



A concise review of current guidelines for the clinical management of hepatocellular carcinoma in Asia

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Background: Hepatocellular carcinoma (HCC) has been the fifth most common malignancy worldwide and is particularly endemic in Asia, accounting for around 80% of new cases around the world. Currently, with many new studies and evidences coming into being in Asia, various HCC guidelines have been newly issued or updated. The aim of the present study is to incorporate new evidence on the management of HCC by assessing and comparing the main Asian guidelines.

Methods: Electronic databases of MEDLINE, the Chinese SinoMed and the Japanese CiNii were systematically searched. AGREE II instrument was utilized for the quality assessment of guidelines.

Results: A total of 11 main Asian guidelines were included. There still remain variances in guideline structures and certain contents. We briefly compared the guidelines and summarized the newly updated recommendations to help hepatobiliary surgeons to catch the latest information.

Conclusions: The present review might help focus and target advocacy to improve clinical management of HCC. Further research and more straightforward guidelines are essential to improve the prognosis of HCC in the future.

Keywords: Hepatocellular carcinoma (HCC); clinical guideline; Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument; assessment; comparison; review

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Introduction

Hepatocellular carcinoma (HCC) has been the fifth most common malignancy worldwide, with over 500,000 new cases every year, and it serves as the third most common cause of tumor-related mortality globally (1-4). Furthermore, it is particularly endemic in Asia, accounting for around 80% of new cases around the world (5,6). In the last 20 years, numerous researches have explored the clinical management of HCC (7-10). However, the overall

prognosis are still unsatisfactory, especially seen in Asian countries. Guidelines are defined as “*systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances*” (11). The full performance of guidelines could accomplish the following aims: (I) up-to-date for individualized decision-making algorithms by clinicians; (II) promotion of the healthcare quality; (III) better resource apportion by superior administrations (9). Since the Korean Liver Cancer Study Group and National Cancer Center jointly issued

the first HCC guideline in Asia in the year of 2003, various Asian guidelines have been published or updated till now. Despite of this, controversies in certain aspects of HCC management evidently existed. Thus, the aim of the present study is to incorporate new evidence on the management of HCC by assessing and comparing the main Asian guidelines.

Methods

Study identification

For this review, electronic databases of MEDLINE (via PubMed), the Chinese SinoMed (<http://www.sinomed.ac.cn/zh/>) and the Japanese CiNii (<http://ci.nii.ac.jp/>) were systematically searched from the initiation of the databases to September, 2017. No language restriction was applied to the search strategy. Search terms (medical subject headings or keywords) included: “hepatocellular carcinoma”, “guidelines/practice guidelines”, “consensus”, “liver cancer”, and “liver carcinoma”. Inclusion criteria were as follows: (I) influence, records were drafted with the support of government or academic/medical societies, then cited by subsequent guidelines or other publications on the management of HCC; (II) multifaceted, records at least covered the contents of diagnosis and treatment of HCC; (III) drafting body, records were created and endorsed by the Asian countries or academic organizations; and (IV) publication form, records should be issued in the form of clinical guidelines or expert consensus. A study meeting all four criteria was regarded eligible to be included. Furthermore, reference lists of guidelines were searched manually for potential target articles. In the case of one guideline having different updated versions, only the most recent version was included.

Guidelines appraisal

As a highly useful evaluation tool for guidelines, the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument was utilized for the quality assessment of guidelines by examining six domains covering 23 key items (six domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, editorial independence) (12). Each item in the AGREE II was separately graded by three reviewers (H Tang, Y Huang, and C Li) on a 7-point scale (1, strongly disagree to 7, strongly agree) (12).

Each domain score will be calculated by summing up all

the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain (12). The formula is:

$$\text{Domain score} = \frac{\text{Obtained score} - \text{Minimum possible score}}{\text{Maximum possible score} - \text{Minimum possible score}} \times 100\%$$

Minimum possible score refers to number of items multiplied by number of reviewers, multiplied by 1 (strongly disagree); minimum possible score = (number of items) × (number of reviewers) × (1, strongly disagree). Maximum possible score refers to number of items multiplied by number of reviewers, multiplied by 7 (strongly agree); minimum possible score = (number of items) × (number of reviewers) × (7, strongly agree).

To ensure accuracy and minimize bias of guidelines appraisal, the intra-class correlation coefficient was introduced for the assessment of between-reviewer agreement (the two-way random model, by SPSS) (13).

Results

Current main guidelines of HCC in Asia

Figure 1 showed the process of study selection. A total of 396 references were produced using the outlined search strategy. Finally, 11 guidelines were identified and then included for comparison (14-24). Ten of the total 11 guidelines were published in the academic journals, and one was in a book (*Japanese clinical practice guidelines for hepatocellular carcinoma, J-HCC*); the majority (8 of 11) was published in English, two were in Chinese, and one was in Japanese. The guidelines were drafted in Singapore (one guideline), China (three guidelines, including one in Hong Kong, SAR), Republic of Korea (one guideline), Japan (two guidelines), India (one guideline), or Saudi Arabia (one guideline) or that were multinational (two guidelines) between 2009 and 2017. Guideline characteristics were summarized in Table 1.

Results of guidelines appraisal

Results of guideline appraisal by AGREE II were illustrated in Table 2 and Figure 2. In Table 2, domain score and overall assessment for each guideline were demonstrated. Most guidelines obtained average scores over 50%. From an overall perspective, Korea practice guideline for the management of HCC (Korean Guideline) that covered all 6 aspects (epidemiology, prevention, surveillance, staging & diagnosis, treatment, and follow-up) featured the highest

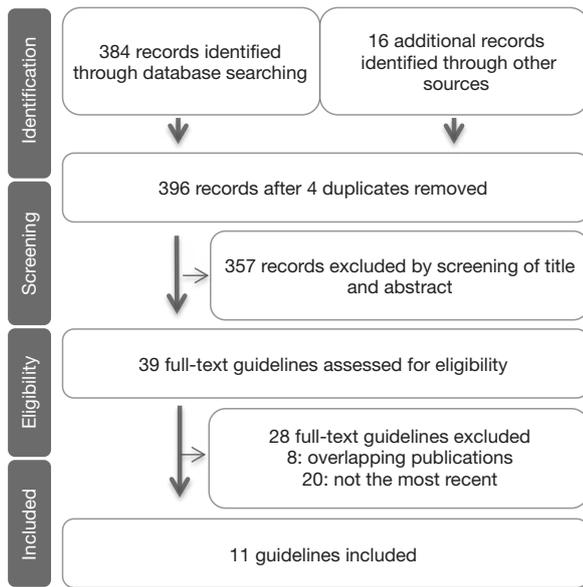


Figure 1 The process of study selection.

score. At the same time, five guidelines being scored less than 6 in overall assessment might be recommended with modifications according to the AGREE II. By calculating the mean score of each domain for the included guidelines, comparatively high mean scores were granted for the domains of ‘Scope and purpose’ (mean 62.88, standard deviation 18.01) and ‘Clarity of presentation’ (68.37, 4.15), and low score for the domain of ‘Applicability’ (43.43, 14.71), which was shown in *Figure 2*. The intra-class correlation coefficients range from 0.61 to 0.83, indicating fair-to-good agreements between reviewers.

Comparison of the guidelines

Based on the appraisal results of AGREE II, six guidelines that were rigorously drafted and developed achieved no less than 6 score in overall assessment and could be recommended without modifications. Then, on this occasion, a concise comparison of the guidelines was then conducted mainly focusing on three sections concerning HCC clinical management (risk factors and surveillance, diagnosis, and treatment). Meanwhile, special focus was relatively placed on the guidelines achieving higher overall score or domain score.

Risk factors and surveillance

Totally, 8 of the total 11 guidelines clearly involved

the content of surveillance (*Table 1*). Although most of the content about the risk factor and surveillance are commensurate, variances still existed among guidelines.

Risk factors for HCC can be divided into two aspects: cirrhosis-related and non-cirrhosis-related. The former consists of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, alcoholic cirrhosis, genetic causes, nonalcoholic steatohepatitis, stage four primary biliary cirrhosis, alpha one antitrypsin deficiency, and other causes of cirrhosis; the latter covers HBV carrier with family history of HCC, Asian population with older ages (males ≥ 40 years and females ≥ 40 years), and Africa/North American Blacks with Hepatitis B (25). Hepatitis B serves as the leading cause of HCC in China, and hepatitis C in Japan (26,27). Cirrhosis that could be caused by various etiologies is the most powerful HCC predictor (28,29).

Regarding screening method, the combined use of ultrasonography (US) and alpha-fetoprotein (AFP) are the most common and effective measure for HCC detection around the world (30,31). Of note, increased AFP level might be found in less than 20% of patients with early stage HCC (32-34). On this occasion, AFP was ruled out (11,35,36). However, certain Asian experts still believed AFP is a useful surveillance tool (37) and the role in combination with US, which could contribute to the early detection of HCC (38). Among currently included guidelines, eight guidelines involved the use of AFP for surveillance (or screening). Six guidelines recommended US in combination with AFP (16,18,19,22-24), while two guidelines suggested US alone (20,21).

Yet, controversies remain over the use of other biomarkers, such as lens culinaris agglutinin-reactive fraction of AFP (AFP-L3) or des-gamma-carboxy prothrombin (DCP). So far, their role in surveillance requires further validation, and only Japanese guidelines included DCP and AFP in their recommendation of screening (19,39-41).

Although there is still a lack of definite consensus on the most recommended surveillance interval to take, the general interval of surveillance is 6 to 12 months among worldwide guidelines. In Asian perspective, performing surveillance every 6 months instead of annually was uniformly recommended. Furthermore, as to high risk patients, a close surveillance interval is preferred. In Japan Society of Hepatology-HCC Guideline (JSH Guideline), a 3-month surveillance interval is essentially performed for patients at super high risk for HCC (i.e., those with cirrhosis of HBV

Table 1 Description of main HCC Guidelines in Asia

No.	Guidelines (abbreviations)	Year	Content					Language	Drafting body	Ref.	
			Epidemiology	Prevention	Surveillance	Staging & diagnosis	Treatment				Followup
1	National Cancer Centre Singapore Consensus Guidelines for HCC (NCCSCG)	2016	-	-	-	√	√	-	English	National Cancer Centre Singapore	(15)
2	Expert consensus on selection of surgical treatments for HCC (Chinese consensus)	2016	-	-	-	√	√	-	Chinese	Section of Hepatic Surgery, Branch of Surgery, CMA	(16)
3	The guideline of primary liver cancer (Chinese guideline)	2011	-	-	√	√	√	√	Chinese	Ministry of Health PRC	(17)
4	Hong Kong consensus recommendations on the management of HCC (HK consensus)	2015	-	-	-	√	√	-	English	Multiple authors	(18)
5	Korea Practice Guideline for the Management of HCC (Korean guideline)	2015	√	√	√	√	√	√	English	KLCSG & NCC	(19)
6	JSH Consensus-Based Clinical Practice Guidelines for the Management of HCC: 2014 Update (JSH guideline)	2014	-	-	√	√	√	-	English	Japan Society of Hepatology	(24)
7	Clinical practice guidelines for HCC (J-guideline)	2013	-	√	√	√	√	√	Japanese	Japanese Ministry of Health, Labor and Welfare	(20)
8	INASL Consensus on Prevention, Diagnosis and management of HCC (INASL consensus)	2014	√	√	√	√	√	√	English	INASL	(21)
9	Saudi guidelines for the diagnosis and management of HCC (Saudi guidelines)	2012	√	√	√	√	√	√	English	SASLDT & SOC	(22)
10	Asian Pacific Association for the Study of the Liver Consensus Recommendations on HCC: 2017 update (APASL guideline)	2017	√	√	√	√	√	-	English	Asian Pacific Association for the Study of the Liver	(25)
11	Management of HCC in Asia (AOS consensus)	2009	√	√	√	√	√	-	English	the Asian Oncology Summit 2009	(23)

√, certain guideline covers corresponding content. HCC, hepatocellular carcinoma; CMA, Chinese Medical Association; PRC, People's Republic of China; KLCSG & NCC, Korean Liver Cancer Study Group and National Cancer Center, Korea; INASL, The Indian National Association for Study of the Liver; SASLDT & SOC, Saudi Association for the Study of Liver Diseases and Transplantation and the Saudi Oncology Society.

Table 2 Appraisal of Guidelines for Research and Evaluation II assessment of main HCC guidelines in Asia

Guidelines	Year	Domain scores (%)							Overall assessment	Recommendation
		Scope and purpose	Stakeholder involvement	Rigor of development	Clarity of presentation	Applicability	Editorial independence			
NCCSCG	2016	66.67	60.42	54.76	62.50	38.89	62.50	5.5	Yes, with modifications	
Chinese consensus	2016	36.11	47.92	44.05	62.50	47.22	54.17	4.5	Yes, with modifications	
Chinese guideline	2011	80.56	60.42	70.24	72.92	58.33	70.83	6.5	Yes	
HK consensus	2015	44.44	43.75	46.43	68.75	44.44	50.00	5	Yes, with modifications	
Korean guideline	2015	80.56	72.92	78.57	75.00	77.78	75.00	7	Yes	
JSH guideline	2015	72.22	56.25	66.67	72.92	33.33	29.17	5.5	Yes, with modifications	
J-guideline	2013	83.33	56.25	75.00	66.67	47.22	66.67	6.5	Yes	
INASL consensus	2014	52.78	45.83	55.95	68.75	25.00	33.33	6	Yes	
Saudi guidelines	2012	80.56	58.33	58.33	68.75	41.67	37.50	6	Yes	
APASL guideline	2017	48.66	40.40	43.56	72.73	36.23	34.10	5.5	Yes, with modifications	
AOS consensus	2009	55.56	31.25	47.62	64.58	30.56	50.00	6	Yes	

HCC, hepatocellular carcinoma; NCCSCG, National Cancer Centre Singapore Consensus Guidelines for HCC; Chinese consensus, Expert consensus on selection of surgical treatments for hepatocellular carcinoma (2016 3rd edition); Chinese guideline, the guideline of primary liver cancer; HK consensus, Hong Kong consensus recommendations on the management of hepatocellular carcinoma; Korean guideline, 2014 Korean Liver Cancer Study Group-National Cancer Center Korea practice guideline for the management of hepatocellular carcinoma; JSH guideline, JSH Consensus-Based Clinical Practice Guidelines for the Management of Hepatocellular Carcinoma: 2014 Update by the Liver Cancer Study Group of Japan; J-guideline, Evidence-based Clinical Practice Guidelines for Hepatocellular Carcinoma: the Japan Society of Hepatology 2013 update; INASL consensus, the Indian National Association for Study of the Liver (INASL) Consensus on Prevention, Diagnosis and Management of Hepatocellular Carcinoma in India: the Puri Recommendations; Saudi guidelines, Saudi guidelines for the diagnosis and management of hepatocellular carcinoma: technical review and practice guidelines; APASL guideline, Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma; AOS consensus, Management of hepatocellular carcinoma in Asia: consensus statement from the Asian Oncology Summit 2009.

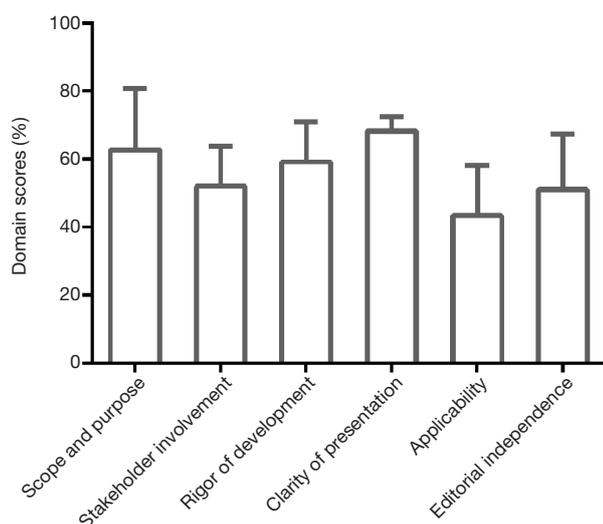


Figure 2 Assessment of each domain (expressed by mean score and standard deviation) by AGREE II. AGREE II, Appraisal of Guidelines for Research and Evaluation II.

or HCV) (23,42). For HBV patients, 6-month surveillance is demonstrated to be superior to 12-month one with regards to the detection of early HCC and overall survival (43).

In Japanese guidelines, population who are associated with high risk of HCC and need surveillance are classified as super high risk population and high risk population (19,23,42). Super high-risk population covers: (I) hepatitis B related liver cirrhosis; (II) hepatitis C associated cirrhosis. Surveillance plan for those is US examination and tumor marker (AFP/PIVKA-II/AFP-L3) measurements every three to four months, or dynamic computed tomography (CT)/magnetic resonance imaging (MRI) every 6 to 12 months for cirrhosis and obesity patients with difficulty in US evaluation. High risk population includes: (I) chronic hepatitis B; (II) chronic hepatitis C; (III) liver cirrhosis (non-HBV or HCV related). The recommended surveillance is US examination and tumor marker measurements semiannually.

Diagnosis

Although variations exist among these guidelines, the final diagnosis of HCC relied on imaging techniques or biopsy.

Imaging techniques feature significant value in clinical management of HCC, including screening and surveillance, diagnosis, staging, and follow-up. Among common imaging techniques, US carries a vital role in the HCC detection for its cost-effectiveness and wide availability.

However, it has the limitation of relatively low sensitivity for the identification of smaller nodules in a cirrhotic liver (44). Of note, the Asian Pacific Association for the Study of the Liver consensus recommendations (APASL guideline) implies that contrast enhanced US could be of equal sensitivity in HCC diagnosis in comparison with CT and MRI (45). Moreover, contrast enhanced US brings the advantage of real-time scanning throughout the whole arterial phase, with a contrast agent which is purely intravascular and can be safely administered in patients with renal failure. On this occasion, although contrast enhanced US was ruled out in certain western guidelines (35,46), it is still in use of certain diagnostic algorithm issued by some expert panel. Dynamic CT or dynamic MRI is suggested as the first-line diagnostic tools for HCC when a screening examination produces a suspected finding. Hallmark of a tumor during dynamic CT or dynamic MRI scan (arterial hyperenhancement with “washout” in the portal venous or delayed phase), regardless of tumor size, will suffice for a diagnosis of HCC, and obviates the need for biopsy. Moreover, MRI might perform better than CT in distinguishing HCC lesions from cirrhotic nodules in cirrhotic livers.

Serum AFP concentration serves as a helpful diagnostic tool in case that imaging technology fails to suffice for a definite diagnosis of HCC. It is generally accepted that serum AFP at least 400 mcg/L in a high-risk population would be of diagnostic value for HCC (47).

Currently, biopsy is limitedly utilized in the diagnosis of HCC for the reduction of potential bleeding or needle-track tumor seeding (approximately 2.7%) (48). Particularly, if patients present with typical imaging and are candidates for curatively intended surgery, then biopsy should be avoided. Moreover, it is emphasized that a negative biopsy result could not rule out HCC when the nodule size is increasing (25). Biopsy could only be the last choice for nodule diagnosis in cirrhotic patients who lack classical imaging presentation. But it's still recommended for nodules in non-cirrhotic livers.

Furthermore, we analyzed the diagnostic algorithms in each guideline and found that there are two main types of diagnostic pathways on the detection of a nodule or mass by US: size-based pathway, and non-size-based pathway. The former was proposed by five guidelines (14,16,18,20,21), and the latter by 4 (19,22-24).

In regard to size-based pathway, diagnostic algorithms will be initiated with tumor size (whether size exceeding 1 cm). Small HCC nodules are rather hard to distinguish

from cirrhotic nodules and previous guidelines recommend a close follow up by repeating US at 3 or 4 months for those patients (35,46). Moreover, a contrast-enhanced CT, MRI or US every 3 to 6 months was advised (25). Earlier researches found that hyperenhancement presented by MRI T2 and diffusion weighted image is of significance to differentiation hyper-vascular HCC nodules smaller than 1 cm in diameter (49). Thus, Korean guideline set rigid criteria for diagnosis of HCC nodules less than 1 cm.

Liver nodules with size more than 1 cm ought to receive by dynamic contrast enhanced CT/MRI or gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) MRI.

As with non-size-based pathway, patients will ought to undertake dynamic imaging techniques regardless of tumor size. The diagnosis of HCC would be supported by the presentation of an arterial hyperenhancement followed by “washout” in enhanced CT/MRI. Unlike other diagrams, the JSH guideline takes Gd-EOB-DTPA MRI as the first-line surveillance and diagnostic tool for HCC (23). HCC nodules without normal hepatocytes are hypo-intensified, which would assist the differentiation of tumors from non-tumorous nodules (50,51).

In the Japanese Clinical practice guidelines for HCC (J-guideline), the recommendation relied on tumor size (19). When the tumor size was larger than 1 cm, additional tests ought to be scheduled. They included Gd-EOB-DTPA MRI, superparamagnetic iron-oxide (SPIO) MRI, contrast enhanced US, CT angiography and biopsy. However, the selection of further approach only depended on the purpose of the surgery and no specific recommendation was provided in JSH guideline. On the other hand, a follow up of every three months ought to be scheduled for those with tumor size less than 1 cm and increased tumor markers.

When the arterial phase of CT/MRI identified a hypo-vascularity mass, the best diagnostic algorithm was, so far, in debate. The Japanese guideline advocated that additional test ought to be performed for patients with tumor size larger than 1.5 cm and 3 months of follow-up for those with tumor size less than 1.5 cm.

Treatment

A principal purpose of guideline is to collect concrete, convincing evidence currently available to help clinicians adopt the state-of-art therapeutic allocation.

The Barcelona Clinic Liver Cancer (BCLC) staging

system overall covering tumor stage, liver function, and physical status was commonly adopted for HCC staging and treatment (52,53). Moreover, it is the only staging system that enables prognostication and informs strategies of first line (54). Here, we briefly and graphically summarized the treatment strategies mainly based on the BCLC staging (*Figure 3*). Generally, curative strategies contain liver resection, liver transplantation, and ablation. Patients allocated to stage 0 or stage A might get a 5-year survival of 40–70% after the curative intent treatments. Hepatectomy forms the first-line therapy for HCC in non-cirrhotic patients or in selected-cirrhotic patients with a single lesion. Liver transplantation is chosen for patients in BCLC stage A within the Milan criteria (single HCC nodule less than 5 cm in size or fewer than three nodules, none larger than 3 cm in diameter) (55). Patients within the Milan criteria featured a 5-year overall survival of 65–78% after liver transplantation (56). In the view of the Indian National Association for Study of the Liver (INASL) guideline, the University of California San Francisco criterion which expanded the Milan criteria had been validated with identical outcomes (57). Totally speaking, major presentations for liver transplantation stayed unchanged.

Percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA) are the most commonly utilized ablative arms, which have been taken as therapy of choice for patients belonging to BCLC stage 0–A. Recently, initial treatment by RFA or PEI has returned a comparable result with hepatectomy for BCLC stage 0 patients with tumor size less than 2 cm (58,59).

Transarterial chemoembolization (TACE) serves as the principal therapeutic method for BCLC stage B HCC (60). The recommendations of TACE kept almost the same with that in previous versions. Recent studies have shown transarterial radioembolization could do a better job than TACE to downstage tumor, and its joint use with yttrium-90 microspheres could produce an inspiring prognosis (17,18,20,21,24,61,62).

Sorafenib is indicated for BCLC stage C or BCLC stage B HCC progressed after TACE. RCTs have already demonstrated that sorafenib might act as the treatment of choice for HCC patients with well-preserved liver function who are not suitable for potentially more effective arms (63,64). Concerning update of sorafenib is about certain safety data and the efficacy in survival prolongation (65–67).

Teriminal stage (BCLC stage D) patients ought to be given the best supportive care.

Discussion

In the present study, through a broad search strategy covering major medical publication repositories, 11 main HCC guidelines in Asia were identified. All of the guidelines included were published or finally updated (Most of them have several updated versions.) in the last 8 years and could represent the most recent recommendations in the clinical management of HCC in Asia.

On AGREE II evaluation, overall quality was considered to be moderate among the 11 included guidelines with the majority being suitable for recommendation in practice. Most of the appraisal results stayed in agreement with the current literature (68). The different scores for each domain implied that guideline drafters comparatively placed their focus on different areas. Overall, Korean Guideline obtained the highest score, followed by the J-guideline. Upon closer examination, we found that these guidelines were in compliance with strict methodological rigor (such as the rule of evidence-based recommendation) and updated for several times. This illustrated the drafters' commitment on continued improvement of their recommendations along with bettering the overall quality of guidelines for clinical practice. Furthermore, it is broadly accepted that evidence based guidelines are superior to non-evidence-based ones in terms of helping clinicians to effectively choose suitable treatment allocations. By contrast, the lowest overall score guideline was the Chinese consensus by Section of Hepatic Surgery, Branch of Surgery, Chinese Medical Association, which was primarily due to a lack of statement of methods and other vital components throughout. However, it was merely expert consensus on selection of surgical treatments for HCC.

By calculating the mean score of each domain, the greatest score of all six domains was found in clarity of presentation, followed by scope and purpose. The former domain is concerned with the language, structure and format of the guideline; and the latter deals with the purpose, clinical issues and target population. This might be explained by the following reasons: (I) most of the guidelines were published in reputable academic journals or books that likely require strict language editing; (II) most of the guidelines had been updated (or modified) several times by a group of multi-disciplinary experts. As to this, commensurate findings were revealed by earlier researches (69-71). Reversely, the applicability domain had the lowest average score, which kept in line with previous researches (69,72). The applicability domain was defined by AGREE

II as the facilitators, barriers and resource implications that are associated with guideline use (12). This domain was basic for clinicians, a good score of which indicated the rigor and feasibility of a guideline. Guidelines drafters and users should lay enough priority in this domain. Hence, we propose that it is essential to strengthen the implementation of pilot studies, barrier analyses and clinician feedback aspects when constituting the guidelines (73).

Although analysis was primarily focused on the Asian guidelines, we could not ignore that eastern and western perspectives on clinical practice guidelines for HCC have a lot of commonalities but may also differ in some sections, as described in the present article. This might be due to the regional differences in epidemiology, risk factor, or healthcare policies. Of note, massive new findings about HCC were produced by recent researches, but changes are minor by and large; and they are not easy to take notice of among guidelines. Additionally, there still remain variances in Asian guideline structures and certain contents (particularly in recommendations of surveillance and treatment allocation). For example, the recommendation of AFP use in screening and surveillance was still in dispute. Significances of certain novel biomarkers also require further validation. Hence, better biomarkers are urgently needed for the screening and surveillance of HCC. Similarly, differences in epidemiology which might change with time and region still existed. For example, HBV's causal role to HCC is weakening; meanwhile the importance of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis as risk factors for HCC are rising (74).

To our best knowledge, there is only one similar article concerning this topic (75). However, it mainly focused on the evaluation of the methodological quality of guidelines concerning HCC resection; additionally, only English guidelines were included for final analysis. Comparatively speaking, there were two main strengths in the present study: (I) this work serves as a study evaluating and comparing current guidelines for the clinical management of HCC in Asia; (II) through a broad search strategy covering major medical publication repositories, main guidelines from different areas in Asia has been incorporated. In spite of this, limitations of the present study had to be taken into consideration: (I) supplementary materials or background information on certain guidelines had been missed and thus could not be reviewed thoroughly. Thus, it is likely that guideline quality in some instances had been underestimated; (II) we did not re-examine the evidence base of the guidelines.

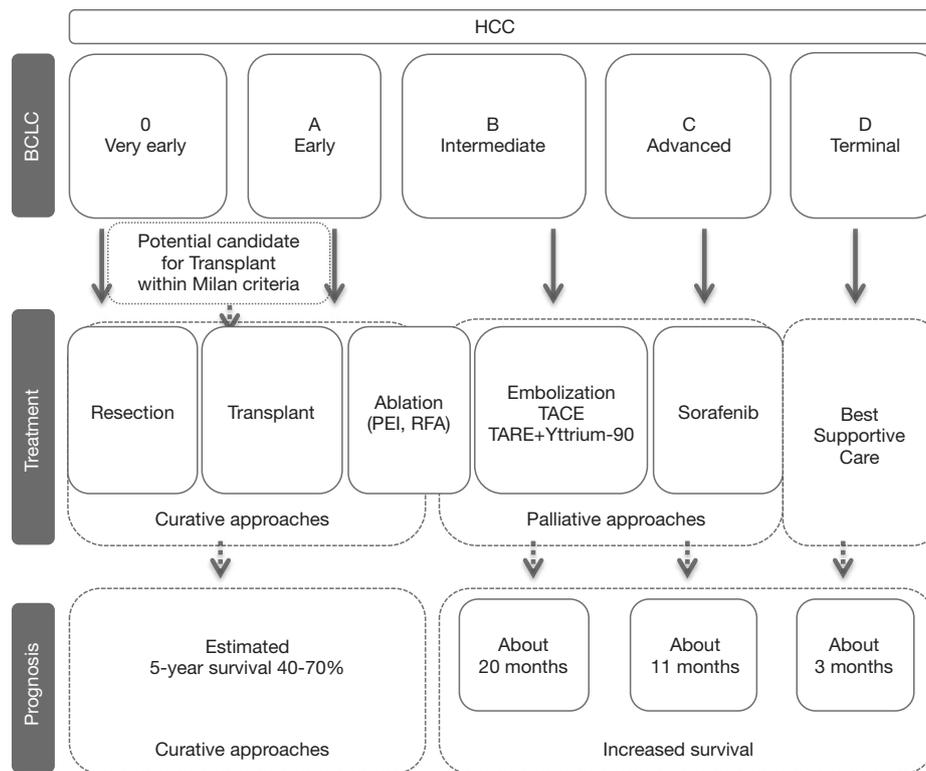


Figure 3 The treatment strategies of HCC based on the BCLC staging. HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer.

Conclusions

To summarize, the present review might help focus and target advocacy to promote clinical management of HCC in Asian countries. However, further research and more straightforward guidelines are essential to improve the prognosis of HCC in the future.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2017.11.05>). The authors have no conflicts

of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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