RESEARCH ARTICLE

A year of hepatocellular carcinoma at a glance. Demographics, biochemical and radiological characteristics and treatment modalities from a specialized facility of Pakistan

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Abstract

Objectives: To analyse the relation of demographics of hepatocellular carcinoma with the aetiology in order to analyse tumour characteristics in relation to anti-viral therapy and the presence of viral-deoxyribonucleic acid/ribonucleic acid, and the treatment modalities offered.

Method: The cross-sectional study was conducted at the Department of Gastroenterology, Pak Emirates Military Hospital, Rawalpindi, Pakistan, from January 1 to December 31, 2019, and comprised patients aged 18-70 years with diagnosed hepatocellular carcinoma. Demographic variables, biochemical analysis, including liver profile and stage of cirrhosis, viral-status, tumour staging and the treatment modalities offered were noted.

Results: Of the 195 patients, 148(76%) were males and 47(24%) were females. The overall mean age was 59.8±8.9 years. There were 187(96%) patients with cirrhosis, 183(94%) corresponded to viral hepatocellular carcinoma, 160(82%) had hepatitis C, 18(9%) had hepatitis B and 6(3%) had co-infection. Platelets and alanine transaminase had a significant relation across aetiological groups ($p<0.05$). The presence of viral polymerase chain reaction had a significant impact on tumour aggressiveness ($p<0.05$). And, 62(32%) patients were amenable to curative treatment.

Conclusion: Viral infection was found to be the main cause of rising prevalence of hepatocellular carcinoma. Treatment modalities were found to be expensive, and expertise was lacking.

Keywords: Cirrhosis, Hepatocellular carcinoma, Hepatitis B, Hepatitis C, Liver transplant. (JPMA 71: 1849; 2021)

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Introduction

Malignancy is emerging as the main aetiology of death in the modern world, with hepatocellular carcinoma (HCC) being the fifth most common cancer and the third most common cancer-related cause of death around the world.[1] Asia as well as northern and southern Africa have been reported to have the highest incidence of primary liver cancers, with the highest age-standardised incidence rate (ASIR) seen in eastern Asia, and the lowest in northern Europe.[2] Population bloom, aging, socio-demographic conditions, access to care and viral infections are the main attributable factors for the rising cancer burden in under-privileged communities.[3]

While HCC incidence is higher in Asian and African countries, mortality from liver cancer has shown a growing trend in the more effluent societies, like the United States[4] and may be attributable to the changes in risk factors, like obesity, metabolic syndrome (MS) and alcoholism.[5] The 5-year relative survival rate is only 14% for HCC in the US and even lesser in under-developed countries.[6]

In around three quarters of all HCC cases, the aetiological factor has been recognised as chronic infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) or both.[7] Other risk factors listed include cirrhosis secondary to alcoholism, non-alcoholic fatty liver disease (NAFLD), which includes non-alcoholic steatohepatitis (NASH), tobacco, arsenic, cirrhosis of any aetiology, tyrosinaemia, several porphyrias, aflatoxin and oral contraceptive pills.[8]

In Pakistan, the ASIR for HCC is 7.6 per 100,000 per year for the male population, and 2.8 for the females.[9] It has been reported that 60-70% of all HCC cases can be attributable to chronic HCV infection. This is in contrast to many other neighbouring Asian countries where chronic HBV is the main culprit.[9] Many of the local epidemiological studies are single-centre in approach, and comparative studies with application of international guidelines remain questionable for the local population as there is no national cancer registry available.[9]

Despite the slowly decreasing mortality and morbidity secondary to other major carcinomas, the collective HCC burden is on the rise[10] and, therefore, needs robust research. The current study was planned to analyse the relation of demographics of HCC with its aetiology in order to analyse tumour characteristics in relation to anti-viral therapy and the presence of viral-deoxyribonucleic acid/ribonucleic acid (DNA/RNA), and the treatment modalities

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Patients and Methods

The cross-sectional study was conducted at the Department of Gastroenterology, Pak Emirates Military Hospital, Rawalpindi, Pakistan, from January 1 to December 31, 2019. After approval from the institutional ethics review board, the sample was raised from among HCC patients who presented to the outpatient-department (OPD) or from the HCC multi-disciplinary team (MDT) discussions both retrospectively and prospectively.

Those included were patients aged 18-70 years with HCC diagnosed through triphasic contrast-enhanced computed tomography (CECT) scan and/or magnetic resonance imaging (MRI) or core biopsy.[11] Those excluded were patients outside the age range, patients lost to follow-up and those with incomplete data, history of previous treatment for the same tumour, recurrence of the same tumour after successful therapy, concomitant tumours of other organs unrelated to HCC, patients who refused to take part in the study, and pregnant and lactating women. Patients aged >70 years were excluded since limited curative modalities, like liver transplant (LT), are available with poor response towards palliative procedures.[12] After taking informed consent from the patients, they were segregated into 6 groups according to the presence/absence and aetiology of cirrhosis.

A detailed history of symptoms, time since diagnosis, previous treatment modalities, viral treatment used and co-morbids was taken and a detailed physical examination, including body mass index (BMI) was done for all patients. Baseline investigations, including haemoglobin (Hb), white blood cell (WBC) count, platelets, bilirubin, alanine transaminase (ALT), alkaline phosphatise (ALP), albumin, international normalisation rate (INR), sodium (Na) and alpha fetoprotein (AFP) as a tumour marker, were carried out for all the participants. Liver cirrhosis was established by radiological characteristics and laboratory tests of hepatic synthetic function. Hepatitis C was defined as positive anti-HCV antibodies with or without positive quantitative HCV RNA. Hepatitis B was defined as a positive hepatitis B surface antigen (HBsAg) with or without a positive DNA polymerase chain reaction (PCR). NASH was defined by the presence of MS with a positive liver shear-wave elastography or histological evidence of ballooning, cellular degeneration, mixed leukocyte infiltration and fibrosis.[12] Cryptogenic cirrhosis was the term used when all the resources, including liver biopsies, were exhausted to find the cause of cirrhosis.[11] Child Turcotte Pugh (CTP) score was calculated for the severity of cirrhosis using bilirubin, albumin, presence of ascites, Prothrombin time (PT) and the presence and degree of porto-systemic encephalopathy.[11] The tumour was staged using the Barcelona Clinic of Liver Cancer (BCLC) criteria that included tumour size, tumour number, CTP score, performance score calculated using the Eastern Cooperative Oncology Group (ECOG) criteria, vascular invasion and extra-hepatic metastasis.[12] In case of multiple liver lesions, the largest one was selected for size measurement.[12]

Data was expressed as mean ± standard deviation (SD) and as frequencies and percentages, as appropriate. One-way analysis of variance (ANOVA) and Kruskal Wallis tests were used to compare normal and non-normal quantitative data respectively, whereas chi-square test and Fisher exact test were used to compare qualitative data. P<0.05 was considered statistically significant. All data was analysed using SPSS V.19.

Results

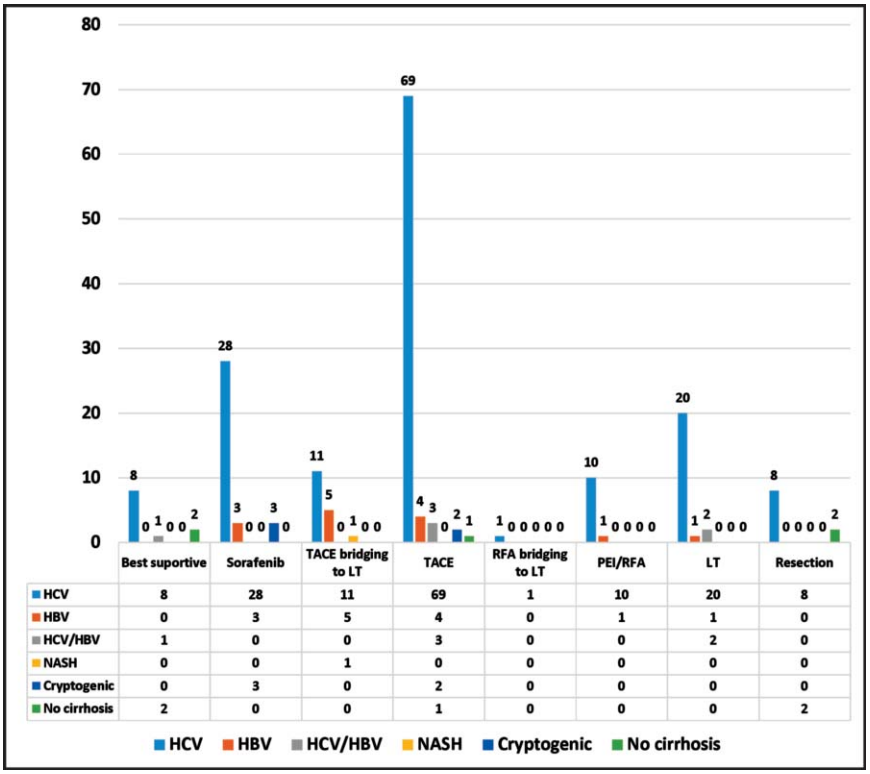

Figure-1: Treatment modalities offered by the HCC multi-disciplinary team meeting.

Table-1: Characteristics of patients with hepatocellular carcinoma (HCC) in relation to the cause of cirrhosis.

Variable	Frequency in n(%) or Mean ± SD							
	Total	HCV	HBV	HCV/HBV	NASH	Cryptogenic	No cirrhosis	p
Number of patients	195	160(82)	18(9)	6(3)	3(1.5)	3(1.5)	5(3)	
Age* (years)	59.8±8.9	59.4±8.7	61±10	57.5±6.4	61.7±15.6	75±8	59±10	0.94
Gender								≤0.001
-Male	148(76)	119(74)	16(89)	5(83)	1(33)	3(100)	4(80)	
-Female	47(24)	41(26)	2(11)	1(17)	2(67)	0	1(20)	
BMI**	21.5 ±2.8	21.4±2.6	22±3.1	19.6±3.5	23.5±4.9	20.3±1.2	23.5±3.3	0.130
CTP score								≤0.001
A	116(60)	95(59)	13(72)	4(67)	2(67)	1(33.3)	-	
B	62(32)	53(33)	5(28)	2(33)	1(33)	1(33.3)	-	
C	11(6)	10(6)	0	0	0	1(33.3)	-	
BCLC staging								≤0.001
0	2(1)	2(1.3)	0	0	0	0	0	
A	25(13)	21(13)	2(11)	1(17)	0	0	1(20)	
B	85(44)	69(43)	7(39)	4(67)	2(67)	1(33.3)	2(40)	
C	65(33)	55(34)	8(44)	0	1(33)	1(33.3)	0	
D	18(9)	13(8)	1(6)	1(17)	0	1(33.3)	2(40)	
History of viral treatment								
-Yes	51(26)	115(72)	4(22)	2(33)	0	0	0	≤0.001
-No	144(74)	45(28)	14(78)	4(67)	3(100)	3(100)	5(100)	
Viral PCR								≤0.001
-Positive	114(59)	100(63)	11(61)	2(33)	0	0	0	
-Negative	81(42)	60(38)	7(39)	4(67)	3(100)	3(100)	5(100)	

CTP: ChildTurcotte Pugh, BCLC: Barcelona Clinic of Liver Cancer, PCR: Polymerase chain reaction, ($p<0.05$ wass considered significant).
*one-way analysis of variance (ANOVA) test.
**Kruskal Wallis test.

Table-2: Biochemical analysis of patients with hepatocellular carcinoma (HCC) in relation to the cause of cirrhosis.

Variable	Frequency in n(%) or Mean ± SD							
	Total	HCV	HBV	HCV/HBV	NASH	Cryptogenic	No cirrhosis	p
Haemoglobin (g/dl)*	11.6±1.9	11.7±1.8	12±2.5	11.3±1.5	11.4±2.7	10.5± 2.5	11.9±1.8	0.75
WBC (x109/L)	6.4±2.5	6.4±2.6	6.6±2.6	5.3±1.8	6.1±1	7.3±3	7.3±2	0.65
Platelets (x109/L)	155±81.8	149±78.7	177±74	124±33	145±21.7	259±120	215±153	0.05
Albumin (g/dl)*	35±6.2	35±6.4	35±5	31.2±6.6	33±2.6	32±5.6	36±5.8	0.47
Bilirubin (umol/L)	26.8±32	26.2±28	21.4±18	20±12.3	11.3±5.5	85±110	10±3.9	0.37
ALT (IU/L)	78±69.5	76±63	104±117	74±35	75.3±45	38±10.6	38±12	0.03
Alkaline phosphatase (IU/L)	306±237	299±220	359±382	239±92	243±75.1	665±387	205±108	0.62
INR	1.1±0.2	1.1±0.2	1.1±0.2	1.2±0.4	1.1±0.1	1.5±0.5	1±0	0.32
Sodium (mEq/L)	137±2.4	137±2.4	137±3.3	137±1.8	135±0.8	138±1	136±2.9	0.39
AFP	4701±29337	4624±30782	6784±45987	389±1945	1608±3217	6695±13390	177±707	0.71

HCV: Hepatitis C virus, HBV: Hepatitis B virus, NASH: Non-alcoholic steatohepatitis, WBC: White blood cell, ALT: Alanine transaminase, INR: International normalisation rate, AFP: Alpha fetoprotein, ($p<0.05$ wass considered significant).
*one-way analysis of variance (ANOVA) test.

Of the 195 patients, 148(76%) males and 47(24%) were females. The overall mean age was 59.8±8.9 years, and the mean BMI was 21.5±2.8kg/m^2. There were 187(96%) patients with cirrhosis, 183(94%) corresponded to viral HCC, 160(82%) had HCV, 18(9%) had HBV and 6(3%) had co-infection, while BMI was the highest for NASH group (Table-1). Overall, 144(74%) patients had no history of anti-viral treatment, and, among them, 97(67.4%) were actively viral PCR-positive.

Biochemical analysis across the groups was only significant for ALT, which was highest for those with HBV (Table-2).

Single lesion was the commonest finding, followed by

Table-3: Characteristics of hepatocellular carcinoma (HCC) in relation to the cause of cirrhosis.

Variable	Total	HCV	HBV	HCV/HBV	NASH	Cryptogenic	No cirrhosis	p
No of lesion(s)								≤0.001
1	87(45)	69(79)	7(8)	4(5)	2(2)	1(1)	4(5)	
2	36(19)	32(89)	3(8)	0	0	0	1(3)	
3	8(4)	7(88)	1(12)	0	0	0	0	
Multiple bilateral	64(33)	52(81)	7(11)	2(3)	1(2)	2(3)	0	
Size of the largest lesion (cm)	5.5±3.5	5.5±3.7	6.1±2.9	5.3±1.9	4.1±0.8	9.1±1.9	7.5±1.9	0.139
Portal vein thrombosis								≤0.001
Nil	153(79)	121(79)	16(10)	6(4)	3(2)	2(1)	5(3)	
Bland	10(5)	10(100)	0	0	0	0	0	
Tumour	32(16)	29(90)	2(6)	0	0	1(3)	0	
Extra-hepatic metastasis								1.00
-Lymph nodes	4(40)	2(50)	1(25)	0	1(25)	0	0	
-Adrenals	2(20)	2(100)	0	0	0	0	0	
-Lungs	2(20)	2(100)	0	0	0	0	0	
-Spleen and bones	1(10)	1(100)	0	0	0	0	0	
-Lungs and bones	1(10)	1(100)	0	0	0	0	0	

HCV: Hepatitis C virus, HBV: Hepatitis B virus, NASH: Non-alcoholic steatohepatitis. (p<0.05 was considered significant).

Table-4: Relation of viral polymerase chain reaction (PCR) and prior antiviral therapy with tumour characteristics.

	Viral PCR			Prior anti-viral therapy		
Variables	Positive (n=114)	Negative (n=81)	p	Given (n=51)	Not given (n=144)	p
BCLC			≤0.001			≤0.001
0	0	2(2)		2(4)	0	
A	15(13)	10(12)		10(20)	14(10)	
B	49(43)	36(44)		20(39)	66(46)	
C	42(37)	23(28)		16(31)	49(34)	
D	8(7)	10(12)		3(6)	15(10)	
Tumour size (cm)			0.17			0.99
1 - 5	57(50)	54(67)		33(65)	88(61)	
6 - 10	46(40)	24(30)		16(31)	45(31)	
11 - 15	10(9)	4(5)		1(2)	11(8)	
16 - 20	1(1)	0		1(2)	0	
Number of lesion(s)			≤0.001			≤0.001
1	38(33)	49(60)		28(55)	59(41)	
2	24(21)	12(15)		7(14)	29(20)	
3	7(6)	1(1)		2(4)	6(4)	
Multiple bilateral	45(39)	19(23)		14(27)	50(35)	
Portal vein thrombosis			≤0.001			≤0.001
-Bland thrombus	4(3)	7(9)		2(4)	8(6)	
-Tumour thrombus	20(17)	11(14)		11(22)	21(15)	
- No thrombus	90(79)	63(78)		38(75)	115(80)	
Extra-hepatic metastasis (n=10)	2(2)	8(10)	0.99	1(10)	9(90)	1.00

BCLC: Barcelona Clinic of Liver Cancer. (p<0.05 was considered significant).

multiple bilateral lesions (Table-3). The largest lesions with a mean of 9.1±1.9cm were found in the cryptogenic cirrhosis group, followed by those with no cirrhosis 7.5±1.9cm and HBV (6.1±2.9cm) (p>0.05). Tumour thrombus was found in 32(16%) patients and bland thrombus in 10(5%). Extra-hepatic metastasis was seen in 10(5%) patients.

The presence of viral PCR and the absence of prior anti-viral treatment were statistically related to the tumour stage (p<0.001), number of tumour nodules (p≤0.001) and vascular invasion (p≤0.001) (Table-4). No relation was found for distant metastasis and tumour size (p>0.05).

Majority of the patients were offered transarterial

chemoembolisation (TACE), followed by chemotherapy, liver transplant (LT), TACE as bridging to LT and best supportive care as treatment modalities (Figure).

Discussion

The current study highlighted the cancer burden of a single high-output specialised hospital of Pakistan over a period of one year with the available treatment facilities and the relation of tumour aggressiveness with viral PCR positivity that has not been studied by the local researchers previously.

HCC is considered one of the least curable cancers, with 564,000 new cases per year globally.[13] About 4 million people get infected with HCV yearly, whereas 240 million patients have chronic infection secondary to HBV globally.[14] Eastern Asia, European and American regions have a predominance of HBV-related HCC, whereas, in Pakistan,[15] Japan, Egypt, most of the African countries except northern Africa and the Mediterranean countries,[16] the most common aetiology for HCC is chronic HCV infection. This is substantiated by the current study. Socio-demographics, illiteracy and sharing of needles along with poor sterilisation of medical and surgical equipment are the major risk factors for the higher incidence of HCV in Pakistan and similar countries.[9]

Non-B and Non-C related HCC has been reported to be 9.68% in a study from Karachi[15] in contrast to the current study where it accounted for only 6% which is lower than many Asian and western countries.[17] Many of the developed countries are seeing a surge in NASH-related HCC, with incidence as high as 44 per 100,000 people per year,[18] depicting a state of emergency regarding obesity and MS. None of our patients had alcoholic cirrhosis. just like many studies from Pakistan,[19] probably because of the stigmata associated with the disclosure. Alcoholic cirrhosis and NASH as risk factors for HCC development have been reported to be 20% and 10-12%, respectively for the western world.[20]

Globally, men tend to be afflicted with HCC in higher percentages compared to women. The same is true for Asian countries and various studies from Pakistan confirm this relation,[9,15,19] just like the current study. But regions like Zimbabwe, Columbia, Costa Rica, Cali, Harare and southern Karachi[21] showed no gender predilection for HCC. The higher risk of exposure to alcohol, tobacco and viral infections are postulated to be the reason for male preponderance.

Majority of patients in the current study belonged to the fifth and sixth decades of life which is in accordance with many local and international studies.[9,15,19] The age distribution of HCC seems to be region-dependent, with older population seen predominantly in Japan, North America and Europe, whereas Asian and several African countries have reported HCC in the age range of 30-60 years.[22] This disparity may result from aetiology and risk factors for HCC which are different regionally and socioeconomically.

The mean BMI for the current population was 21.5±2.8 kg/m^2 and was lower than that reported by local studies.[19] A Japanese study showed a BMI of >25kg/m^2 for 39% patients with NASH-related HCC and a positive correlation of unhealthy lifestyle, obesity and MS.[23]

A study from Karachi showed that only 1.7% of HCC cases were diagnosed with CT alone and a combination of CT, AFP and histological diagnosis was required for 62.5% of the population.[9] In contrast, the current study had 96.4% cases diagnosed solely on the basis of a triphasic CECT scan, and only 3.6% required the help of a core biopsy. A descriptive study from Brazil reported 33.3% cases having been diagnosed through histology[24] although American Association for the Study of Liver Diseases (AASLD) guidelines recommend liver biopsy only in cases where two radiological modalities fail to provide a diagnosis.[11]

In the current study, 60% patients landed in CTP score A and 43.6% corresponded to tumour stage BCLC B, followed by BCLC C with a 33% correspondence. This was in contrast to similar studies from Pakistan which had a predominant population with decompensated cirrhosis and subsequently, higher BCLC stage with poor survival outcomes.[15,25] The findings of the current study, however, are in accordance with one study.[23] The present study also reported 14% HCC cases landing in the definitive curative group and almost all belonging to the viral HCC category, which is higher than any of the local studies.[25] This highlights the importance of a successful surveillance campaign. Also, 56% of our patients had more than one tumour nodule in their livers, which was in accordance with a similar study.[9]

A meta-analysis disclosed racial disparity regarding the stage of presentation being late, standard of care offered and consequently the survival rates being much lower for the black population compared to the whites.[26]

Larger lesions were found associated with non-viral HCC and HBV-infected patients in the present study with vascular invasion and distant metastasis common for the viral HCC; just like some previous studies.[19,22,27] The larger non-viral HCC lesion could be because of the late presentation of such patients as surveillance ultrasounds

are frequently offered to the viral infected patients, ignoring NASH and NAFLD patients.

No statistical relation was found between the baseline laboratory investigations and AFP levels for the different aetiologies except platelets and ALT, with low platelet counts for viral HCC and higher ALT levels for HBV-associated HCC in the current study. The findings are in accordance with previous studies.[19,24]

The present study showed a statistically significant relation between tumour aggressiveness in terms of stage at presentation, number of tumour nodules and vascular invasion, with the presence of viral DNA/RNA and lack of anti-viral nucleoside analogues (NAs) and directly acting anti-viral (DAA) treatment. This relation has also been studied earlier, concluding that HCV-positive patients who achieved sustained virological response (SVR) had a significantly reduced HCC risk, and even among those who developed HCC, the tumour stage, progression and response to therapy were better compared to those with positive PCR and no history of DAAs.[28] Furthermore, serologically-negative patients whose liver biopsy samples demonstrated viral markers were at a higher risk of a more aggressive tumour course. One research explored the same phenomenon in chronically infected HBV patients in a large cohort of 5908 patients who were followed up over time.[29] This relation has not been studied by any local research.

In the current study, 32% patients were amenable to curative therapy, which was higher than a similar epidemiological study from Pakistan.[9] A study reported an even lower percentage of 13.5% for patients who were offered definitive curative treatments.[19] The same study reported TACE for 61.7% of the patients which was higher than any of the locally reported data.[19] Only 5% of our patients underwent resection, and the lesser numbers are supported by local studies[9,15] with the main reasons being lack of expertise, late presentation, larger lesions and poor performance status due to poor nutrition. A Japanese study reported 20.3% resection and 20% ablation rate which is directly proportional to the widespread surveillance programmes and early detection of small-sized tumours.[23] A study from Brazil reported 77.5% curative treatment modalities, including resection, LT and percutaneous ethanol injection (PEI), being utilised, which is the highest for anywhere in the world.[24] The greatest hurdle in providing prompt and effective therapy for many developing and some of the developed countries is the socioeconomic difference, with racial disparity being an alarming observation in the modern era.[27]

The current study has many limitations, including its a single-centre, cross-sectional approach which might not be the true representative of the country's population. Survival rate and response rate to therapy were also not studied. The strict exclusion criteria might have led to sample bias as well.

Due to the lack of an organised nationwide cancer registry, disparity within the local data was obvious. A collaborative multi-centre study with extensive follow-up is essential in order to know the tumour behaviour for the local population.

Conclusion

Viral HCC, like many developing countries, was found to be the commonest aetiology for the study population. The diagnosis was often late, patients presented with advanced tumours and there was little hope for curative therapy. Treatment modalities are expensive and expertise is lacking. Viral PCR positivity and the association of its impact on the aggressiveness of HCC, despite the widespread availability of highly effective DAAs and NAs, was something alarming.

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References

1. Giannitrapani L, Zerbo M, Amodeo S, Pipitone E, Galia M, Li Cavoli TV et al. The changing epidemiology of hepatocellular carcinoma : Experience of a single center. Biomed Res Int. 2020; 2020:5309307.
2. Arabsalmani M, Mirzaei M, Soroush A, Towhidi F, Salehiniya H. Incidence and mortality of liver cancer and their relationship with the human development index in the world. Biomed. Res. Ther.2016; 3:800-7.
3. Yang L, Parkin DM, Ferlay J, Li L, Chen Y. Estimates of cancer incidence in China for 2000 and projections for 2005. Cancer Epidemiol Biomarkers Prev. 2005; 14:243-50.
4. Ryerson A, Eheman C, Altekruse S, Ward J, Jemal A, Sherman R, et al. Annual report to the nation on the status of cancer, 1975-2012, featuring the increasing incidence of liver cancer. Cancer. 2016; 122:1312-37.
5. Bosetti C, Turati F, La Vecchia C. Hepatocellular carcinoma epidemiology. Best Pract Res Clin Gastroenterol.2014; 28:753-70.
6. McGlynn K, Petrick J, London W. Global Epidemiology of Hepatocellular Carcinoma. Clin Liver Dis. 2015; 19:223-38.
7. Welzel T, Graubard B, Quraishi S, Zeuzem S, Davila J, El-Serag H, et al. Population-attributable fractions of risk factors for hepatocellular carcinoma in the United States. Am J Gastroenterol. 2013; 108:1314-21.
8. Jones P, Diaz C, Wang D, Gonzalez-Diaz J, Martin P, Kobetz E. The Impact of Race on Survival after Hepatocellular Carcinoma in a Diverse American Population. Dig Dis Sci. 2018; 63:515-28.
9. Hafeez Bhatti A, Dar F, Waheed A, Shafique K, Sultan F, Shah N. Hepatocellular Carcinoma in Pakistan: National Trends and Global Perspective. Gastroent Res Pract. 2016; 2016:1-10.

10. Yang J, Hainaut P, Gores G, Amadou A, Plymoth A, Roberts L. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol. 2019; 16:589-604.
11. Chalasani N, Younossi Z, Lavine J, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2017; 67:328-57.
12. Marrero J, Kulik L, Sirlin C, Zhu A, Finn R, Abecassis M, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018; 68:723-50.
13. Parkin D, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin.2005; 55:74-108.
14. Hepatitis C. World Health Organization [Online] 2020 [Cited 28 May 2020]. Available from: URL: http://www.who.int/mediacentre/factsheets/fs164/en/index.html
15. Munaf A, Memon M, Kumar P, Ahmed S, Kumar M. Comparison of Viral Hepatitis-Associated Hepatocellular Carcinoma Due to HBV and HCV - Cohort from Liver Clinics in Pakistan. Asian Pac J Cancer Prev. 2014; 15:7563-7.
16. Franceschi S, Raza S. Epidemiology and prevention of hepatocellular carcinoma. Cancer Lett. 2009; 286:5-8.
17. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology. 2005; 42:1208-36.
18. Younossi Z, Koenig A, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of non-alcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016; 64: 73-84.
19. Butt A, Hamid S, Wadalawala A, Ghufran M, Javed A, Farooq O, et al. Hepatocellular carcinoma in Native South Asian Pakistani population; trends, clinico-pathological characteristics & differences in viral marker negative & viral-hepatocellular carcinoma. BMC Res Notes. 2013; 6:137.
20. Galle P, Forner A, Llovet J, Mazzaferro V, Piscaglia F, Raoul J, et al. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018; 69:182-236.
21. McGlynn K, London W. The Global Epidemiology of Hepatocellular Carcinoma: Present and Future. Clin Liver Dis. 2011; 15:223-43.
22. Yang J, Hainaut P, Gores G, Amadou A, Plymoth A, Roberts L. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol. 2019; 16:589-604.
23. Tateishi R, Okanoue T, Fujiwara N, Okita K, Kiyosawa K, Omata M, et al. Clinical characteristics, treatment, and prognosis of non-B, non-C hepatocellular carcinoma: a large retrospective multicenter cohort study. J. Gastroenterol. 2014; 50:350-60.
24. Paranaguá-Vezozzo D, Ono S, Alvarado-Mora M, Farias A, Cunha-Silva M, França J, et al. Epidemiology of HCC in Brazil: Incidence and risk factors in a ten-year cohort. Ann Hepatol. 2014; 13:386-93.
25. Yusuf M, Badar F, Meerza F, Khokar R, Ali F, Sarwar S,et al. Survival from hepatocellular carcinoma at a cancer hospital in Pakistan. Asian Pac J Cancer Prev. 2007; 8:272-4.
26. Franco R, Fan Y, Jarosek S, Bae S, Galbraith J. Racial and Geographic Disparities in Hepatocellular Carcinoma Outcomes. Am J Prev Med. 2018; 55:S40-8.
27. Hatanaka K, Kudo M, Fukunaga T, Ueshima K, Chung H, Minami Y, et al. Clinical Characteristics of NonBNonC- HCC: Comparison with HBV and HCV Related HCC. Intervirology. 2006; 50:24-31.
28. D'Ambrosio R, Della Corte C, Colombo M. Hepatocellular Carcinoma in Patients with a Sustained Response to Anti-Hepatitis C. Int J Mol Sci. 2015; 16:19698-712.
29. Lin D, Yang H, Nguyen N, Hoang J, Kim Y, Vu V, et al. Reduction of chronic hepatitis B-related hepatocellular carcinoma with anti-viral therapy, including low risk patients. Aliment Pharmacol Ther. 2016; 44:846-55.