

DIAGNOSTIC ACCURACY OF DOPPLER ULTRASOUND IN DETECTION OF PORTAL VEIN THROMBOSIS IN HEPATOCELLULAR CARCINOMA

Mehreen Samad¹, Rabia Shah¹, Mahnoor Rehman Khan¹, Maimoona Afsar¹, Ghazala Wahid¹, Naila Tamkeen¹

ABSTRACT

Objective: To determine diagnostic accuracy of Doppler ultrasound in detection of portal vein thrombosis in hepatocellular carcinoma keeping findings on multi-detector Computed tomography as the gold standard.

Methods: A cross-sectional study was conducted at Radiology Department, Hayatabad Medical Complex, and Peshawar from November 2019 to April 2020. 129 known cases of hepatocellular carcinoma were subjected to Doppler ultrasound to detect portal vein thrombus. Thrombus detected was carefully examined for internal color signals. After that all patients were subjected to multi-detector computed tomography to detect the presence or absence of portal vein thrombus.

Results: The mean age of patients in our study was 56 ±8 years. The frequency of portal vein thrombosis in patients with hepatocellular carcinoma was 28%. Color Doppler sonography had 89.3% sensitivity and 95.8% specificity in detection of portal vein thrombosis in comparison with multidetector computed tomography. For the detection of arterial flow in the thrombus (malignant thrombus) its sensitivity and specificity were 80.7% and 100% respectively.

Conclusion: Color Doppler sonography is an effective, non-invasive and radiation free method in detecting and evaluating the nature of portal vein thrombosis in HCC.

Key words: Doppler sonography, hepatocellular carcinoma, multidetector computed tomography, portal venous thrombosis

INTRODUCTION:

Hepatocellular carcinoma (HCC) is a malignant tumor of hepatocytes. It is the commonest primary cancer of the liver and accounts for more than 90% of primary liver tumors [1]. It ranks fifth among cancers worldwide [2]. It is the third most common cause of deaths resulting from carcinomas globally. Over the past 20 years the incidence of HCC is increasing and its incidence is expected to increase further till 2030 in some countries [3]. Pakistan appears to be in an area of intermediate endemicity for HCC [4]. More than 80% of patients developing HCC have liver cirrhosis [5, 6].

Hepatitis B and hepatitis C infections are responsible for more than 80% cases of HCC in the world [2, 7]. Main cause of liver cirrhosis in USA are non-alcoholic fatty liver disease, alcohol abuse and hepatitis B,C infection [8].

Portal vein thrombosis is frequently associated with hepatocellular carcinoma and signifies an advanced tumoral stage [9, 10]. Portal vein thrombosis by tumor usually arise by direct extension of HCC into portal vein [10]. Prevalence of portal vein thrombus by direct venous extension or metastasis occurs in up to 20-70% of HCC patients [11]. HCC complicated by portal vein thrombus has an immensely grave prognosis, with a median survival time of merely 2 months to 4 months [12].

Patients with invasion of major branches of portal vein (PV) are graded as stage IV by the tumor-node-metastasis (TNM) classification and have poor prognosis. These patients are considered unsuitable for majority of treatment options like trans-arterial chemoembolization, ethanol ablation, liver resection, and even liver transplantation. Five-year survival after surgical resection is 12%–39% in patients with neoplastic vascular invasion and 59% in those without vascular invasion [13]. It has been documented

1. Department of Radiology, Hayatabad Medical Complex, Peshawar, Pakistan.

Address for Correspondence,

Rabia Shah

Specialist Registrar

Department of Radiology, Hayatabad Medical Complex, Peshawar, Pakistan

dr.rabiashah@yahoo.com

that advanced hepatocellular carcinoma are treated aggressively by hepatic resection or transplantation, malignant tumor thrombus is still considered extremely significant predictor of tumor recurrence in patients selected for liver transplantation. In order to determine the treatment plan, morbidity and mortality it is of paramount significance to detect bland portal vein tumor thrombus in patients with HCC, especially in patients meeting the Milan criteria for liver transplant [14].

Ultrasound is used as first line radiological investigation to detect PVT. Thrombus appears on ultrasound as solid intraluminal material with hypo-, iso-, or hyperechoic echogenicity [15]. Color doppler sonography shows blood flow and local hemodynamics in various organs. On Doppler spectral ultrasound the visualization of arterial waveforms pattern in a thrombus is regarded a very specific indicator of neoplastic thrombus. The diagnostic sensitivity of Doppler ultrasound for the detection of portal vein thrombus in HCC reaches up to 78.6% and specificity reaches up to 100% [16]. In another study the sensitivity and specificity of Color doppler ultrasound was 89.3% and 95.8% respectively in the detection of portal vein thrombosis [17]. CT detects PVT by detecting an intraluminal material and enhancement of the thrombus. In case of hepatocellular cancers, enhancing expansile PVT is indicative of malignant thrombus. CT is highly effective in detection and staging of hepatocellular carcinoma [18]. The sensitivity and specificity of CT in detection of thrombus in portal vein, in hepatocellular carcinoma is 86-100% and 100% respectively [2].

In Pakistan there is a surge in incidence of HCC due to an alarming increase in number of cases of hepatitis B and C. The management of HCC is directly dependent on PVT. Ultrasound is an easily available, cost effective and readily performed modality. The rationale of my study is to assess the diagnostic accuracy of color doppler sonography in evaluation of portal venous system in HCC keeping findings on multidetector computed tomography as gold standard. To our knowledge very limited data is available on this research topic in our region. Availing such evidence will help in planning of better medical strategies to deal with such cases and help them manage in a better way to obtain the required results.

MATERIALS AND METHODS:

A Cross-sectional study was conducted at Radiology department, Hayatabad Medical Complex, Peshawar from November 2019 to April 2020. Non-probability sampling technique was done. Both male and female patients with age more than 15 years were included. Diagnosed cases of fine needle aspiration cytology proven cases of HCC were included in the study. Patients with portal vein thrombosis of etiologies other than HCC like were excluded. The study was conducted after approval from hospital's ethical and research committee. All patients were subjected to doppler ultrasound to detect portal vein thrombus, if a thrombus was detected, it was vigilantly analyzed for color signals. Afterwards doppler spectral ultrasound was performed. Then all patients were subjected to multidetector CT to detect the presence or absence of portal vein thrombus. All the Doppler ultrasonic procedures and CT reporting were done by same consultant radiologist having minimum of 7 years of experience. The above-mentioned information including name, age, and gender were recorded in a pre-designed proforma. All the analysis was done in SPSS 20. On doppler sonography portal vein thrombus appears as solid intraluminal material with hypo-, iso- or hyperechoic echogenicity. The presence of pulsatile flow and arterial waveforms in the thrombus on spectral analysis are diagnostic for malignant portal vein thrombus. An iso- to hyperdense intraluminal material in the portal vein showing enhancement on arterial phase of CT is strongly evident of malignant invasion of the thrombus. Diagnostic accuracy was measured in terms of sensitivity, specificity, positive & negative predictive values.

RESULTS

A total of 129 patients were included in this study that were diagnosed cases of HCC based on histopathology results. The mean age was 56 ±8 years. 61% of patients were male and 39% were female.

Out of 129 patient's portal vein thrombus was visualized on CT in 36 patients. Malignant tumor thrombus was seen in 33 (92%) patients as enhancement on arterial phase CT. Doppler ultrasound successfully detected tumor thrombus in 27 (75%) patients. Rest of the 6 cases were labeled as benign thrombus. Diagnosis of tumor (malignant) thrombus was established when arterial flow was detected in the thrombus i.e., pulsatile flow on doppler sonography and arterial waveforms on spectral analysis within the thrombus, and on spiral CT

enhancement in the thrombus on arterial phase. None of the cases of benign tumor thrombosis on CT were labeled as malignant thrombosis on doppler sonography. Specificity of doppler U/S

was 100%. The positive and negative predictive values of the doppler ultrasonography in depicting malignant PVT as compared to CT scan are 100% and 33% respectively.

Table 1: Arterial Flow in Thrombus on Doppler U/S

Nature of Thrombus	Frequency	Percent
Yes (Malignant)	27	75
No (Benign)	9	25
Total	36	100.0

Table 2: Arterial Flow in Thrombus on CT

Nature of thrombus	Frequency	Percent
Yes (Malignant)	33	92
No (Benign)	3	8
Total	36	100.0

Table 3: Sensitivity and Specificity of the Doppler Ultrasonography

Sensitivity and Specificity of the Doppler Ultrasonography in depicting Portal vein thrombosis as compared to the CT Scan (Gold Standard)				
Doppler Ultrasonography of Portal Vein		CT of the Portal Vein		Total
		Portal Vein Thrombosis (n)	No Portal Vein Thrombosis (n)	
	Portal Vein Thrombosis (Sensitivity%= a/a+c)	32 (89%)	4	36
No Portal Vein Thrombosis (Specificity%= d/b+d)	4	89 (95.7%)	93	
Total	36	93	129	

Table 4: PPV and NPV of the Doppler Ultrasonography

PPV and NPV of the Doppler Ultrasonography in depicting Portal vein thrombosis as compared to the CT Scan (Gold Standard)				
Doppler Ultrasonography of Portal Vein		CT of the Portal Vein		Total
		Portal Vein Thrombosis (n)	No Portal Vein Thrombosis (n)	
	Portal Vein Thrombosis (PPV%= a/a+b)	32 (89%)	4	36
No Portal Vein Thrombosis (NPV%= d/c+d)	4	89 (95.7%)	93	
Total		36	93	129

DISCUSSION

Hepatocellular carcinoma is one of the leading causes of cancer related deaths in the world [1]. Persistent hepatitis B and hepatitis C are responsible for over 80% of HCC cases worldwide; increasing the burden of disease at an alarming rate [2]. As compared to the rest of the world, relatively high rates of incidence are found in South Asia and Africa [4].

Presence of cirrhosis greatly affects the survival and prognosis of these patients, limiting therapeutic options and hence shortening the survival time. Patients having both cirrhosis and HCC have the greatest risk of portal vein thrombosis [19]. Portal vein tumor thrombus in HCC is one of the most significant factors for poor prognosis decreasing the survival time even more [20]. Surgical resection and transplant are contraindicated in case of malignant portal vein thrombosis. It is associated with increased risk of complications like spread of tumor throughout liver, portal varices and their rupture, hepatic encephalopathy and liver failure [21].

On Ultrasound portal vein thrombus appears as intraluminal echogenic area with increased diameter of portal vein, collateral formation and cavernous transformation [22]. However, the sonographic appearance of the thrombus is not specific. Benign and neoplastic thrombi cannot be distinguished on the basis of their sonographic appearances. The recent progress of sonographic technology has helped not only in diagnosing PVT but has also provided detailed hemodynamics about portal vein thrombi etiology. It is a helpful tool in differentiating noninvasively, benign and malignant thrombi,

attaining increased specificity and sensitivity. The arterial flow detected in the thrombus is very specific in diagnosing thrombus of neoplastic etiology [23].

HCC is complicated by portal vein thrombosis in up to 44% of cases [24]. In our study comprising of 129 patients, frequency of portal vein thrombosis was 28%.

Doppler sonography is helpful tool in detecting vascularity in a thrombus. Arterialization in a neoplastic thrombus is easily detected both on color and spectral Doppler ultrasounds in the form of arterial waveform patterns. These are readily differentiated from venous flow because of their pulsatile nature. In few patients it was difficult to perform spectral ultrasound either because of anatomical location of thrombus or due to patient noncooperation. In our study, sensitivity of doppler sonography in detecting arterial flow in the malignant thrombus was 82%. Tanaka K, et al. [25] in their study, found 89% sensitivity, while Rossi S, et al. [26] determined 86.7% sensitivity of color doppler sonography. The specificity of doppler sonography in detecting malignant thrombus was 100% in our study which was the same as that of sensitivity shown by of Tanaka K, et al. [25] in their study.

This study shows that color Doppler sonography reliably demonstrates portal venous system anatomy and pathological changes including thrombus. The high sensitivity and specificity demonstrated makes Doppler sonography a useful tool in our setup because of its easy availability, no radiation/ contrast complications and less financial burden on poor patients. It is thus beneficial as it reduces extra diagnostic measures, specifically invasive ones like liver

biopsy along with avoiding irrelevant therapeutic procedures. Having said that, we must note that main limitations of sonography are patient cooperation, poor visualization of splanchnic vessels, difficulties caused by large hepatic lesions or lobar hypertrophy, anatomical changes, pneumobilia and operator dependency.

CONCLUSIONS

Color doppler sonography is a reliable diagnostic tool for demonstrating portal vein thrombosis in hepatocellular carcinoma.

DECLARATIONS

Authors' contributions: RS designed and collected the data with drafting of manuscript, MS designed and reviewed the manuscript, MRK collected the data for the manuscript, MA analyzed the data, GW collected data for the manuscript, NT, reviewed the manuscript.

Conflicts of Interests: authors declared no conflict of interest.

Funding: none.

REFERENCES

1. Kalinin, D., E. Solodinina, and E.J.U.o.D.L.f.L.R. Usova, Pancreatic Hemangioma. 2010. **15**(4): p. 26.
2. Phulpoto, J.A., et al., Prevalence of hepatocellular carcinoma in cirrhotic patients of Northern Sindh attending liver clinics at Ghulam Mohammad Mahar Medical College Hospitals Sukkur and Khairpur. 2012. **11**(1): p. 29-33.
3. International Agency for Research on Cancer. Liver. World Health Organization. [cited 2020; Available from: <http://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf>.
4. Butt, A.S., Z. Abbas, and W.J.H.m. Jafri, Hepatocellular carcinoma in pakistan: where do we stand? 2012. **12**(10 HCC).
5. Adami, H.-O., D. Hunter, and D. Trichopoulos, Textbook of cancer epidemiology. 2008: Oxford University Press.
6. Fong, Y., et al., Cancer of the Liver. 2015. **123**.
7. Saaed, F.M. and J.E.J.m. Ongerth, Prevalence of hepatitis B and hepatitis C in migrants from sub-Saharan Africa

8. Kim, H.-s. and H.B.J.C.g.r. El-Serag, The epidemiology of hepatocellular carcinoma in the USA. 2019. **21**(4): p. 1-8.
9. Poddar, N., et al., Hepatocellular carcinoma presenting as an incidental isolated malignant portal vein thrombosis. 2012. **43**(3): p. 486-489.
10. Bae, J.S., et al., How to best detect portal vein tumor thrombosis in patients with hepatocellular carcinoma meeting the Milan criteria: gadoteric acid-enhanced MRI versus contrast-enhanced CT. 2020. **9**(3): p. 293-307.
11. Spârchez, Z., et al., B-mode and contrast enhanced ultrasound guided biopsy of portal vein thrombosis. Value in the diagnosis of occult hepatocellular carcinoma in liver cirrhosis. 2010. **12**(4): p. 286-294.
12. Zhang, X.B., et al., Hepatocellular carcinoma with main portal vein tumor thrombus: treatment with 3-dimensional conformal radiotherapy after portal vein stenting and transarterial chemoembolization. 2009. **115**(6): p. 1245-1252.
13. Catalano, O.A., et al., Differentiation of malignant thrombus from bland thrombus of the portal vein in patients with hepatocellular carcinoma: application of diffusion-weighted MR imaging. 2010. **254**(1): p. 154-162.
14. Panel, C.P.G. and E.A.f.t.S.o.t.L.J.J.o. hepatology, EASL clinical practice guidelines: drug-induced liver injury. 2019. **70**(6): p. 1222-1261.
15. Jha, R.C., S.S. Khera, and A.D.J.A.J.o.R. Kalaria, Portal vein thrombosis: imaging the spectrum of disease with an emphasis on MRI features. 2018. **211**(1): p. 14-24.
16. Yang, L., et al., Ultrasound-guided fine needle aspiration biopsy in differential diagnosis of portal vein tumor thrombosis. 2005. **4**(2): p. 234-238.
17. Alam, S. and R.J.J.o.t.P.M.A. Pervez, Validity of colour doppler sonography for evaluation of portal venous system in hepatocellular carcinoma. 2013. **63**(3): p. 365-368.
18. Silverman, P.M. and J.J.C.I. Szklaruk, Controversies in imaging of newly arrived at Al Kufra in SE Libya in transit toward Europe. 2022.

- hepatocellular carcinoma: multidetector CT (MDCT). 2005. **5**(1): p. 178.
19. Ögren, M., et al., Portal vein thrombosis: Prevalence, patient characteristics and lifetime risk: A population study based on 23 796 consecutive autopsies. 2006. **12**(13): p. 2115.
 20. Minagawa, M., et al., Selection criteria for hepatectomy in patients with hepatocellular carcinoma and portal vein tumor thrombus. 2001. **233**(3): p. 379.
 21. Llovet, J.M., et al., Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma. 2012. **18**(8): p. 2290-2300.
 22. Gawande, R., et al., MRI in differentiating malignant versus benign portal vein thrombosis in patients with hepatocellular carcinoma: value of post contrast imaging with subtraction. 2019. **118**: p. 88-95.
 23. Dodd 3rd, G., et al., Portal vein thrombosis in patients with cirrhosis: does sonographic detection of intrathrombus flow allow differentiation of benign and malignant thrombus? 1995. **165**(3): p. 573-577.
 24. Quirk, M., et al., Management of hepatocellular carcinoma with portal vein thrombosis. 2015. **21**(12): p. 3462.
 25. Tanaka, K., et al., Diagnosis of portal vein thrombosis in patients with hepatocellular carcinoma: efficacy of color Doppler sonography compared with angiography. 1993. **160**(6): p. 1279-1283.
 26. Rossi, S., et al., Contrast-enhanced ultrasonography and spiral computed tomography in the detection and characterization of portal vein thrombosis complicating hepatocellular carcinoma. 2008. **18**(8): p. 1749-1756.