analyze these high-dimensional data with conventional approach of statistical modeling, which usually starts with a limited number of independent and well-known variables. Algorithmic approaches provide a promising alternative handling data dimensionality as well as accounting for nonlinearity and interactions of predictors. In fact, algorithmic approaches with machine learning have been applied in patients with chronic liver diseases, for instance, to predict cirrhosis mortality,[88] disease progression of hepatitis C virus infection,[89] and presence of nonalcoholic fatty liver disease.[90] Introduction of machine learning algorithms to predict incident HCC in CHB patents seems to us just a matter of time. However, algorithmic methods focus primarily on predictive accuracy and do not seek to be simple, transparent, or even interpretable.[91] Difficulties in evaluating individual predictors in the "black box" algorithms by the machine learning approach largely limit its clinical utility. In addition, overfitting frequently arises during model selection in machine learning algorithms.[92] Again, external validation in an independent dataset is a prerequisite for clinical application.

In conclusion, 26 risk scores have been reported to predict HCC occurrence in CHB patients with or without receiving antiviral treatment. Through accurate risk stratification, these scores may inform clinical practice to tailor the management according to individual needs. Risk scores derived from patients who did not receive antiviral treatment may help to depict outcome determinants in the natural history of CHB and guide treatment decision accordingly. Biomarkers of viral activities (i.e., HBV DNA level and HBeAg status) are frequently included in the risks scores from untreated patients, but these virological markers are not included in nearly all risk scores developed from patients on antiviral therapy. Instead, measurements that gauge severity of liver fibrosis and/or reserve of hepatic function are essential components in the scores from treated patients. Not all of the scores have been externally validated in independent patient populations outside the derivation cohort. Despite good performance in untreated patients, predictive accuracy of REACH-B is suboptimal in patients on antiviral therapy. Currently, PAGE-B is the most widely validated score for treated patients and more scores are expected to come in the era of antiviral therapy. Comprehensiveness of the data is believed to be crucial to improve predictive accuracy over the existing scores. Finally, machine learning algorithms may be introduced for CHB patients to classify their risks of HCC in the near future.

Main Concepts and Learning Points

- Accurate risk prediction for hepatocellular carcinoma (HCC) may guide treatment strategies and inform HCC surveillance in patients with chronic hepatitis B (CHB).
- Age is invariably included in all HCC risk scores for CHB patients with or without receiving antiviral therapy.
- Virological biomarkers of replicative activities (i.e., hepatitis B virus DNA level and hepatitis B e antigen status) are frequently included in the scores derived from untreated CHB patients.
- Measurements that gauge severity of liver fibrosis and/or reserve of hepatic function (i.e., cirrhosis diagnosis, liver stiffness measurement, platelet count, or albumin) are essential components in the scores developed from treated patients.
- External validation independently performed in different patient populations is mandatory prior to clinical application but data are not yet available for all scores.

Authorship
All authors had access to the reviewed data and participated in the drafting, editing, and final approval of the manuscript for publication.

Competing Interests
Yao-Chun Hsu has received research grants from and served as an advisory committee member for Gilead Sciences, and received lecture fees from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, and Novartis, outside the submitted work. Dr. Tseng reports personal fees from Abbvie, personal fees from Bristol-Myers Squibb, personal fees from Gilead Sciences, personal fees from Merck Sharp & Dohme, personal fees from Roche,

personal fees from Bayer, outside the submitted work. Yen-Tsung Huang and Hwai-I Yang have nothing to declare.

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