
DETECTION OF HEPATOCELLULAR CARCINOMA USING PERFUSION COMPUTED TOMOGRAPHY OF THE LIVER

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Abstract: Hepatocellular carcinoma is the seventh most prevalent cancer globally and the second leading cause of cancer-related deaths, with its incidence markedly increasing with age. Chronic infections with hepatitis B and C, exposure to aflatoxin B1, and alcohol consumption, with tumor development are often linked to chromosomal abnormalities in cirrhotic livers. The use of perfusion computed tomography is a promising diagnostic tool that assesses tissue perfusion and provides insights into blood flow and capillary permeability within the liver, though its exact diagnostic and prognostic capabilities, especially for early-stage tumors, remain uncertain. Challenges in accurately quantifying perfusion parameters arise from the liver's dual blood supply, and current methods have limitations in practical application. The objective of this study is to assess the diagnostic capabilities of perfusion computed tomography in detecting hepatocellular carcinoma and assess the effectiveness of visual analysis of perfusion maps, ultimately seeking to improve diagnostic accuracy and inform therapeutic decisions for patients with this condition. The work was conceived as a scientific review of the literature, various databases from journals, scientific research, scientific and professional papers obtained from Cochrane Library, Crossref, Google Scholar, and PubMed were used, focusing on studies published between 2015 and 2021 that analyzed the potential of perfusion computed tomography in detecting this type of cancer. The review included English-language studies involving patients over 20 years old with suspected hepatocellular carcinoma while excluding children, pregnant or breastfeeding women, and studies not related to human subjects. Hepatocellular carcinoma exhibits unique vascular characteristics that enhance the diagnostic and prognostic capabilities of this imaging technique. The condition is characterized by complex angiogenesis and vascularization from the portal vein, highlighting the method's diagnostic and prognostic potential. Research indicates that this approach effectively distinguishes hepatocellular carcinoma from benign lesions through the use of perfusion maps and maximum intensity projection reconstructions. Studies have demonstrated that it is more sensitive than dual-phase computed tomography in detecting lesions and can also serve as an alternative to tri-phase computed tomography for therapy monitoring. Overall, this imaging method provides crucial insights into diagnosis, tumor behavior, and treatment response, establishing it as a crucial method in the management of individuals with this type of cancer. This systematic literature review highlights the significance of perfusion computed tomography in the non-invasive detection of this cancer, confirming its effectiveness in tumor assessment, neoangiogenesis monitoring and staging, while analysis of the imaging results indicates promising outcomes in disease identification.

Keywords: hepatocellular carcinoma, computed tomography, liver

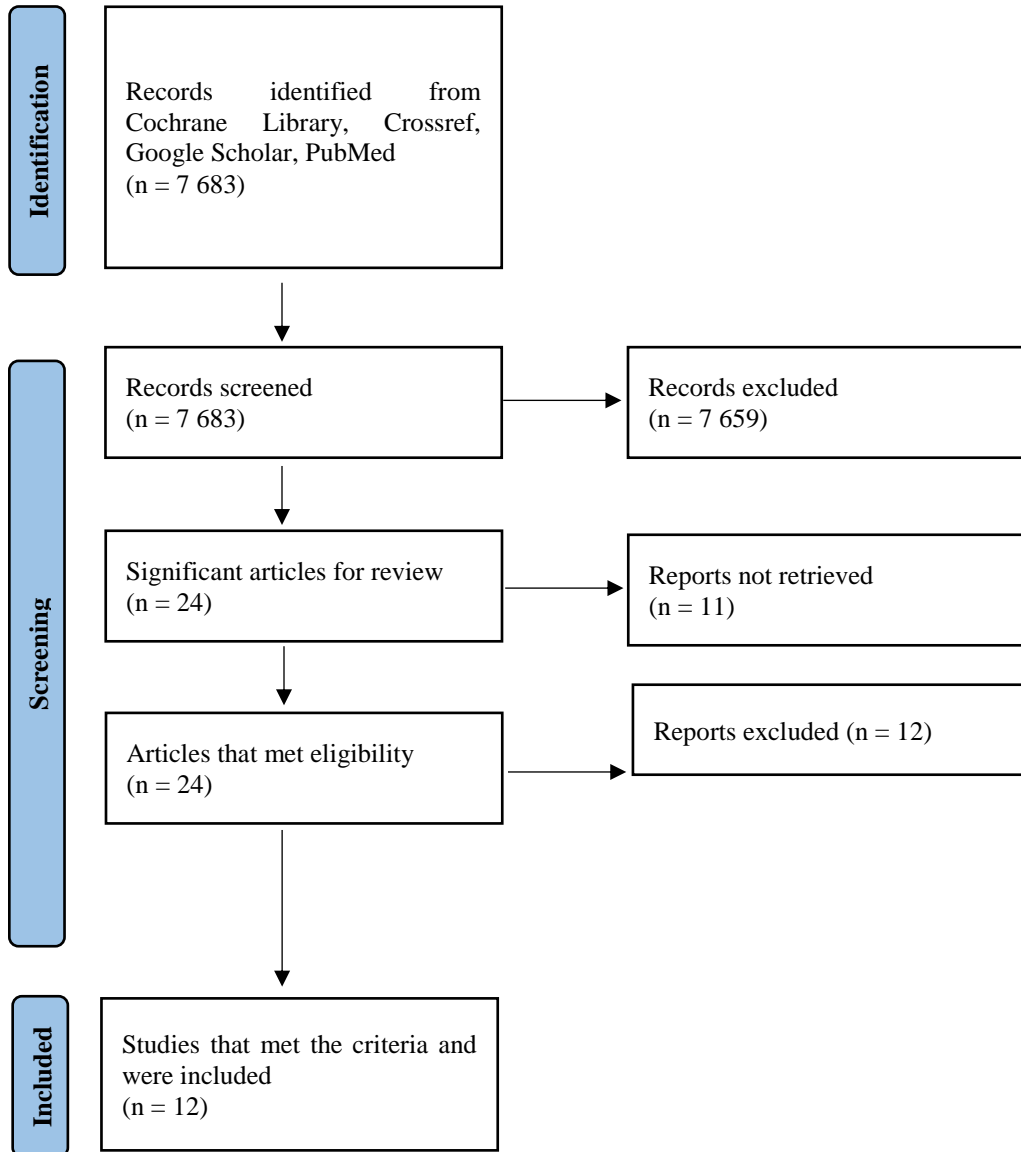
1. INTRODUCTION

Hepatocellular carcinoma (HCC) ranks as the seventh most prevalent cancer worldwide and is the second most frequent cause of cancer-related deaths (Johnson, P., 2022). The main risk factors consist of chronic infections with hepatitis B and C, exposure to aflatoxin B1, and the consumption of alcohol. The pathogenesis of HCC often involves chromosomal aberrations in cirrhotic livers, with tumor development originating from dysplastic nodules exhibiting chromosomal abnormalities similar to HCC (Toh, M. R., 2023). Tumor growth arises from hepatocytes or progenitor cells, with vascularization critical to malignancy. In diagnostic imaging, perfusion computed tomography (PCT) effectively evaluates the blood flow in tissues by tracking dynamic changes in contrast enhancement, providing quantitative insights into blood flow and capillary permeability within the liver, aiding in HCC evaluation (Li, Y. K., 2024). Despite advancements in PCT, this technique's exact diagnostic and prognostic value in detecting HCC remains uncertain, particularly in distinguishing early-stage tumors. A key challenge is accurately quantifying perfusion parameters, such as hepatic arterial perfusion (HAP), portal venous perfusion (PVP), and the hepatic perfusion index (HPI), due to the liver's dual blood supply (Zhao, F., 2021). Existing methods, including the maximum slope and compartmental models, offer some insights, but have limitations in practical use, especially with high injection speeds and complex dual blood flow characteristics in the liver (Kalarakis, G., 2021). Furthermore, the effectiveness of visually analyzing perfusion maps for early HCC detection requires further evaluation. The objective of this study is to assess the potential of PCT for identifying HCC and assess the effectiveness of visual analysis of perfusion maps, ultimately seeking to improve diagnostic accuracy and inform therapeutic decisions for HCC patients.

2. METHODS

A systematic literature search of relevant databases, Cochrane Library, Crossref, Google Scholar, and PubMed was carried out following the guidelines of PRISMA (Page, M.J., 2021), covering the introduction, methods, results, and discussion sections of this work for studies from 2015 to 2021 (Figure 1). Only studies published in English were included, focusing on those analyzing the potential of PCT in detecting HCC. The literature search took place from March to May 2021. Inclusion criteria were: patients aged over 20 years, and patients with suspected HCC. Exclusion criteria included: children, breastfeeding and pregnant women, and any patient with contraindications to contrast agents. Animal studies, along with comprehensive reviews of the topic, were also excluded.

Figure 1. PRISMA diagram of research included in the review



Source: Page, M.J., 2021.

3. RESULTS

Due to the significant variability among the studies, a narrative approach was used for the review (Table 1).

Table 1. Summary of study characteristics

Author, year of publication	Name of the study	Study objective/s	Research method/s	Conclusion
Fischer, M., et al., 2015	Perfusion computed tomography for detection of hepatocellular carcinoma in patients with liver cirrhosis	To evaluate the effectiveness of dynamic PCT in identifying HCC in patients with liver affected by cirrhosis.	26 patients with suspected HCC underwent liver PCT. Two readers evaluated HAP, PVP, HPI, and arterial maximum intensity (MIP) for the detection of HCC, while a second reader analyzed the perfusion maps of the lesions.	PCT exhibits strong effectiveness in identifying HCC in the liver affected by cirrhosis. A numerical assessment can help reduce false positives and increase the specificity of HCC diagnosis.
Gordic, S., et al., 2016	Perfusion-CT analysis for assessment of hepatocellular carcinoma lesions: diagnostic value of different perfusion maps	To evaluate various CT perfusion maps based on their capability to differentiate between liver parenchyma affected by cirrhosis and that which is not, as well as identify malignant tumors.	26 patients diagnosed with HCC underwent liver PCT, resulting in the creation of nine distinct perfusion representations. Areas of interest were designated for healthy liver tissue and HCC lesions. The perfusion metrics for livers affected by cirrhosis were contrasted with those not affected.	Maximum slope perfusion maps increase diagnostic accuracy in differentiating HCC from nontumorous tissue. The perfusion metrics for healthy liver tissue and HCC did not show significant differences between patients with cirrhosis and those without.
Kalarakis, G., et al., 2020	CT liver perfusion in patients with hepatocellular carcinoma: can we modify acquisition protocol to reduce patient exposure?	To explore the possibility of minimizing the number of scans and the accompanying radiation exposure in dynamic PCT's for assessing HCC.	Using PCT, 24 datasets of HCC patients were analyzed. Data was compared according to the precision of perfusion metrics, the effectiveness of the map in distinguishing HCC from liver tissue, and the related radiation dose.	By extending the time interval between scans to twice the original duration, radiation dose can be reduced without compromising the diagnostic effectiveness in the evaluation of HCC.
Kaufmann, S., et al., 2015	Characterization of hepatocellular carcinoma lesions using a novel CT-based volume perfusion technique	To characterize HCC by perfusion parameters using volumetric PCT and two different approaches, and analyze the outcomes.	79 patients with HCC and liver parenchyma affected by cirrhosis were included. The mentioned method was performed, and blood flow (BF), blood volume (BV) and k-trans were derived using the steepest slope and a deconvolution approach.	Volumetric PCT allows for noninvasive measurement of perfusion and can quantify how much HCC has become arterialized.
Kurucay, M., et al., 2017	Multiparametric imaging for detection and characterization of hepatocellular	To evaluate the effectiveness of imaging data obtained from PCT and MRI in individuals who have HCC.	36 patients diagnosed with cirrhosis of the liver and 67 lesions suspicious for HCC underwent perfusion CT and MRI. BF, BV, k-trans, HAP, PVP, and HPI were	PCT and MRI were similar in identifying lesions. An average HPI of PCT exceeding 96% was found to be a highly reliable parameter for detecting and

	carcinoma using gadoxetic acid-enhanced MRI and perfusion-CT: which parameters work best?		obtained for PCT.	characterizing HCC.
Lee, D., et al., 2016	Multiphase dynamic computed tomography evaluation of liver tissue perfusion characteristics using the dual maximum slope model in patients with cirrhosis and hepatocellular carcinoma	To examine the practicality of this method in effectiveness of perfusion characteristics in the liver, employing the dual peak gradient method in individuals with liver disease and hepatic cancer.	36 patients who were scanned with perfusion CT for therapeutic evaluation of HCC were analyzed. To obtain the perfusion parameters, in the form of HAP and PVP, 5-phase dynamic CT data with three arterial phases were chosen.	The results were similar to those achieved through PCT.
Mulé, S., et al., 2017	Can dual-energy CT replace perfusion CT for the functional evaluation of advanced hepatocellular carcinoma?	To assess the relationship between the level of iodine obtained from dual-energy CT and PCT parameters in individuals with HCC receiving care.	16 individuals who have advanced HCC completed dynamic PCT and multiphase CT simultaneously. Perfusion maps associated with BF and BV were calculated.	Combined analysis of the level of iodine variation in the late arterial and venous phases of HCC lesions may be useful for evaluating perfusion changes after targeted therapies.
Pang, G., et al., 2018	Heterogeneity analysis of triphasic CT scan perfusion parameters in differential diagnosis of hepatocellular carcinoma and hemangioma	To examine the numerical and variability of perfusion metrics in distinguishing between HCC and hemangioma.	32 cases of HCC and 44 hemangiomas were included in the study. Metrics and their related percentages were analyzed in relation to HCC and hemangioma, and also between lesions and normal tissue.	The use of triphasic PCT is effective detection of HCC. Perfusion metrics reveals notable disparities in the early identification and differentiation of this hepatic cancer and hemangioma.
Perl, R., et al., 2021	Differences between CT-perfusion and biphasic contrast-enhanced CT for detection and	To evaluate the diagnostic effectiveness of PCT versus biphasic contrast-enhanced CT (bpCECT) in identifying and characterizing HCC,	325 HCC's were evaluated using PCT and bpCECT. For PCT, an acquisition time of 40 seconds, 80 kV, 100 mAs, and 50 ml of iodine-based contrast agent were used. bpCECT consisted of 120	Both methods demonstrated improved identification of smaller HCC lesions. Additionally, lesions exhibiting reduced HAP and HPI were more effective, emphasizing the

	characterization of HCC	as well as to determine possible reasons for inconsistencies.	kV, 200-250 mAs, 100 ml of contrast agent, with 50 ml of saline.	significant contribution of PCT.
Shalaby, M., et al., 2017	CT perfusion in hepatocellular carcinoma: Is it reliable?	To prove that PCT serves as an important method in HCC diagnosis and therapy evaluation.	126 patients with 150 focal changes were comprised. Perfusion parameters were quantified and then compared with findings from three-phase CT imaging.	PCT is a reliable and precise imaging method for diagnosis and evaluation of intervention procedures in HCC.
Su, T., et al., 2017	Early response of hepatocellular carcinoma to chemoembolization: volume computed tomography liver perfusion imaging as a short-term response predictor	To assess the effectiveness of lesion-oriented PCT in predicting early outcome to intra-arterial chemotherapy in individuals who have HCC.	PCT imaging was conducted on 39 individuals who have 46 HCC's. The treatment outcomes were evaluated, and lesions were categorized into a responsive and non-responsive group.	Whole-liver PCT enables hemodynamic assessment of HCC lesions, with parameters such as HAP, HPI, offering potential as factors that indicate immediate treatment effectiveness.
Wu, D., et al., 2015	Liver computed tomographic perfusion in the assessment of microvascular invasion in patients with small hepatocellular carcinoma	To obtain a set of perfusion metrics from CT scans in patients with small HCC's and evaluate their efficacy in detecting microvascular invasions.	A total of 56 individuals scheduled for liver excision due to small HCC's (less than 3 cm) underwent CT evaluation. Examination of biopsies revealed that 18 patients had small HCC with microvascular invasion, while 38 patients had small HCC without microvascular invasion.	Liver PCT offers a minimally invasive, numerical approach, capable of forecasting microvascular invasion in individuals who have small HCC by measuring three perfusion parameters: PVFtumor, Δ PVF, and rPVF.

Source: Author

4. DISCUSSION

Liver cancer presents distinct vascular characteristics, with complex angiogenesis and parenchymal vascularization originating from the portal vein, which underscores the diagnostic and prognostic potential of advanced imaging methods. Fischer et al. (2015) first highlighted the precision of analysis of detecting liver tumors in cirrhotic livers, using protocols designed to minimize respiratory artifacts. Perfusion maps and maximum intensity projection reconstructions allowed clearer imaging, distinguishing tumors from benign lesions. Gordic et al. (2016) proposed dual-energy computed tomography as an alternative for liver cancer detection, finding a strong correlation between concentration of iodine on dual-energy computed tomography and arterial perfusion. Kalarakis et al. (2020) and Kaufmann et al. (2015) further confirmed that arterialization metrics correlate well, when it comes to tumor characteristics regardless of lesion size, while Kurucay et al. (2017) showed high hepatic perfusion index levels, effectively differentiating cancerous lesions from normal liver tissue. Other studies, such as those by Mule et al. (2017) and Pang et al. (2018), examined hemodynamic parameters, finding that detailed perfusion metrics enhance diagnostic specificity and sensitivity in assessing liver cancer. Perl et al. (2021) demonstrated that perfusion-based imaging detects more cancer lesions than dual-phase computed tomography, indicating higher diagnostic sensitivity, while Shalaby et al. (2017) suggested perfusion analysis as an alternative to tri-phase computed tomography,

offering high sensitivity in lesion detection and therapy monitoring. Su et al. (2017) identified arterial liver perfusion and hepatic perfusion index as essential prognostic markers, and Wu et al. (2015) highlighted perfusion imaging's capability in detecting microvascular invasion, a marker of aggressive cancer progression.

5. CONCLUSION

The value of perfusion computed tomography for detecting hepatocellular carcinoma is significant, as confirmed by a systematic literature review. The studies highlight the technique's ability to assess and characterize tumors, monitor neoangiogenesis, and determine the stage of hepatocellular carcinoma. Additionally, visual analysis of perfusion maps shows promise in effectively detecting the disease, reinforcing perfusion computed tomography's role as a valuable diagnostic method for hepatocellular carcinoma.

Conflicts of interests: The author states that there are no conflicts of interest to report.

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