Hepatocellular carcinoma: A local registry on risk factors, imaging patterns, treatment strategies and overall survival

Manju Tambe Raja, Dr.Rad[1], Nur Yazmin Yaacob, M.Rad[1], Wong Zhiqin, FRCP[2], Chik Ian, Dr.Surg[3]

[1]Department of Radiology, Faculty of Medicine, Hospital Canselor Tunku Mukhriz, [2]Department of Internal Medicine, Faculty of Medicine, Hospital Canselor Tunku Mukhriz, [3]Department of Surgery, Faculty of Medicine, Hospital Canselor Tunku Mukhriz

ABSTRACT

Introduction: Hepatocellular carcinoma (HCC) is among the common death-causing cancers worldwide. This liver malignancy is primarily diagnosed using radiological imaging techniques. Most of the patients in Malaysia present late and were diagnosed at an intermediate or advanced stage of Barcelona Clinic of Liver Cancer (BCLC). This causes a limitation on the treatment options for the patients.

Materials and Methods: We performed a retrospective cross-sectional study of HCC cases within a five-year period in our center with data collected from Hospital Canselor Tunku Mukhriz (HCTM). This study examines the HCC risk factors, the pattern of diagnosis, treatment options and overall survival.

Results: The findings from this study showed that viral hepatitis was the highest risk factor in which most of the patients were elderly males who presented with abdominal distension. In addition, given the high prevalence of metabolic diseases Malaysia, it is predicted that the number of non-alcoholic steatohepatosis (NASH)-related HCC cases might increase. Alpha-fetoprotein (AFP) proved to have no significant role in the detection of the disease. The number of patients detected at early BCLC was minimal, resulting in limited options of treatment. Overall survival of our HCC patients was poor at 17 months.

Conclusion: We conclude that HCC patients in HCTM mostly presented at late stage to hospital, hence limiting the treatment options and resulted in poor survival rate. Disease awareness should be implemented at primary care level to detect HCC at its early stage. Subsequently, a multidisciplinary hospital team is required to manage the disease at its different stages of presentation.

KEYWORDS:
Death-causing cancer, liver, prevalence, detection

INTRODUCTION

Hepatocellular carcinoma (HCC) is among the most common death-causing cancers worldwide[1,2,3] with Hepatitis B virus (HBV) infection as the most prevalent cause.[4,5] Among the HCC patients in peninsular Malaysia in 2015, 57.6% had HBV while 2.4% had hepatitis C virus (HCV). The numbers of HCC cases have increased dramatically in proportion to the high prevalence of non-alcoholic steatohepatosis (NASH) in the population.[4,5]

An algorithm had been established by a local consensus on hepatobiliary imaging in 2015 to diagnose HCC based on Barcelona Clinic Liver Cancer (BCLC) algorithm (Figure 1).[6,7] Many cases were diagnosed late partially due to lack of technical and imaging expertise, such as in ultrasonography (USG), computed tomography (CT) scan, magnetic resonance imaging (MRI) or liver biopsy facilities.[3,6] This subsequently restricted the choice of treatment options when the patients present at a later stage of HCC in our center.

According to an epidemiological study conducted in Malaysia in 2013 on BCLC, only 34.2% of stage A patients underwent surgery whereas more than half of the patients underwent radiofrequency ablation (RFA). In stage B and C patients, one-third underwent trans-arterial embolization (TAE) while others were offered supportive therapy.[5] In this article, for simplification, most locoregional therapy procedures will be addressed under a common term of TAE. This includes conventional trans-arterial chemoembolization (cTACE), TACE with drug eluting beads, as well as bland embolization. Another locoregional therapy is thermal ablation, which includes radiofrequency ablation (RFA) and microwave ablation. In Malaysia, these procedures were offered based on operator preference, which includes skill and funding.

This is a very timely study in view of the relatively high number of HCC cases with late presentation to hospital in Malaysia. The aim of this study is to improve understanding of the disease as it has a wide range of clinical presentations and diagnostic imaging findings. This study also aims to highlight the requirement of multidisciplinary team (surgery, hepatology, and radiology) in managing the disease.[8,9]

MATERIALS AND METHODS

The objective of the study was to assess for diagnostic imaging of HCC, the pattern of HCC imaging, the common risk factor, the primary team referrals, and treatment strategy for early HCC in the local setting.

This is a retrospective, cross-sectional prevalence descriptive study of HCC patients in HCTM presented over five years period starting from January 2011 until December 2015. A

This article was accepted: 10 January 2021
Corresponding Author: Manju Tambe Raja
Email: 697078@gmail.com

follow up were conducted until December 2019 for survival rate. OpenEpi online program (version 3) was used to calculate the correct sample size to compare the means. With a power of 80%, 95% confidence interval and a ratio of 1 between the groups of 180 and 200 patients, a total of 146 patients were calculated for the total sample size. The list of the patients was derived from a Case mix group in our hospital. The list of imaging modalities to diagnose HCC was obtained from Juke raid, Raid server, and RIS-PACS [Radiology Information System and Picture Archiving & Communications System]. The details of the patient were obtained from C-HETS [Caring Hospital Enterprise System]. Data were only collected for patients who fulfil the inclusion and exclusion criteria. The findings were recorded in SPSS [Statistical Package for the Social Sciences] version 22 based on the BCLC stages.

The patients with viral or non-viral hepatitis have had once in three months liver function test (LFT) surveillance. Patients with raised LFT were screened for USG and Alpha-fetoprotein (AFP) level in the blood. An elevation of AFP (cut off point of 200 úg/mol) and detection of a suspicious liver nodule on USG warranted a further CT scan for liver 4-phase assessment. Inconclusive CT scan on liver 4-phase findings required a further assessment by an MRI of the liver. Regular weekly multidisciplinary meetings were performed between the hepatologist, surgical team and radiologist to decide on mode of intervention as early HCC is considerably challenging to diagnose and treat. The final diagnosis of a typical pattern of HCC was confirmed by diagnostic imaging, whereas the atypical pattern of HCC was confirmed by histopathological diagnosis.

Inclusion criteria were all HCC patients who performed CT/MRI images at our centre and HCC patients referred from other hospitals with digitised CT/MRI images. Exclusion criteria involved patients diagnosed with HCC without CT/MRI images and as well as patients who are not diagnosed with HCC histopathologically.

Statistical analysis was performed using SPSS version 22.0. Descriptive statistics were used to obtain a percentage with a mean at a standard deviation of 95% confidence level. Cross-tabulation tests were used to estimate choice of CT or MRI in detecting HCC at early stage and to estimate ideal treatment option at early BCLC stage. One-way ANOVA test was used to assess the significant difference of AFP mean value in the BCLC stages. A p-value of less than 0.05 was used as a statistically significant. Kaplan-Meier method using a log-rank test was used to estimate the patients' median overall survival (OS) and to compare survival distribution between the stages of BCLC.

RESULTS

Details of 237 patients listed as HCC were derived from a Case mix. Out of the 237 patients, 66 patients were excluded from the study in which 18 patients were non-HCC at a final diagnosis while 48 patients had no digitized images. The details of the 171 patients were entered into the SPSS program.

The average age of the patients was between 50 to 72 years old with the median age of 61 years old. The minimum age was 19 years and the maximum age was 82 years old. Majority of the patients diagnosed with HCC were males with 80% while only 20% were females. About half of the patients (48.8%) were HBV carriers while 17.7% were HCV carriers and 1.8% of the patients were a combination of HBV and HCV carriers. 26.9% of viral hepatitis patients had overlapping steatohepatosis/ alcohol influence as well. NASH affected 36.5% of the patients while 10.0% experienced alcohol-induced hepatitis. 41.2% of the subjects have hypertension, 36.5% of them had diabetes mellitus (DM) and 29.8% had dyslipidemia. In conclusion, viral hepatitis is considered as the main risk factor of HCC in our center with HBV infection in the lead. No attempt was made to look at association between viral and non-viral hepatitis in this study.

Majority of the patients had abdominal pain (64.1%) as the common symptom while other symptoms include loss of appetite at 34.1%, fatigue at 32.9%, and jaundice at 24.7% [Table I].

Only 49 patients (29.7%) diagnosed with HCC in HCTM had been screened prior to disease manifestation. Twenty of these patients (40.8%) were diagnosed at an early stage of BCLC. Other than screening for HCC, we had 65 patients (39.4%) who presented upon onset of symptoms. Majority of these patients presented at an intermediate or advanced stage of the disease. Fifty-seven of our patients (30.9%) were referred from primary care and district hospitals with the majority of these patients presented with an advanced stage of HCC.

In this study, the AFP values in 104 patients were scored to look for correlation between AFP value and detecting suspicious liver lesion on USG. One-way ANOVA test was used for the mean difference. The result showed no significant correlation between high AFP value and positive USG findings, as p-value was 0.36 (>0.05). Hence, decision to perform USG liver should not be made solely based on AFP result.

USG images were available for 116 patients prior to HCC diagnosis and 71.6% of the patients showed the presence of liver nodule/ mass. The average tumor size found on CT and MRI were between 2.2 cm to 12.4 cm with a mean diameter of 7.3 cm. A portal vein thrombosis was noted in 52 patients (30.4%) while 3 patients had hepatic vein involvement and 7 patients had IVC involvement.

Hundred forty patients (82.4%) with HCC were diagnosed using CT scan images whereas 30 patients (17.6%) were diagnosed using MRI images. Only 11.8% of cases diagnosed using CT scan and 4.1% of cases diagnosed using MRI were detected at an early stage of BCLC.

The initial treatment options were tabulated for 171 patients as shown in Figure 3. 28 patients (19.8%) presented at an early BCLC stage of HCC (stage O and A). Ten (35.6%) of these patients had surgery, 15 patients (53.6%) had locoregional therapy, which includes TAE and thermal ablation, while 3 (10.8%) patients received systemic

Table I: Demographic data of the HCC patients

Demographic data	Mean ± Standard Deviation (SD)	n (%)
Age	61± 11 years	
Male: Female Ratio		4:1
Viral Hepatitis		
HBV		80 (48.8)
HCV		29 (17.7)
HBV+HCV Combination		3 (1.8)
Metabolic Disorder		
Hypertension		70 (41.2)
Diabetes		62 (36.5)
Dyslipidemia		51 (29.8)
Non-viral Hepatitis		
NASH (Non Alcoholic Steatohepatitis)		62 (36.5)
Alcohol- Induced		17 (10)
Common Symptoms		
Abdominal Distension/ Pain		109 (64.1)
Weight Loss/ Loss of Appetite		58 (34.1)
Fatigue		56 (32.9)
Jaundice		42 (24.7)

Table II: Correlation between high AFP levels and HCC in patients

Findings	Sum of Squares	Sig.
Between Groups	.702	.360
Within Groups	56.354	
Total	57.057	

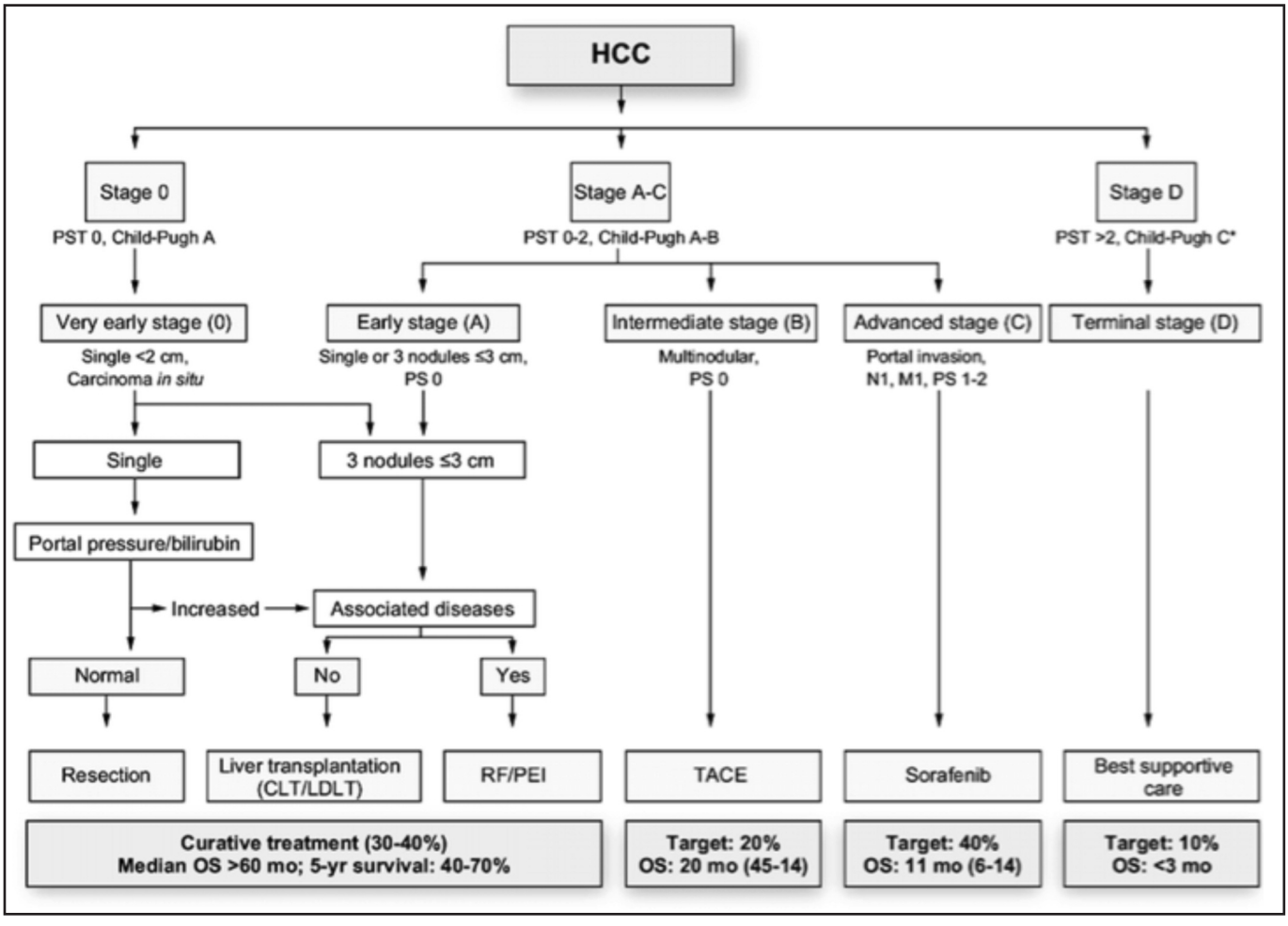

Fig. 1: Barcelona Clinic Liver Cancer Algorithm for Management of HCC[7]

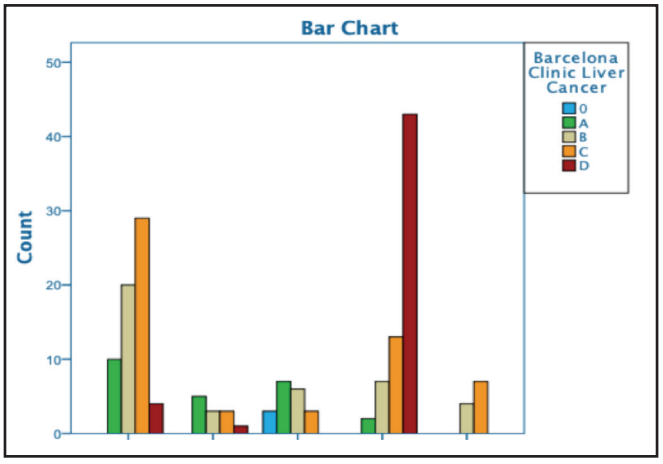

Fig. 2: Initial treatment given to HCC patients.

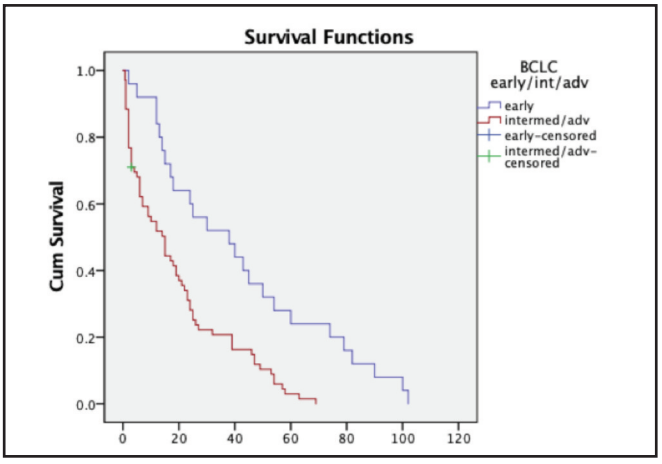

Fig. 3: Survival curve of HCC patients (in months).

treatment. Moreover, 143 patients (80.2%) presented at an intermediate (stage B) and advanced stage (stage C & D) with 9 (6.3%) patients had surgery, 61 patients (42.7%) had locoregional therapy, and 62 (43.3%) patients received systemic treatment. Eleven patients (7.7%) default treatment and lost to follow up.

Kaplan-Meier analysis showed the median overall survival estimation of 17 months (SD ±2.4) in 94 patients that were followed up until December 2019. Log-rank test in Figure 4 demonstrates a significantly longer survival rate in the early stage of BCLC compared to intermediate/advanced stages. Thirteen patients (20.3%) had a survival rate of 5 years and above after HCC diagnosis and treatment in our center, with majority of the patients diagnosed at an early stage of HCC (BCLC 0 and BCLC A). Twenty patients (21.3%) had a survival rate of 2 to 4 years with majority of them diagnosed at intermediate/advanced stages. Sixty-one patients (58.4%) had a survival rate of less than 2 years, which were diagnosed at intermediate/advanced stages. Only 1 patient belonging to the intermediate/advanced group was censored in view of unknown outcome. Overall findings indicate the importance of detecting the disease at an early stage to improve the survival rate of the patients.

DISCUSSION

This study identifies viral and non-viral hepatitis factors causing HCC as well as radiology diagnostic pattern that leads to detecting radiological diagnostic pattern that can detect HCC at its early stage. This will eventually enable us to administer promising treatment options and improving the OS of the patients.

In this study, the gender factor demonstrates 4:1 male to female ratio. This finding is similar as described in Asian Pacific Association for Study of Liver (APASL) 2017 Clinical Practice Guidelines (CPG) of HCC wherein male patients were more likely to be affected by disease, than female ranging from 2:1 to 4:1 ratio.[8,9] HBV infection is the leading risk factor of HCC in our study. This could be due to the lack of public awareness on HBV/HCV vaccination programme. Most of the patients in our study are elderly males with an underlying comorbid disease and a carrier of hepatitis B.[7-12] The CPG of Japan Society of Hepatology (CPG-JSH) of HCC highlights that patients requiring surveillance of HCC have been categorized as high-risk (cirrhosis type A, chronic HBV and HCV) and extreme high-risk patients (cirrhosis type B-involving portal hypertension and C-liver atrophy).[9] This emphasizes the need for active screening of viral hepatitis at a primary care level. Recently in August 2020, the Ministry of Health of Malaysia had launched a 1- week campaign for World Hepatitis Day. Rapid test kits for Hepatitis C had been distributed to various public health centers and about 1.9% of 11813 patients had been detected with the virus and referred to liver clinics.[10]

In our study, a high number of metabolic disorders were observed, raising risk of developing NASH-related HCC. According to recent studies, NASH-related HCC is becoming the major concern in developing countries as the viral hepatitis rates drop.[14] Hence it is necessary to raise awareness of controlling metabolic disorders as these can lead to HCC. This study demonstrated that most of the HCC patients presented to HCTM experienced abdominal pain. This is likely due to the lack of HCC screening in high-risk patients, thus most patients were in the late stage of HCC with mass-like symptoms.[15]

AFP results proved to be non-significant in determining the requirement of USG for HCC surveillance in this study. According to APASL, AFP is not a sensitive screening tool.[16,18] Therefore, since AFP is not significant in this study, patients with abdominal mass and a normal AFP level will still be warranted for imaging.

Among one-third of HCC patients who have been screened prior to diagnosis, only 40% were in the early stage of HCC. As per CPG-JSH for HCC, USG for extreme high-risk group patients is more frequently performed between 3 to 4 months.[8,9] We could follow this by increasing the frequency of USG surveillance from 6 months to 3 or 4 months for patients with underlying moderate to severe cirrhosis.

The mean tumor size detected on CT/MRI in our center was in the intermediate stage of BCLC and one-third of the patients

had portal vein thrombosis. As per CPG-JSH of HCC, 6 to 12 monthly CT/MRI surveillance is performed by option for patients in the extreme high-risk group.[8,9] In Malaysia, 4-monthly CT/MRI screening may not be practical due to limited resources and expertise in the hospital as well as burden of high cost for patients.[3,4]

In HCTM, CT scan and MRI of the liver is warranted for patients with high suspicion of HCC. Unfortunately, less than one-fifth of the HCC diagnosed patients were detected at an early stage of the disease. Few journals mention that there is no difference of efficacy in delayed phase (up to 1 hour) of contrast-enhanced MRI, in regards to detecting the disease at its early stage. Therefore, an image-guided biopsy is recommended for patients who had atypical CT/MRI findings, as histopathological tests are able to differentiate HCC from other liver malignancies.[19,22]

There is a wide variety of locoregional treatments offered based on the BCLC stages of HCC.[24,25] However, the cost for the treatment increases according to the severity of the disease.[23] Patients that defaulted treatment in this study were from the intermediate and advanced stage of the disease in which these patients rely highly on medical insurance or government subsidy.[4] Thus, early detection of the disease will reduce the burden of the cost for the treatment hence will improve compliance of the patients.

From the HCC survival curve, patients at the early stage of HCC have a longer survival rate compared to the advanced stage patients. This emphasizes the need for early detection and prompt treatment for HCC patients to improve the survival rate of HCC patients.

The limitation of this study is the sample size in which only HCC patients within the 5 years period were included since it is a retrospective analysis study. Only minimal data could be retrieved from patients referred from other hospitals as the case history was summarized in referral letters. 48 patients had to be excluded from this study due to the non-availability of their digitized CT or MRI images in our PACS system. Another 18 cases were excluded as histopathological test were confirmed to be non-HCC in origin.[11] Patients defaulted some treatments such as locoregional therapy due to financial constraint. Besides this, only initial procedure of treatment of patients was recorded in this study, thus we were not able to determine optimum treatment outcome.

CONCLUSION

The HCC patients in our center mostly presented at late stages, hence limiting the treatment options and resulting in poor survival rate. Disease awareness should be implemented at primary care level to detect HCC at its early stage. Subsequently, a multidisciplinary hospital team is required to manage the disease at its different stages of presentation.

ETHICAL APPROVAL

This study was approved by the Sekretariat Penyelidikan Perubatan dan Inovasi (SPPI) UKM (JEP2017-028).

DISCLOSURE STATEMENT

There is nothing to be disclosed by the authors.

REFERENCES

1. Globocan 2020. Global cancer observatory (cited Dec 2020). Available from http://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf
2. Sayiner M, Golabi P, Younossi Z. Disease Burden of Hepatocellular Carcinoma: A Global Perspective. Digestive Diseases and Sciences 2019; 64(4): 910-7.
3. Norsa'adah BN, Nurhazlini Z. Epidemiology and survival of hepatocellular carcinoma in North-east Peninsular Malaysia. Asian Pacific J Cancer Prevention 2013; 14(11): 6956-58.
4. Goh KL, Hartono JL, Qua CS. Liver cancer in Malaysia: epidemiology and clinical presentation in a multiracial Asian population. J Digest Dis 2015; 16(3): 152-8.
5. Raihan R, Azzeri A. Hepatocellular Carcinoma in Malaysia and Its Changing Trend. Euroasian J Hepato-Gastroenterol 2018; 8(1): 54-6.
6. Yaacob Y, Ranjini U, Omar H. Consensus on Hepatobiliary Imaging: A Malaysian Perspective. Coll Radiol 2015; 1: 2-7.
7. Forner A, Llovet J, Jordi B. Hepatocellular Carcinoma. The Lancet 2012; 379(9822): 1245-55.
8. Omata M, Lesmana LA. Tateishi R, Chen PJ, Lin SM, Yoshida H. Asia Pacific Clinical Practice Guidelines of the Management of Hepatocellular Carcinoma 2017 Update. Hepatology International 2017; 11(4): 317-70.
9. Kokudo N, Takemura N, Hasegawa K. Clinical Practice Guidelines for Hepatocellular Carcinoma: The Japan Society of Hepatology 2017 (4 th JSC-HCC guidelines) 2019; 49(10): 1109-13.
10. Said R, Zain R, Chan H. Find the Missing Millions: Malaysia's experience with nationwide hepatitis C screening campaign in the general population. Journal of Viral Hepatitis 2020; 27(6): 638-43.
11. Park J, Chen M, Colombo M. Global Patterns of Hepatocellular Carcinoma Management from Diagnosis to Death: The BRIDGE Study 2015; 35(9): 2155-66.
12. Aljumah A, Kuriry H, Zunaitan M. Clinical Presentation and Risk Factors of Hepatocellular Carcinoma in Saudi Arabia: A Tertiary Centre Experience. Saudi Journal of Gastroenterology 2016; 22(1): 1-9.
13. Dhanasekaran R, Limaye A, Roniel C. Hepatocellular Carcinoma: Current trends in worldwide epidemiology, risk factors, diagnosis and therapeutics. Journal of Hepatic Medicine 2012; 4(19): 37.
14. Piscaglia F, Svegliati B, Barchetti A. Clinical Patterns of Hepatocellular Carcinoma in Non Alcoholic Fatty Liver Disease: A Multicenter Perspective Hepatology 2016; 63(3): 827-38.
15. Willscott E, Angel E, Catherine T. Building the MultiDisciplinary Team for Management of Patients with Hepatocellular Carcinoma. Clin. Gastroenterol. Hepatol 2015; 13(5): 827-35.
16. Tunissiolli N, Castanhole-nunes M, Biselli P. Hepatocellular Carcinoma: Comprehensive Review of Biomarkers, Clinical Aspects and Therapy. Asia Pacific Journal of Cancer Prevention 2017; 18: 863-72.
17. Carr B, Akkiz H, Üsküdar O, Yalçin K. HCC with Low and Normal Serum Alpha Fetoprotein Levels. Clinical Practice (London, England) 2018; 15(1): 453-64.
18. Li B, Guo T, Sun Z, Li X, Wang H et al. The Clinical Values of Serum Markers in the Early Prediction of Hepatocellular Carcinoma. Biomed Research 2017; 2017: 5358615.
19. Chow P, Choo S, Ng D, Lo R, Wang M. National Cancer Centre Singapore guidelines for hepatocellular carcinoma. Liver Cancer 2016; 5(2): 97-106.
20. Pantongrag-Brown L. X-Ray Corner Role of Imaging in Hepatocellular Carcinoma. Thai Gastroenterology 2014; 15(1): 56-60.

21. Shriki J, Seyal A, Dighe M. CT Atypical and Uncommon Presentation of Hepatocellular Carcinoma 2015; 205(4): 411-23.
22. Rastogi A. Changing Role of Histopathology in the Diagnosis and Management of Hepatocellular Carcinoma. World Journal of Gastroenterology 2018; 24(35): 4000-13.
23. Rahman F, Naidu J, Ngiu CS. Conventional versus Doxorubicin-Eluting Beads Transarterial Chemoembolization for Unresectable Hepatocellular Carcinoma in a Tertiary Medical Centre Experience 2016; 17: 4037-41.
24. Yarchoan M, Agarwal P, Villanueva A. Recent Developments and Therapeutic Strategies Against Hepatocellular Carcinoma. Cancer Research 2019; 79(7): 4326-30.
25. Mercado-Irizarry A, Torres EA. Cryptogenic Cirrhosis: Current Knowledge and Future Directions. Clinical Liver Disease 2016; 7(4): 69-72.