

Hepatocellular Carcinoma in Oman

An analysis of 284 cases

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سرطان الكبد في عُمان نتائج تحليل 284 حالة

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ABSTRACT: Objectives: Hepatocellular carcinoma (HCC) is the most common type of primary liver tumour worldwide and is increasing in incidence. This study aimed to describe the clinical characteristics of HCC among Omani patients, along with its major risk factors, outcomes and the role of surveillance. **Methods:** This retrospective case-series study was conducted between January 2008 and December 2015 at the three main tertiary care hospitals in Oman. All adult Omani patients diagnosed with HCC and visited these hospitals during the study period were included. Relevant data were collected from the patients' electronic medical records. **Results:** A total of 284 HCC patients were included in the analysis. The mean age was 61.02 ± 11.41 years and 67.6% were male. The majority had liver cirrhosis (79.9%), with the most common aetiologies being chronic hepatitis C (46.5%) and B (43.2%). Only 13.7% of cases were detected by the HCC surveillance programme. Approximately half of the patients (48.5%) had a single liver lesion and 31.9% had a liver tumour of >5 cm in size. Approximately half (49.2%) had alpha-fetoprotein levels of ≥ 200 ng/mL. The majority (72.5%) were diagnosed using multiphase computed tomography alone. Less than half of the patients (48.9%) were offered one or more HCC treatment modalities. **Conclusion:** The majority of Omani HCC patients were male and had cirrhosis due to viral hepatitis. In addition, few patients were identified by the national surveillance programme and presented with advanced disease precluding therapeutic or even palliative treatment.

Keywords: Hepatocellular Carcinoma; Liver Cirrhosis; Human Viral Hepatitis; Public Health Surveillance; Early Detection of Cancer; Alpha-Fetoprotein; Oman.

المخلص: الهدف: تتزايد معدلات حدوث سرطان الكبد والذي يعد أحد أكثر أورام الكبد الأولية شيوعاً في جميع أنحاء العالم. تهدف الدراسة الحالية إلى وصف الخصائص السريرية والمسببات الرئيسية للمرضى العمانيين المصابين بسرطان الكبد، وعرض نتائج المرض، وإبراز أهمية التشخيص المبكر للمرض. **الطريقة:** أجريت دراسة وصفية استرجاعية على الملفات الصحية الإلكترونية لجميع مرضى سرطان الكبد العمانيين البالغين والذين تم متابعتهم وعلاجهم في المستشفيات المرجعية الرئيسية الثلاثة في سلطنة عمان خلال الفترة الزمنية بين يناير 2008 وديسمبر 2015. **النتائج:** شملت الدراسة 284 مريض مصاب بسرطان الكبد، حيث بلغ متوسط أعمار المصابين 61.02 ± 11.41 سنة، وكانت غالبيتهم من الذكور (67.6%). كما كانت الغالبية (79.9%) من المصابين تعاني من تزامن تليف الكبد، وكانت أكثر الأسباب شيوعاً للإصابة بتليف الكبد هي التهابات الكبد المزمنة من جراء الإصابة بفيروس ج (بنسبة 46.5%) أو فيروس ب (بنسبة 43.2%). أظهرت الدراسة أن 13.7% فقط من حالات سرطان الكبد تم تشخيصها كنتيجة لخضوع المصابين لفحوصات الكشف المبكر عن سرطان الكبد. كما أوضحت الدراسة أن ما يقرب من نصف المرضى (48.5%) كان لديهم بؤرة سرطانية كبدية واحدة، وما يقرب من ثلث عدد المرضى (31.9%) كان مصاباً بورم في الكبد بحجم أكبر من 5 سم، وما يقرب من نصف المرضى (49.2%) كانت مستويات ألفا فيتوبروتين لديهم أعلى من 200 نانوغرام/مل. تم تشخيص غالبية المرضى (72.5%) باستخدام الأشعة المقطعية متعددة المراحل فقط. بينت الدراسة أن حوالي نصف المرضى المشمولين في الدراسة (48.9%) خضع لوسيلة واحدة من الوسائل المتعارف عليها لعلاج سرطان الكبد أو أكثر. الخلاصة: كان غالبية المرضى العمانيين المصابين بسرطان الكبد من الذكور الذين يعانون من تليف الكبد من جراء الإصابة بالتهابات الكبد الفيروسيه. تم التعرف على نسبة قليلة من المرضى من خلال برنامج الكشف المبكر عن سرطان الكبد، و تم تشخيصهم في مراحل متقدمة من المرض حالت دون تقديم علاج شاف أو الرعاية التلطيفية لهم.

الكلمات المفتاحية: سرطان الكبد؛ تليف الكبد؛ التهاب الكبد الفيروسي؛ مراقبة الصحة العامة؛ الكشف المبكر عن السرطان؛ ألفا فيتوبروتين؛ عُمان.

ADVANCES IN KNOWLEDGE

- This study provides clear descriptive data regarding the epidemiology of hepatocellular carcinoma (HCC) and its risk factors in Oman, along with the most frequent presentation of HCC cases and commonly used treatment modalities.

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APPLICATION TO PATIENT CARE

- *The findings of this study emphasise the importance of appropriate HCC screening for high-risk patients and the implementation of primary prevention strategies and early detection to reduce the rate of HCC and the negative patient outcomes associated with the disease.*

HEPATOCELLULAR CARCINOMA (HCC) IS ONE of the most common cancers around the globe and represents a leading cause of cancer-related mortality.¹ However, there is marked variation in the prevalence of HCC in different parts of the world, with more than two-thirds of cases reported from East and South Asia as well as sub-Saharan Africa.² This is mainly due to differences in the prevalence of viral hepatitis, particularly hepatitis B and C, the predominant causes of liver cirrhosis, a known risk factor for HCC.³ The introduction of hepatitis B vaccination in many countries has led to a marked reduction in HCC cases. The improvements in medical facilities with designated screening programmes similarly expected to help increase the detection rate and, therefore, improve the outcome of HCC.⁴⁻⁹

Despite recent marked improvements in treatment modalities, the prognosis for HCC patients remains poor, with an average five-year survival rate of approximately ~5–6%.¹⁰ Unfortunately, this is largely attributable to a lack of access to medical facilities in many underdeveloped countries.¹¹ International guidelines recommend that HCC surveillance be performed on a six-month basis using liver ultrasonography (US), with or without measurement of alpha-fetoprotein (AFP) levels, for adults with liver cirrhosis and high-risk patients without cirrhosis such as patients with hepatitis B virus (HBV) infections.^{12,13} According to a meta-analysis of 47 studies, there is a significant association between HCC surveillance and detection of the tumour at an early stage, thereby increasing the likelihood of success for curative treatments such as surgical resection and liver transplantation and ultimately improving overall survival.¹⁴

In Oman, the estimated prevalence of the hepatitis C virus (HCV) is approximately 0.4% with genotype 1 being the most common followed by genotypes 3 and 4.¹⁵ Moreover, prior to the introduction of mass hepatitis B vaccinations in 1990, the estimated prevalence of HBV was 2–7%.^{16,17} Overall, HCC is ranked the fourth most common solid tumour among Omani male patients.¹⁸ However, there is a lack of national data evaluating the characteristics of HCC cases. As such, the primary objective of this study was to describe the clinical characteristics of HCC cases in Oman, with the secondary objectives being to

determine the major risk factors, role of surveillance and outcomes of HCC among Omani patients.

Methods

This retrospective case-series study was conducted from January 2008 to December 2015 at the Sultan Qaboos University Hospital, Armed Forces Hospital and The Royal Hospital. All adult Omani patients with one or more hepatic lesions who have been diagnosed with HCC were included in the study. Non-Omani patients and those with benign liver lesions, liver metastasis from a primary distant tumour, cholangiocarcinomas or hepatoblastomas were excluded, as were patients for whom there was no data concerning the number and size of HCC lesion(s). The sample was considered to be nationally representative as these three hospitals are the main tertiary hospitals in the capital city of Muscat and are the centres to which all HCC cases are referred to from other regions of Oman.

Relevant data were collected from the electronic medical records at each hospital including information regarding the patients' sociodemographic characteristics, laboratory findings, tumour aetiology, characteristics and radiological features at the time of presentation as well as the treatment modalities offered. In all cases, the diagnosis of HCC was based on the criteria of the American Association for the Study of Liver Disease in terms of typical enhancement patterns upon radiological examination or histopathological analysis.^{13,19} Moreover, the severity of liver cirrhosis cases was classified using the Child-Pugh scoring system as either class A (scores of 5–6), class B (scores of 7–9) or class C (scores of 10–15).²⁰

Detailed information concerning each patient was available from the electronic medical record systems of each of the three participating hospitals along with the findings of any laboratory and radiological investigations conducted both at first presentation and during subsequent visits. Patients were either seen initially at one of the three tertiary hospitals or were referred immediately after the initial diagnosis of HCC. Laboratory and radiological investigations were repeated for all referred patients at presentation to each of the three tertiary hospitals.

In addition, HCC cases were assessed according to the Milan criteria regarding their suitability for

Table 1: Sociodemographic and clinical characteristics of Omani patients with hepatocellular carcinoma (N = 284)

Characteristic	n (%)
Mean age in years ± SD	61.02 ± 11.41
Gender	
Male	192 (67.6)
Female	92 (32.4)
Presence of liver cirrhosis	
Yes	227 (79.9)
No	57 (20.1)
Class of liver cirrhosis*	
Class A	76 (34.1)
Class B	82 (36.8)
Class C	65 (29.2)
Aetiology of liver cirrhosis[†]	
HCV	99 (46.5)
HBV	92 (43.2)
Alcoholic liver disease	20 (9.4)
Cryptogenic	2 (0.9)

SD = standard deviation; HCV = hepatitis C virus; HBV = hepatitis B virus.

*According to the Child-Pugh scoring system.¹⁹ Total dataset for this variable was 223 as four patients were excluded due to missing data. [†]Total dataset for this variable was 213 as aetiology could not be determined in 10 cases.

liver transplantation.²¹ Based on overall and disease-free survival rates, these guidelines state that only patients with one lesion of <5 cm in size or up to three lesions of <3 cm each and with no evidence of extrahepatic disease or vascular invasion are eligible for transplantation.²¹ Performance status was assessed using the Eastern Clinical Oncology Group (ECOG) scale as follows: grade zero (fully active and able to continue all pre-disease activities without restriction); grade 1 (restricted in physically strenuous activities but ambulatory and able to carry out work of a light or sedentary nature); grade 2 (ambulatory, out of bed for >50% of waking hours and capable of unrestricted self-care, but unable to carry out any work activities); grade 3 (capable of limited self-care and confined to a bed or chair for >50% of waking hours); or grade 4 (completely disabled, unable to perform any self-care and totally confined to a bed or chair).²²

The statistical analyses were conducted using Stata[®] data analysis and statistical software, Version 14.2 (StataCorp LLC, College Station, Texas, USA). Categorical variables were reported using frequencies and percentages, while continuous variables were presented using means and standard deviations.

Table 2: Tumour characteristics of Omani patients with hepatocellular carcinoma (N = 284)

Characteristic	n (%)
Number of lesions*	
1	127 (48.5)
2–3	34 (13)
>3	65 (24.8)
Diffuse lesions	36 (13.7)
Size of lesions in cm[†]	
<2	36 (13.7)
2–5	101 (38.4)
>5	84 (31.9)
Diffuse lesions	42 (16)
AFP level in ng/mL[‡]	
<200	123 (50.8)
200–400	13 (5.4)
>400	106 (43.8)
Eligibility for transplantation[§]	
Eligible	65 (22.9)

AFP = alpha-fetoprotein. *Total dataset for this variable was 262 as 22 patients were excluded due to missing data. [†]Total dataset for this variable was 263 as 21 patients were excluded due to missing data. [‡]Total dataset for this variable was 242 as 42 patients were excluded due to missing data. [§]According to the Milan criteria.²⁰

The association between AFP levels and status of transplantation eligibility according to the Milan criteria was examined using a Pearson's Chi-squared test. The a priori two-tailed level of significance was set at $P < 0.050$.

This study was approved by the individual institutional research and ethics committees of the Sultan Qaboos University Hospital, Armed Forces Hospital and The Royal Hospital.

Results

A total of 284 HCC patients were included in the final analysis. The mean age was 61.02 ± 11.41 years (range: 24–84 years) and 67.6% were male. Overall, 227 patients (79.9%) had liver cirrhosis, most frequently classified as Child-Pugh class B (36.8%) followed by class A (34.1%) and class C (29.2%). The underlying aetiology of the liver cirrhosis could be determined in 213 patients (75%); of these cases, the majority were caused by HCV (46.5%) or HBV (43.2%) infections [Table 1].

Only 39 patients (13.7%) were identified via the surveillance programme using AFP and liver US every

Table 3: Association between alpha-fetoprotein levels and eligibility for transplantation among Omani patients with hepatocellular carcinoma (N = 284)*

Eligibility for transplantation [†]	AFP category, [‡] n (%)		P value
	Low (n = 131)	High (n = 102)	
Eligible	48 (36.6)	17 (16.7)	0.001
Ineligible	83 (63.4)	85 (83.3)	

AFP = alpha-fetoprotein.

*Total dataset was 233 as 51 patients were excluded due to missing data;

[†]According to the Milan criteria;²⁰ [‡]AFP levels were considered high or low at >400 and ≤400 ng/mL, respectively.

six months. To confirm the diagnosis, the majority of patients (72.5%) required one modality of imaging (multiphase computed tomography [CT] of the liver), with the remaining patients (27.5%) requiring two modalities (both multiphase CT and contrast-enhanced magnetic resonance imaging [MRI] of the liver). Just under half of the patients (48.5%) had a single focal lesion. In 38.4% of patients, the focal lesions ranged in diameter from 2–5 cm. Approximately half of the cohort (50.8%) had AFP levels of <200 ng/mL, while only 21.8% were considered suitable for liver transplantation as per the Milan criteria [Table 2].

There was a significant association between AFP levels and transplantation eligibility according to the Milan criteria, with 36.6% and 16.7% of patients with AFP levels of ≤400 and >400 ng/mL, respectively, considered suitable for liver transplantation ($P < 0.001$) [Table 3]. Overall, 48.9% were offered one or more modalities of treatment including tumour resection, radiofrequency ablation (RFA), transarterial chemoembolisation, kinase inhibitor drug therapy (in the form of sorafenib) and liver transplantation. However, the remaining 51.1% of patients were beyond curative treatment due to advanced disease stage, the presence of comorbidities and/or poor performance status (i.e. ECOG scores of >2) at presentation [Table 4].

Discussion

The Oman National Cancer Registry was first established in 1985 as a hospital-based endeavour, before being incorporated under the umbrella of the Department of Non-Communicable Diseases Surveillance and Control of the Ministry of Health in 1996. Subsequently, the notification and record of all cancer cases in the country was made mandatory in 2001.²³ Despite governmental efforts, some cancer cases are still not registered in Oman for a variety of reasons, including the fact that a considerable number of patients choose to seek diagnosis and

Table 4: Treatment modalities offered to Omani patients with hepatocellular carcinoma (N = 284)

Modality	n (%)
None	145 (51.1)
Resection alone	14 (4.9)
Resection plus RFA	2 (0.7)
Resection plus TACE	1 (0.4)
Resection plus transplantation	2 (0.7)
Resection plus sorafenib	2 (0.7)
RFA alone	16 (5.6)
RFA plus TACE	5 (1.8)
RFA, TACE and sorafenib	2 (0.7)
RFA plus sorafenib	3 (1.1)
TACE alone	31 (10.9)
TACE plus sorafenib	20 (7)
TACE plus transplantation	1 (0.4)
Resection, TACE and sorafenib	2 (0.7)
Resection, RFA, TACE and sorafenib	1 (0.4)
Transplantation alone	2 (0.7)
Sorafenib alone	33 (11.6)
Transplantation plus sorafenib	2 (0.7)

RFA = radiofrequency ablation; TACE = transarterial chemoembolisation.

medical treatment abroad. To the best of the authors' knowledge, this study is the first of its kind to analyse the characteristics and risk factors of Omani patients with HCC.

In the current study, the majority of Omani HCC patients were older males. Research has shown that HCC is much more common in men, possibly due to behaviours linked to known HCC risk factors such as alcohol consumption and smoking.²⁴ Moreover, epidemiological studies from other parts of the world have shown that the incidence of HCC increases with age, although the age of peak incidence varies; for example, HCC incidence increases progressively until 70 years of age in Taiwan, whereas it reportedly peaks at 55 years in Africa.^{25,26} High incidence rates in older patients could be attributed to longer durations of viral hepatitis infections leading to advanced fibrosis and cirrhosis. However, the effect of age *per se* cannot be excluded, since other solid organ tumours also occur at a higher rate in older patients.²⁷ McMahon *et al.* reported that an annual HCC incidence of 0.26% in <20-year-old males with HBV, which increased to 1.1% for those aged >50 years.⁴

The most prevalent risk factor for HCC in the present study was cirrhosis affecting 79.9% of cases.

Cirrhosis is a well-known risk factor for HCC; the annual risk of developing HCC is 1–6% for cirrhotic patients with up to 60–80% of HCC patients having underlying cirrhosis.^{28,29} This wide range in reported incidence reflects differences in the population being studied, for instance in terms of age, gender, aetiology and duration of cirrhosis.²⁹ Ethnicity has also been noted to play a role in the incidence of HCC.^{30,31} The high incidence of HCC in young African patients is most likely secondary to multiple additive factors, such as genetic background, HBV infection and exposure to aflatoxins.^{24,32} In the current study, HCV was the most common cause of cirrhosis followed by HBV. This is unsurprising, given the dramatic reduction in the seroprevalence of chronic HBV infections in Oman following the successful introduction of HBV vaccination in 1990.¹⁷ Similar findings have also been reported in Saudi Arabia.³³

Various decision analysis models have demonstrated the cost-effectiveness of HCC surveillance.^{34,35} According to these models, twice yearly surveillance is indicated if the incidence of HCC is $\geq 1.5\%$ per year.^{34,35} Based on international guidelines and recorded tumour doubling time, the HCC surveillance programme in Oman involves biannual liver US and serum AFP level evaluations.^{12,13} Unfortunately, only 13.7% of patients in the present cohort were detected as a result of this programme. This can be attributed to the asymptomatic nature of most liver diseases or the fact that many individuals choose not to seek routine medical attention until later in life. Moreover, many Omani patients may lack awareness of the complications of viral hepatitis and the importance of surveillance in the early detection and treatment of HCC. Furthermore, patients with HBV infections may have been considered to have chronic inactive hepatitis and thus were not included within the surveillance programme.

In a meta-analysis of 19 studies, Singal *et al.* observed that twice yearly surveillance using liver US increased the sensitivity for detecting early-stage HCC to 70%.³⁶ Similarly, Santi *et al.* demonstrated a higher detection rate of early-stage HCC cases with biannual rather than annual surveillance, leading to a high cure rate and better prognosis.³⁷ However, decreasing the surveillance interval from six to three months was not found to result in any additional benefit to survival.³⁸ A systematic review of nine studies showed that HCC surveillance rates were significantly higher among patients seen by gastroenterology subspecialists compared to those attended by primary care physicians (51.7% versus 16.9%; $P < 0.001$).³⁹ Increasing awareness of liver diseases among medical staff, screening high-

risk patients, encouraging early referral of suspected cases and actively counseling patients and their families are recommended measures to enhance the effectiveness of the national HCC surveillance programme in Oman.

Previous research has provided evidence regarding the limited usefulness of AFP as a screening modality for HCC.^{34,35,40} Indeed, 50.8% of HCC patients in the present study had AFP levels of < 200 ng/mL. According to Trevisani *et al.*, an AFP cut-off value of 20 ng/mL provides the optimal balance between sensitivity and specificity; however, at this level, the sensitivity is low.⁴¹ Elevated AFP levels have been described in non-HCC liver lesions such as intrahepatic cholangiocarcinomas and in cases of liver metastasis from the colon and stomach.^{42–44} An interesting observation in the present study was the significant association between high AFP levels (> 400 ng/mL) and ineligibility for liver transplantation as per the Milan criteria.²¹ This confirms findings reported by Tangkijvanich *et al.* in which the researchers described an association between high serum AFP levels and large tumour size, bilobar involvement, massive or diffuse-type tumours and portal vein tumour thrombus.⁴⁵ This is worth investigating further in larger-scale prospective studies.

Abdominal US was the most frequently employed modality for HCC screening in the current study. However, the diagnosis of HCC was based on multiphase liver CT in the majority of patients (72.5%). Generally, US has been reported to have a sensitivity of 65–80% and a specificity of $> 90\%$ when used as a screening test.⁴⁶ However, the accuracy of this modality is operator-dependent as a small HCC lesion may be missed against the background of a multinodular liver. In addition, US has lower sensitivity for the detection of early-stage HCC in obese patients and patients with fatty livers.^{13,47} As such, abdominal US should be followed by multiphase CT of the liver or contrast-enhanced MRI in order to identify small or early-stage and small HCCs.^{13,48} However, only a minority of the patients in the present study required more than one modality for the diagnosis of HCC due to atypical radiological patterns.

Unfortunately, less than half of the patients in the present study were offered treatment. Among those who were, various modalities were employed, either alone or in combination, to treat patients with different stages of HCC. Few patients received curative treatment in the form of liver resection, RFA or liver transplantation. In many cases, treatment was limited due to high Child-Pugh scores—with approximately two-thirds of the patients categorised as class B or C—

poor performance status (ECOG scores of >2) and/or advanced stages of disease based on the Barcelona Clinic Liver Cancer staging system.⁴⁹

This study was limited by certain factors. Due to its retrospective nature, some data were missing for certain variables. Moreover, several patients presented in an advanced stage of disease with comorbidities such as renal failure which precluded the use of radiological investigations such as multiphase CT or contrast-enhanced MRI for definitive diagnosis and staging. Another major limitation was the inability to report the true incidence and trend of HCC cases in Oman due to the fact that some patients were diagnosed and treated outside of the country.

Conclusion

This study represents the first of its kind to describe the clinical characteristics and risk factors of HCC in Oman. The majority of patients were male and had liver cirrhosis caused by viral hepatitis. In addition, approximately two-thirds presented with advanced disease (Child-Pugh classes B or C). There is an urgent need to enhance the existing HCC surveillance programme in order to encourage early detection of HCC and increase the likelihood of curative treatment.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTIONS

All authors participated in this research. KN contributed to the draft conception, concept design and writing of the manuscript, while ZH and SS contributed to the concept design and writing of the manuscript. IZ and HO contributed to the data analysis. All other authors contributed equally to the writing of the manuscript including MM, BB, OS, SAB, AM, HZ, BRK, AK and IAB.

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