ESCOLA SUPERIOR DE TECNOLOGIA DA SAÚDE DE LISBOA
INSTITUTO POLITÉCNICO DE LISBOA

III CONGRESSO BioMedLab
ASSOCIAÇÃO PORTUGUESA DE CIÊNCIAS BIOMÉDICAS LABORATORIAIS

Immunohistochemical Marking in the Diagnosis of Combined Hepatocellular and Cholangiocellular Carcinoma: A Systematic Review

Catarina Quintas[1], Marta Alves[1], Vera Silva[1], Paula Mendonça[1], Amadeu Borges-Ferro[1]

1. Escola Superior de Tecnologia da Saúde de Lisboa, Instituto Politécnico de Lisboa, Lisboa, Portugal.

Introduction

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a rare and biologically aggressive primary hepatic neoplasm, accounting for approximately 2% to 5% of liver tumors. This malignant neoplasm is defined by the coexistence of hepatocellular and cholangiocytic differentiation within the same tumor, integrating morphological and molecular features of both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC). Its phenotypic heterogeneity contributes to a complex clinical behavior and is associated with a poor prognosis, often worse than that of isolated HCC or CC.[1-4]

Diagnosing cHCC-CCA remains a challenge due to overlapping imaging findings and conflicting biomolecular profiles. Currently, the gold standard for definitive diagnosis is histopathological analysis, with immunohistochemistry (IHC) serving as an essential complementary tool to identify the tumor components. Markers such as arginase-1 (Arg-1), HepPar-1, cytokeratin 18 (K18), cytokeratin 7 (K7), and cytokeratin 19 (K19) are commonly employed to aid in tumor characterization (Figure 3–7). However, variability in marker expression hampers diagnostic standardization.[5-8]

This study aims to systematize existing evidence on the use of Arg-1, HepPar-1, K18, K7, and K19 in the diagnosis of cHCC-CCA, evaluating their impact on the standardization of diagnostic criteria for this carcinoma.

Methodology

Following the PRISMA methodology, a search was carried out in the PubMed, Scopus and Web of Science databases, covering articles published in Portuguese, English or Spanish since 2000, using combinations of MeSH terms such as “Combined Hepatocellular Cholangiocellular Carcinoma”, “immunohistochemical markers” and “Arginase-1”.
After the initial identification of the articles, the eligibility criteria were applied, and quality control was carried out based on the Joanna Briggs Institute checklist (Figure 1).

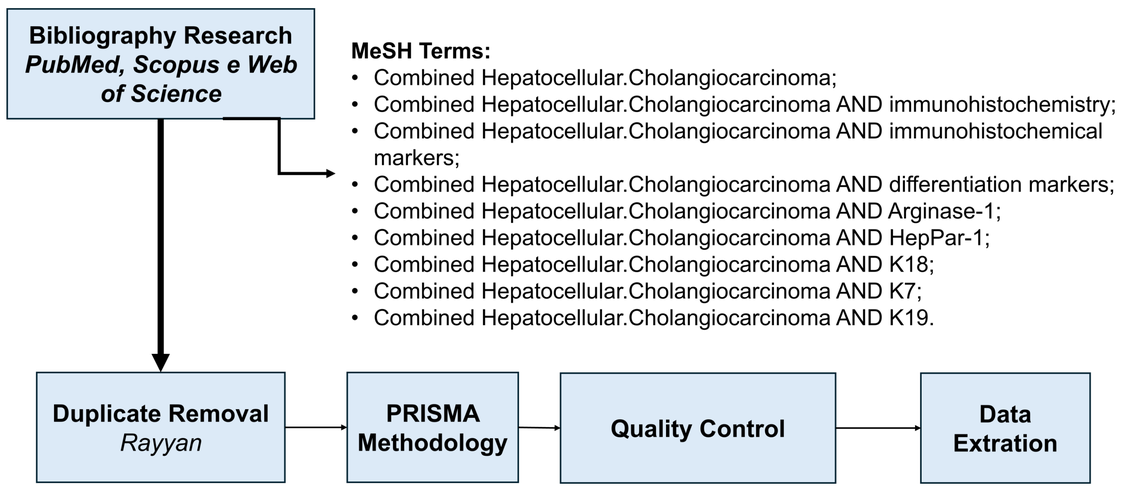

Figure 1 - Flowchart that illustrates the steps developed for the systematic review elaboration process.

Results

Initially, 1853 articles were identified, of which, after removing duplicates, applying eligibility criteria and quality control, only eight articles were selected for analysis (Figure 2).

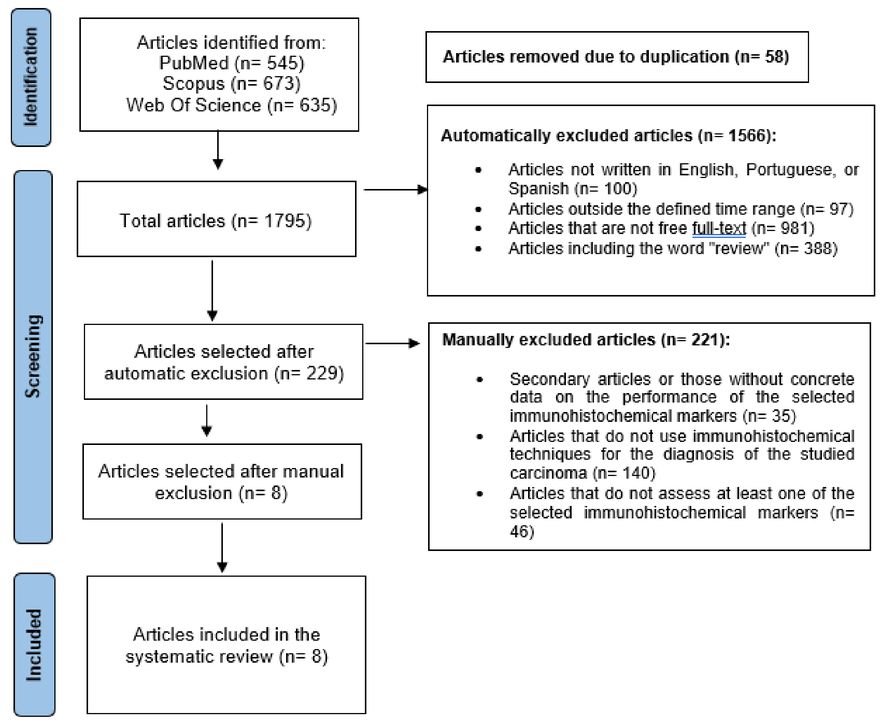

Figure 2: PRISMA flowchart of selected and identified articles after applying eligibility criteria.

The selected articles evaluated at least one of the immunohistochemical markers studied in this systematic review. Information such as the behaviour of the markers in each of the tumour components, clinical conditions and histological characteristics of the tumour were collected for a better analysis of the results (Table 1).

Table 1: Immunohistochemical results of selected studies

Authors	Arginase-1	HepPar-1	K18	K7	K19
Wilhelm et al.	❌ Negative	❌ Negative	---	✅ Strong in ducts	✅ Strong in ducts
Xu et al.	🔹 53% Positive (hepatic)	🔹 53% Positive (hepatic)	---	🔹 80% Diffuse (cholangiocytic)	🔹 83% Diffuse (cholangiocytic)
Terada T.	🔹 Positive (hepatic, interm.)	✅ Positive	✅ Positive (cholangiocytic, hepatic, interm.)	✅ Positive (cholangiocytic, hepatic)	✅ Positive (cholangiocytic), ❌ Negative (hepatic)
Zhang et al.	✅ Positive (hepatic, interm., 83.3%)	---	---	✅ Positive (cholangiocytic)	✅ Positive (cholangiocytic, interm., 83.3%)
Iwahashi et al.	---	---	---	✅ Positive	✅ Positive
Kim et al.	---	---	---	❌ Negative (12 cases), ✅ Positive (1 case)	❌ Negative (12 cases), ✅ Positive (1 case)
Xiang S. et al.	---	---	🔹 Strong in carcinomatous, ❌ Negative in sarcomatous	---	🔹 Strong in carcinomatous, ❌ Negative in sarcomatous
Van Haele et al.	---	---	---	---	✅ 100% Positive

🔹 Moderate | ✅ Positive | ❌ Negative | --- Not Reported

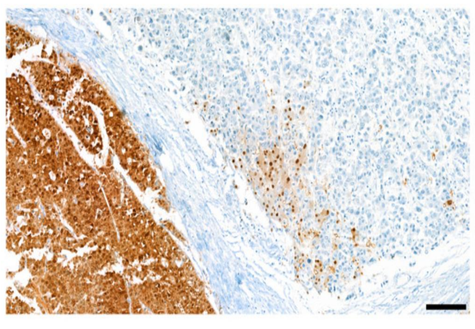

Figure 3: Immunohistochemical staining of Arginase-1 in CHCC-CCA

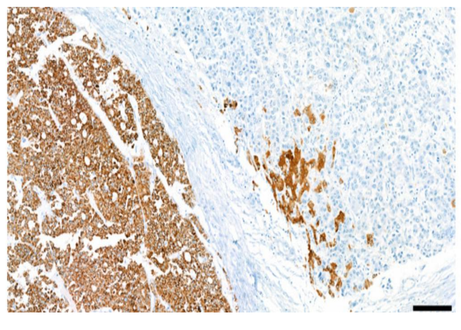

Figure 4: Immunohistochemical staining of HepPar-1 in CHCC-CCA

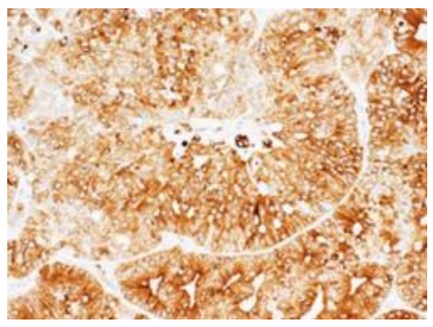

Figure 5: Immunohistochemical staining of K18 in CHCC-CCA

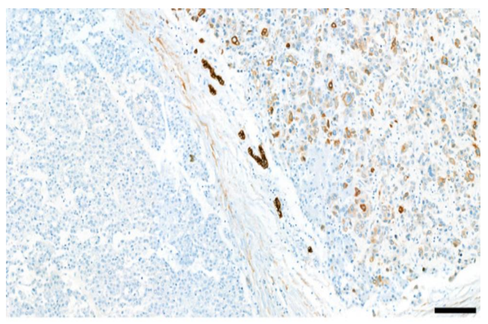

Figure 6: Immunohistochemical staining of K7 in CHCC-CCA

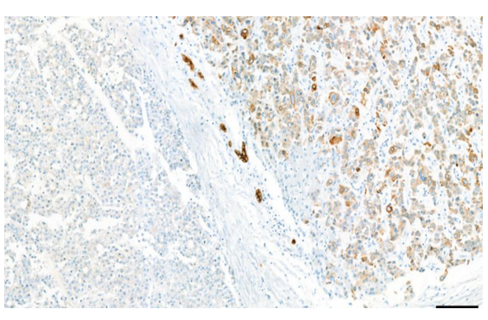

Figure 7: Immunohistochemical staining of K19 in CHCC-CCA

Conclusions

The combination of Arg-1, HepPar-1, K18, K7, and K19 enhances the diagnostic accuracy of cHCC-CCA by effectively distinguishing hepatocellular and cholangiocytic components.
Arg-1 and HepPar-1 show high sensitivity and specificity for hepatocellular components, while K7 and K19 identify the cholangiocytic component. K18, although less specific, aids in detecting hepatocytes and intermediate cells, highlighting the tumor’s mixed nature.

The variability in marker expression, influenced by clinical factors and intratumoral heterogeneity, underscores the importance of using a comprehensive immunohistochemical panel for a more accurate and targeted diagnosis.

References

1. Wilhelm AB, Cunningham AG, Kassab C, Fitz EC, Dong J, Radhakrishnan RS, et al. Pediatric combined hepatocellular-cholangiocarcinoma (cHCC-CC) with neuroendocrine features: distinguishing genetic alterations detected by chromosomal microarray. Diagn Pathol. 2023;18(1).
2. Xu J, Sasaki M, Harada K, Sato Y, Ikeda H, Kim JH, et al. Intrahepatic cholangiocarcinoma arising in chronic advanced liver disease and the cholangiocarcinomatous component of hepatocellular cholangiocarcinoma share common phenotypes and cholangiocarcinogenesis. Histopathology [Internet]. Dezembro de 2011 [citado 28 de Junho de 2024];59(6):1090–9. Disponível em: https://pubmed.ncbi.nlm.nih.gov/22175889/
3. Terada T. Combined hepatocellular-cholangiocarcinoma with stem cell features, ductal plate malformation subtype: a case report and proposal of a new subtype. Int J Clin Exp Pathol. 2013;6(4):737–48.
4. Zhang F, Chen XP, Zhang W, Dong HH, Xiang S, Zhang WG, et al. Combined hepatocellular cholangiocarcinoma originating from hepatic progenitor cells: immunohistochemical and double-fluorescence immunostaining evidence. Histopathology. 2008;52(2):224–32.
5. Iwahashi S, Utsunomiya T, Shimada M, Saito Y, Morine Y, Imura S, et al. High expression of cancer stem cell markers in cholangiolocellular carcinoma. Surg Today [Internet]. Junho de 2013 [citado 28 de Junho de 2024];43(6):654. Disponível em: /pmc/articles/PMC3651534/
6. Kim R, Kim SB, Cho EH, Park SH, Park SB, Hong SK, et al. CD44 expression in patients with combined hepatocellular cholangiocarcinoma. Ann Surg Treat Res. 2015;89(1):9–16.
7. Xiang S, Chen YF, Guan Y, Chen XP. Primary combined hepatocellularcholangiocellular sarcoma: An unusual case. World J Gastroenterol. 2015;21(23):7335–42.
8. Van Haele M, Moya IM, Karaman R, Rens G, Snoeck J, Govaere O, et al. YAP and TAZ heterogeneity in primary liver cancer: An analysis of its prognostic and diagnostic role. Int J Mol Sci. 2019;20(3).

Full Article