Role of Triphasic Computed Tomography in Hepatitis C Patients after Treatment by Direct Acting Antivirals to Detect Hepatocellular Carcinoma

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Abstract

Background: Hepatocellular carcinoma (HCC) is one of the most prevalent neoplasms worldwide which is considered as significant causing of mortality over the past 2 decades. HCC usually progresses in cases with chronic liver diseases, often related to hepatitis C virus (HCV) infection. The goal of the study was to detect of the risk of occurrence of Hepatocellular carcinoma in HCV positive patients after treatment by direct acting antivirals (DAA).

Results: The higher patient age, higher AFP, also the longer duration since last dose of treatment, liver cirrhosis and liver size were significantly correlated with HCC positive cases. By applying multivariate logistic regression on the statistically significant predictors in univariance for HCC development, age above 57 years and AFP >12.5ng\ml were the independent predictors for HCC development.

Conclusion: Triphasic CT is considered the ideal screening examination for the entire abdomen and pelvis. It is considered the most diagnostic CT examination for hepatic tumors such as HCC.

Keywords: HCC, HCV, Triphasic CT, Hepatocellular carcinoma, Computed tomography, serum alpha-fetoprotein.

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1. Introduction

Hepatitis C virus (HCV) is the causative agent for chronic hepatitis-C characterized by necrosis-associated with inflammation targeting liver causing cirrhosis which may lead to hepatocellular carcinoma (HCC) [1]. So HCV infection is a major cause of chronic hepatitis, which leads to cirrhosis and HCC [2].

Despite the advancement of medications, the incidence of HCC caused by HCV still high. The cases with HCV-sustained viral activity had reduced progression into HCC but cases with advanced cirrhosis and fibrosis still had a high risk for HCC [3].

Liver ultrasound evaluation with computed tomography (CT) and serum alpha-fetoprotein (AFP) level were crucial for cases with HCV. CT has a higher specificity and sensitivity than AFP with ability to detect small lesions up to 0.5-1 cm in diameter. Ultrasonography is essential before HCR treatment with assessment after completion by 12 weeks, and at 24-week intervals after that. Nowadays, computed tomography (CT) scan is considered as a promising screening tools [3].

The typical radiological HCC pattern on triphasic CT is characterized by elevated contrast enhancement of the focal lesion occurring during the arterial phase of examination (wash-in) and contrast wash-out of the focal lesion occurring during the portal/venous and late equilibrium phases [4].

During and after the antiviral therapy, the cases with hepatic cirrhosis should be monitored, except cases with kidney disfunction, and severe hepatic impairment, such as cases with residual HCC and decompensated cirrhosis [5].

The present study aimed to detect of the risk of occurrence of HCC in HCV positive cases after treatment by DAA.

2. Subjects and Methods:

This prospective cross-section study was conducted on 71 patients (56 males and 15 females) with age range from 40 to 71 years and a mean age of 55.08 ± 9.21 years. These patients were referred to the Radiodiagnosis Department at Zagazig University Hospitals to perform triphasic CT studies after completion of HCV treatment.

Cases with the following characteristics were included in the study; positive HCV antibody patients regardless the level of viral replication, treatment by direct acting antivirals within 2 years, and all age and sex groups.

The exclusion criteria included patients with severe liver dysfunction as decompensated cirrhosis or HCC, patients unfit for dynamic CT examination such as patients with severe renal impairment, allergy to contrast media, and patients refuse to complete the study.

All cases were subjected to complete history taking: including age, sex and excluding any contraindications to triphasic CT, informed consent from all patients participating in the study, laboratory assessment of liver and renal function tests, serum alpha-

fetoprotein (AFP), and triphasic CT examination.

All submitted patients had dynamic CT examinations of the liver on 128 multidetector CT machine performed with (ingenuity, Philips healthcare, veenluis, Best, Netherlands). The scanning parameters of CT were as follows: 120 Kvp, 250 mAs, section collimation of 2.5-5.0 mm, an image thickness of 5mm, reconstruction interval of 5.0 mm, a pitch of 3 (in the scanner's {HQ} high quality mode), and table speed per rotation of 15 mm/0.8 sec during a single breath-hold.

Cases were fasting for six hours before exam. The radiologist was informed about medications used, allergies to contrast material, and recent illnesses or other medical conditions such as diabetes and kidney disease.

The scan was acquired with the patients in supine position. A 20-gauge plastic intravenous catheter was placed in an ante cubital vein. The line was then connected to a power injector through which 150 mL of (Ultravist 300, Schering Pharmaceutical Ltd, Guangzhou, China) was injected IV at a rate of 4 mL/sec. Precontrast, late arterial, porto-venous and delayed phases were carried out during a single breath-hold. Late arterial phase began at 30 seconds after starting of the contrast injection then the portal and delayed phases began 75 and 180 seconds after initiation of the contrast injection, respectively. The entire liver was scanned in a cephalad-to-caudad direction.

The findings were evaluated by the examination included: the liver size and texture, PV patency and newly developed lesions. Presence or absence of enlarged porta-hepatis lymph nodes. Presence or absence of intra-hepatic biliary dilatation. Assessment of spleen, pancreas, abdominal lymph nodes and ascites if present.

The assessment of the target lesion (if present) regarding: size in the two maximum dimensions, enhancement pattern. When the examination was completed, the patient was asked to wait until the images were verified to be of high quality enough for accurate interpretation. The axial raw data images were processed on a dedicated image processing workstation (Philips, extended brilliance workstation v5.0.2.10010) for multiplanar reformations.

3. Results:

The present study included 71 patients (56 males "78.9%" and 15 females "21.1%") with male to female ratio = 4 :1. Age range: 40-71 years, and a mean age: 55.08 ± 9.21years. On the clinical evaluation of the seventy-one enrolled patients, the mean of month since the last-received dose of anti-viral therapy was 10.71 ± 6.45. On laboratory evaluation of AFP, AFP was distributed as 21.43±25.02 (Table 1).

On Radiological evaluation of the submitted patients, 74.6% had cirrhotic liver and 60.4% had enlarged liver. Enlarged spleen was in 71.8% and 4.2% had removed spleen surgically. 16.9% had PV thrombus. 56.3% had no ascites, 43.7% had ascites and 25.4% had enlarged lymph node About 64.8% of the studied group had hepatic focal lesion and majority were in right lobe,

single were 21 cases and multiple were 25 cases (Table 2).

According to Couinaud classification, the majority of hepatic focals were in segments VII &VIII with 19.7% &16.9%, respectively (Table 3).

On Triphasic CT pattern of included patients. Regarding the enhancement pattern of hepatic focals, 64.8% had enhancement at arterial phase, washout at Porto-venous and delayed phases (Table 4)

On triphasic CT characters we get a ratio between positive and negative criteria of HCC 64.8 % & 35.2% respectively. During our radiological study on submitted patients we found that 12.7% had incidentally other non-HCC focal lesions intra-hepatic or extra-hepatic including regenerative nodules, splenic hemangioma, adrenal metastasis, hepatic hemangioma & pancreatitis (Table 5).

According to previous data, the higher patient age, higher AFP, also the longer duration since last dose of treatment, liver cirrhosis and liver size were significantly associated with HCC positive cases (Table 6)

By applying multivariate logistic regression on the statistically significant predictors in univariance for HCC development, age above 57 years and AFP >12.5ng\ml were the independent predictors for HCC development (Table 7).

Table 1. Demographic, Last dose received of HCV TTT, and AFP distribution among studied group (N=71):

		N	%
Sex	**Female**	**15**	**21.1**
	Male	**56**	**78.9**
Age			
Mean ± SD		**55.08 ± 9.21**	
Last dose received of HCV TTT/MONTH			
Mean ± SD		**10.71 ± 6.45**	
AFP			
Mean ± SD		**21.43±25.02**	

Table 2. CT characters and focal distribution among studied group (N=71):

		N	%
Liver cirrhosis	Cirrhotic	53	74.6
	Non cirrhotic	18	25.4
Liver size	Average	28	39.4
	Mild enlarged	20	28.1
	Moderate Enlarged	23	32.3
Spleen size	Average	17	23.9
	Mild enlarged	12	16.9
	Moderate enlarged	3	4.2
	Marked Enlarged	36	50.7
	Surgically removed	3	4.2
Portal vein patency	Patent	59	83.1
	Thrombus	12	16.9
Ascites	No	40	56.3
	Mild	19	26.7
	Mild to moderate	3	4.2
	Moderate	3	4.2
	Marked	3	4.2
	Massive	3	4.2
Enlarged lymph nodes	No	53	74.6
	Yes	18	25.4
Hepatic lesion or not	No	25	35.2
	Yes	46	64.8
Site of hepatic lesion	No	25	35.2
	Rt lobe	22	30.9
	Lt lobe	5	7.0
	Both lobes	14	19.6
	Lt lobe & caudate	2	2.8
	Rt &Lt& caudate lobes	3	4.2
Number of lesions	No	25	35.2
	Single	21	29.6
	Multiple	25	35.2

Table 3. Focals distribution among studied group in hepatic segments (N=46) (cases may overlapped):

		N	%
Liver segmentation of hepatic lesions	all segments	3	6.5
	II	9	19.5
	III	7	15.2
	IV	9	19.5
	V	5	10.8
	VI	9	19.5
	VII	14	30.4
	VIII	12	26.0

Table 4. Triphasic CT characters suggested HCC:

		N	%
Arterial phase	Poor enhancement	21	29.6
	Good enhancement	25	35.2
Porto-venous phase	Washout	46	64.8
Delayed phase	Washout	46	64.8
	Total	46	100.0

Table 5. HCC and other non-HCC focal lesions diagnosed by Triphasic CT:

		N	%
HCC	-VE	25	35.2
	+VE	46	64.8
Other focal lesions	No	62	87.3
	Yes	9	12.7

Table 6. Relation between HCC development and positive criteria:

			HCC (n= 46)	NO (n= 25)	t/Mann Whitney/ Fisher	X^2	P
Age			61.06±8.12	52.34±8.6	2.98		0.006*
AFP			29.22±23.85	9.25±2.36			
					3.187		0.001**
			18.0 (6-150)	9.0 (5-13)			
Last dose received of HCV TTT\month			12.51±4.23	9.72±3.21	2.312		0.038*
Sex	Female	N	10	5			
		%	21.8%	20.0%	0.028		0.85
	Male	N	36	20			
		%	78.2%	80.0%			
Liver cirrhosis	Non-Cirrhotic	N	7	11			
		%	15.3%	44.0%	7.95		0.007*
	Cirrhotic	N	39	14			
		%	84.7%	56.0%			
Liver size	Average	N	19	9			
		%	41.3%	36.0%	12.84		0.0016*
	Mild enlarged	N	7	13			
		%	15.3%	52.0%			

	Enlarged	N	20	3			
		%	43.4%	12.0%			
Spleen size	Average	N	10	7			
		%	21.8%	28.0%			
	Mild enlarged	N	12	0			
		%	26.1%	0.0%			
	Moderate enlarged	N	0	3	8.41	0.07	
		%	0.0%	12.0%			
	Enlarged	N	23	13			
		%	50.0%	52.0%			
	Surgically removed	N	1	2			
		%	2.1%	8.0%			
Ascites	No	N	20	20			
		%	43.4%	80.0%			
	Mild	N	15	4			
		%	32.6%	16.0%			
	Mild to moderate	N	2	1			
		%	4.3%	4.0%	5.96	0.31	
	Moderate	N	3	0			
		%	6.5%	0.0%			
	Marked	N	3	0			
		%	6.5%	0.0%			
	Massive	N	3	0			
		%	6.5%	0.0%			

Table 7. Multivariate logistic regression for independent predictors of HCC:

	Wald	P	OR	95% C. I	
				Lower	Upper
Age > 57 years	4.436	0.035*	1.516	1.008	1.935
Last dose received of HCV treatment >10.5 months	0.165	0.685	1.025	0.910	1.154
AFP >12.5 ng\ml	3.845	0.041*	1.999	1.108	7.532
Liver cirrhosis	1.896	0.169	6.723	0.446	101.275
Liver size	1.524	0.189	2.141	0.854	5.231

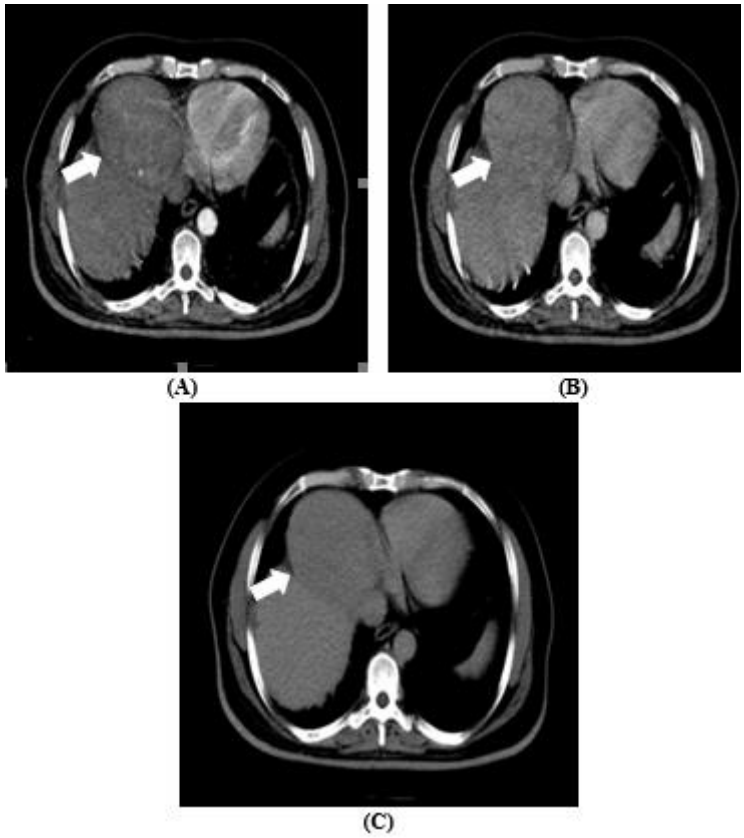

Fig.1. A male patient 62 years old with history of positive HCV antibody and finished DAAs treatment within 3 months before triphasic CT scan. Now he complains upper abdominal pain. The lesion shows homogenous faint enhancement at arterial phase (arrow in image A), and washout in subsequent phases (arrow in images B&C respectively). Portal Vein is good enhanced with no signs of portal vein thrombosis. Spleen is mild enlarged. No ascites is seen.

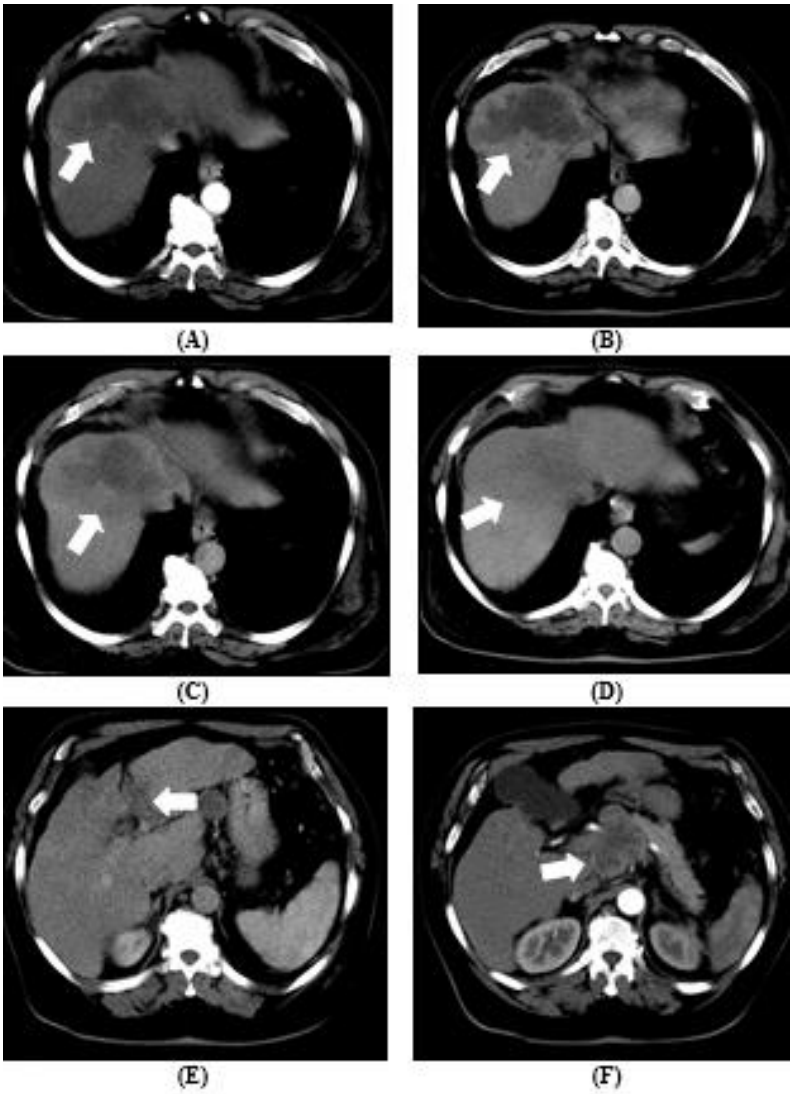

Fig. 2. A male patient 66 years old with history of positive HCV antibody and received DAAs treatment 2 years ago. Now his complain is upper abdominal pain, jaundice and weight loss.

Liver is mildly enlarged with coarse heterogeneous density and irregular contour. There are multiple well-defined variable sized hypodense focal lesions scattered mainly at the left lobe and right lobe, where the largest is noted at segment IVa and VIII showing central area of cystic breakdown and degeneration, all of them shows rapid heterogenous arterial enhancement (Image A) with rapid wash out of contrast at both Porto venous and delayed phases (Images B, C and D). Main Portal vein is dilated and patent as well as dilated patent RT PV while left PV is totally occluded by hypodense thrombus (Image E). Multiple enlarged porta hepatis lymph nodes (image F). No ascites is seen

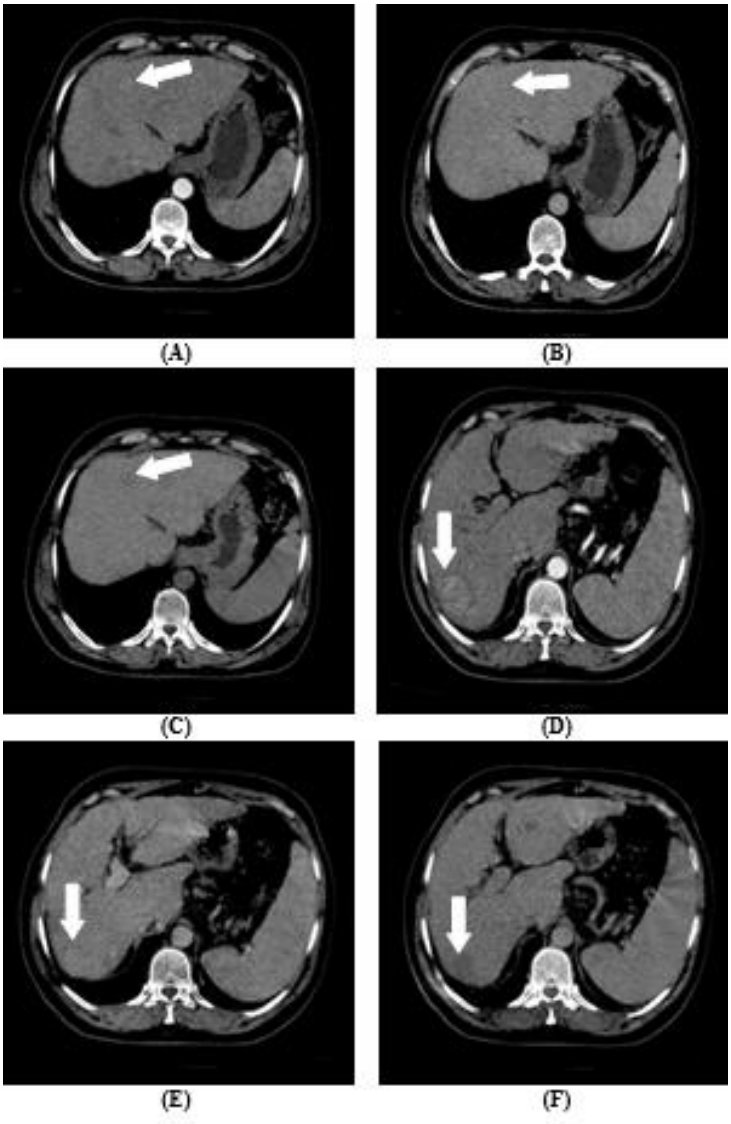

Fig. 3. A male patient 58 years old with history of positive HCV antibody and received DAAs treatment 18 months ago. He presented by abdominal discomfort and weight loss. Liver is average sized, coarse cirrhotic density with irregular wavy border. There are multiple variable sized hypodense focal lesions scattered at the RT lobe, a small lesion is noted at segment VIII measuring 16x14mm, shows arterial enhancement at arterial phase (arrow in image A) and appreciated washout mainly in delayed phase (arrows in images B &C). The largest one of the focal lesions is noted in segment VI measuring 35x33mm, it shows a homogenous enhancement at the arterial phase (arrow in image D), with early washout of contrast in porto-venous and delayed phases (arrows in images E&F respectively). Portal vein is patent and of average caliber with no evidence of PV thrombosis.

No ascites. Enlarged spleen.

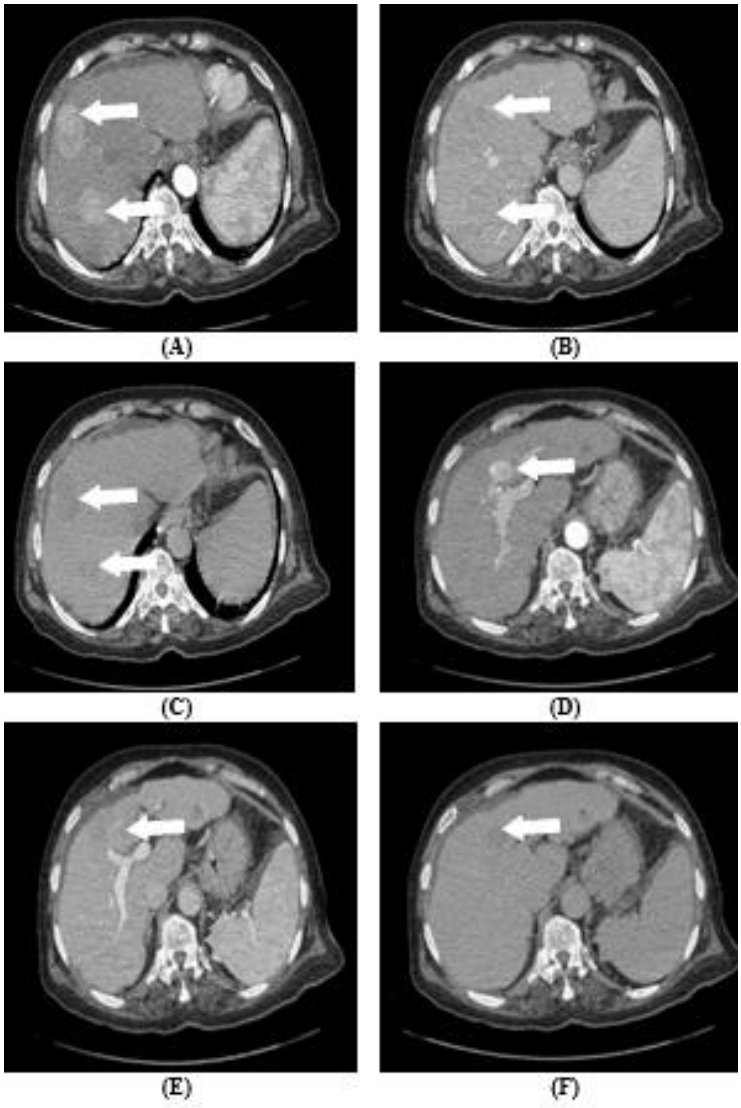

Fig. 4. A female patient 55 years old with history of positive HCV antibody and received DAAs treatment 7 months ago. She presented by abdominal pain and weight loss. Liver shows mild increase in size, cirrhotic pattern, and irregular contour with volume re-distribution in the form of prominent caudate and left lobes. There are multiple variable sized well defined rounded shaped hypodense hepatic focal lesions in the pre contrast study ranging from 25 to 50 mm, seen scattered at the right lobe and left lobe (segments IV, VII, & VIII); the largest one is seen at segment VIII measuring about 50 X 40 mm and show notable enhancement at the arterial phase (arrow in image A) with rapid washout at the portal and delayed phases (arrows in images B&C respectively), another lesion is seen in segment IV shows enhancement at the arterial phase (arrow in image D) with rapid washout at the portal and delayed phase (arrows in images E&F respectively). Normally enhanced main portal vein & its branches. Spleen is enlarged in size. Mild ascites is seen.

4. Discussion

Our inclusion criteria differed from Nahon et al., [6] who included patients age older than 18 years old with absent previous complications of cirrhosis. Our study and Nahon et al., [6] shared in excluding patients with previous HCC, In controversy to Kinoshita et al., [7] who incorporated patients with successful RFA treatment for hepatitis-C related HCC.

Our study was done on 56 males and 15 females with male predominance four times more than female. From all patients' number (n=71), there were 36 males (78.2%) and 10 females (21.8%) who developed HCC.

Although Ringelhan et al., [8] stated that well-known cofactors for HCC development are male gender, there was no significant relation between patient sex and HCC development in HCV patients received DAA in our study.

Other factors mentioned by Ringelhan et al., [8] that linked to pathogenesis of HCC were old age (greater than 40 years old), alcohol consuming, smoking, infection duration, co-infection with HBV/HCV, HIV or HDV. Also, Cucchetti et al., [9] said that at diagnosis of HCC the mean age was 62.8 years.

This endorsed our study as we considered age above 57 years old as an independent predictor for the development of HCC in HCV positive patients.

A recent report revealed that cases with liver cirrhosis treated with DAA had promoted HCC occurrence. HCV-related cirrhosis had annual risk for HCC by 2-8%. Conti et al., [1] assumed that HCC development rate was up to 3% after 6 months of DAA treatment. Also, Nakao et al., [10] reported that HCC incidences was 1.7% after 1 year and 7% after 2 years of treatment with DAA.

We found that 46 out of 71 patients who received DAAs treatment developed HCC while in Nahon et al., [6] the number of patients who developed HCC was 15 of 336 of patients who received DAAs treatment.

Also, Conti et al., [1] in Italy reported that 3.2% of 285 cirrhotic cases progressed HCC after 24 weeks of starting IFN-free DAAs treatment.

This variance may be attributed to our small sample size relative to other studies in addition to inclusion of patients who were referred to our hospital due to hepatic complaint. Our study was not a survey study for all patients received DAA.

Kinoshita et al., [7] who included cases with previous treatment of HCC, stated that the recurrence rates are seemed higher, probably because majority of the patients underwent multiple treatments for tumor recurrence before the initiation of DAA treatments.

So prospective wide scale study on patients received DAA is recommended to detect the actual incidence of HCC occurrence after DAA therapy.

The mean of months since the last-received dose of anti-viral therapy was 10.71 ± 6.45 months and the median time between DAA treatment and HCC development is 12 months which is close to Singal et al., [11] that stated the median time of developing HCC after DAA treatment was 13.2 months.

Serum alpha fetoprotein (AFP) is considered as an main tumor biomarker of liver disease and a predictive marker for HCC development for cases with cirrhosis [12].

HCC produces AFP in 60-75% of patients as well as other serum proteins. However, this is an insensitive parameter because alpha-fetoprotein (AFP) is normal in more than one third of cases of HCC [13].

In this study AFP distributed as 21.43±25.02 with median of 13 and minimum 5 ng\ml and maximum 150 ng/ml. 35 patients in our study had serum AFP within normal range (between 10 ng\ml and 20 ng\ml) and developed HCC after DAA treatment.

It also found that AFP test has a high false positive rate about 20-50% in cases with liver cirrhosis and 20% with CHC [12].

At multivariate analysis in our study, serum AFP > 12.5 ng\ml (p= 0.041, OR: 1.999, 95% CI: 1.108-7.532) was an independent predictor for HCC development. As in Guarino et al., [14] said that one of several risk factors that had been identified for HCC occurrence after DAA treatment was higher AFP levels.

In this study we found that the risk of HCC is increased in cirrhotic patients (84.7%) than the non-cirrhotic patients (15.3%) (p=0.007) which is matched with Hsu et al., [15] who said the risk of HCC was more than four times fold higher in cirrhotic patients than those without cirrhosis.

According to Couinaud classification, the majority of hepatic focals in this study were in segments VII &VIII with 19.7% &16.9% of 71 patients, respectively more than other segments.

HCC diagnosis in our study was based on triphasic CT pattern of the hepatic lesion (arterial enhancement, porto-venous and delayed washout) because HCC derives its blood supply from the hepatic artery which is matched with Nahon et al., [6] who reported that HCC diagnosis was evaluated with histopathological examination or based on noninvasive criteria mainly dynamic imaging which considered non-invasive tool revealing portal washout and early arterial hypervascularization.

Nahon et al., found that portal invasion occurred in 2 of 336 patients who received DAAs treatment while in our study we found that portal invasion occurred in 12 of 71 patients (16.9%) who received DAAs treatment [6].

During our radiological study on submitted patients we found that 12.7% had incidentally other non-HCC focal lesions intra-hepatic or extra-hepatic including hepatic hemangioma, hepatic cyst, hepatic regenerative nodules, splenic hemangioma, adrenal metastasis, & pancreatitis.

The HCC had a significant unpredictable increased incidences under and after cirrhosis treatment with DAA, these findings considered alarming reports [6].

Short length follow up in our study as it was done within 2 years after complete treatment by DAAs is matched with Nahon et al., [6] who said that his study also had limitations including follow-up length, and time periods. Also, Emamaullee et al., were collected their data between 2015 and 2017 with a minimum of 2 years of follow-up [16].

Early screening of patients six months before DAA start and no detectable nodule were factors indicate decreased HCC incidence compared to other DAA cases as explained by previous study [6].

5. Conclusion:

Triphasic CT is considered the ideal screening examination for the entire abdomen and pelvis. It is considered the most diagnostic CT examination for hepatic tumors such as HCC.

Conflict of Interest: None

Abbreviations

AFP: Alpha-fetoprotein

CHC: Chronic hepatitis C virus

CT: Computed tomography

DAA: Direct-acting antiviral

HCC: Hepatocellular carcinoma

HCV: Hepatitis C virus

References

[1] Conti F, Buonfiglioli F, Scuteri A, Crespi C, Bolondi L, Caraceni P, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol 2016;65:727–33. https://doi.org/10.1016/j.jhep.2016.06.015.

[2] Kogiso T, Sagawa T, Kodama K, Taniai M, Katagiri S, Egawa H, et al. Hepatocellular carcinoma after direct-acting antiviral drug treatment in patients with hepatitis C virus. JGH Open Open Access J Gastroenterol Hepatol 2019;3:52–60. https://doi.org/10.1002/jgh3.12105.

[3] Axley P, Ahmed Z, Ravi S, Singal AK. Hepatitis C Virus and Hepatocellular Carcinoma: A Narrative Review. J Clin Transl Hepatol 2018;6:79–84. https://doi.org/10.14218/JCTH.2017.00067.

[4] Iavarone M, Viganò M, Piazza N, Occhipinti V, Sangiovanni A,

Maggioni M, et al. Contrast imaging techniques to diagnose hepatocellular carcinoma in cirrhotics outside regular surveillance. Ann Hepatol 2019;18:318–24. https://doi.org/10.1016/j.aohep.2018.09.002.

[5] Innes H, Barclay ST, Hayes PC, Fraser A, Dillon JF, Stanley A, et al. The risk of hepatocellular carcinoma in cirrhotic patients with hepatitis C and sustained viral response: Role of the treatment regimen. J Hepatol 2018;68:646–54. https://doi.org/10.1016/j.jhep.2017.10.033.

[6] Nahon P, Layese R, Bourcier V, Cagnot C, Marcellin P, Guyader D, et al. Incidence of Hepatocellular Carcinoma After Direct Antiviral Therapy for HCV in Patients With Cirrhosis Included in Surveillance Programs. Gastroenterology 2018;155:1436-1450.e6. https://doi.org/10.1053/j.gastro.2018.07.015.

[7] Nishibatake Kinoshita M, Minami T, Tateishi R, Wake T, Nakagomi R, Fujiwara N, et al. Impact of direct-acting antivirals on early recurrence of HCV-related HCC: Comparison with interferon-based therapy. J Hepatol 2019;70:78–86. https://doi.org/10.1016/j.jhep.2018.09.029.

[8] Ringelhan M, McKeating JA, Protzer U. Viral hepatitis and liver cancer. Philos Trans R Soc Lond B Biol Sci 2017;372:20160274. https://doi.org/10.1098/rstb.2016.0274.

[9] Cucchetti A, D'Amico G, Trevisani F, Morelli MC, Vitale A, Pinna AD, et al. Effect of direct-acting antivirals on future occurrence of hepatocellular carcinoma in compensated cirrhotic patients. Dig Liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver 2018;50:156–62. https://doi.org/10.1016/j.dld.2017.10.004.

[10] Nakao Y, Hashimoto S, Abiru S, Komori A, Yamasaki K, Nagaoka S, et al. Rapidly growing, moderately differentiated HCC: A clinicopathological characteristic of HCC occurrence after IFN-free DAA therapy? J Hepatol 2018;68:854–5. https://doi.org/10.1016/j.jhep.2017.11.011.

[11] Singal AG, Rich NE, Mehta N, Branch A, Pillai A, Hoteit M, et al. Direct-Acting Antiviral Therapy Not Associated With Recurrence of Hepatocellular Carcinoma in a Multicenter North American Cohort Study. Gastroenterology 2019;156:1683-1692.e1. https://doi.org/10.1053/j.gastro.2019.01.027.

[12] Emokpae MA, Adejumol BG, Abdu A, Sadiq NM. Serum alpha-fetoprotein level is higher in hepatitis C than hepatitis B infected chronic liver disease patients. Niger Med J J Niger Med Assoc 2013;54:426–9. https://doi.org/10.4103/0300-1652.126302.

[13] Yang Y, Nagano H, Ota H, Morimoto O, Nakamura M, Wada H, et al. Patterns and clinicopathologic features of extrahepatic recurrence of hepatocellular carcinoma after curative resection. Surgery 2007;141:196–202. https://doi.org/10.1016/j.surg.2006.06.033.

[14] Guarino M, Sessa A, Cossiga V, Morando F, Caporaso N, Morisco F, et al. Direct-acting antivirals and hepatocellular carcinoma in chronic hepatitis C: A few lights and many shadows. World J Gastroenterol

2018;24:2582–95. https://doi.org/10.3748/wjg.v24.i24.2582.

[15] Hsu S-J, Yang S-S, Kao J-H. Risk of hepatocellular carcinoma development after hepatitis C virus eradicated by direct-acting antivirals: Fact or fiction? J Formos Med Assoc Taiwan Yi Zhi 2020;119:3–11. https://doi.org/10.1016/j.jfma.2019.09.006.

[16] Emamaullee JA, Bral M, Meeberg G, Montano-Loza AJ, Bain VG, Burak KW, et al. HCV Eradication with Direct-Acting Antivirals Does Not Impact HCC Progression on the Waiting List or HCC Recurrence after Liver Transplantation. Can J Gastroenterol Hepatol 2019;2019:2509059. https://doi.org/10.1155/2019/2509059.

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