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IMMUNOHISTOCHEMICAL MARKERS AND HISTOCHEMICAL STAINS FOR DIAGNOSING LIVER HISTOLOGY AND PATHOLOGY

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ABSTRACT

Background: In the past, histological and histochemical stains were useful, but more precise and sensitive histopathological techniques are now employed to provide accurate diagnoses. These techniques include the use of immunohistochemical markers for various hepatic tissue components. Immunohistochemistry (IHC) is a useful diagnostic technique that produces great results for both normal tissues and tissues with various pathological insults when examining histopathological alterations in various bodily tissues.

Objective: In this study, we will move to examine classic histological and histochemical stains used for hepatic sections reaching to discussing the many immunohistochemical markers that are often utilized for detection of different histopathological liver disorders.

Conclusion: The use of two or more immunohistochemical markers improves the accuracy of the liver problem's detection, and the combination of histochemical stains with immunohistochemistry markers can occasionally be helpful for confirming diagnosis. There are numerous more instruments and methods used to investigate the pathology of the liver, even though these stains and markers are helpful for examining hepatic tissue.

Keywords: Liver, Histochemical, Immunohistochemistry, Arginase-1, Glypican-3.

1 INTRODUCTION

Immunohistochemistry (IHC) is an applicable diagnostic procedure used for examination of histopathological changes in different tissues of the body with an excellent result both for normal tissues and tissues with different pathological insults [1]. Immunohistochemistry is a method that uses antigen-antibody interactions to identify cellular or tissue components, antigens (such as proteins, amino acids, infectious organisms, or other cellular populations) [2]. By either directly identifying the antibody or via a secondary labeling technique, the location of antibody binding was determined [3].

In pathological procedures, immunohistochemistry has emerged as a potent tool. By determining the pathway of differentiation of a particular tumor. Since oncologists require more precise diagnosis, IHC has been shown to be one of the most significant adjuvant techniques in the characterization of neoplastic disorders in humans [4].

One of the important tissues in the body is the liver. Hepatic tissues are characterized by their specific histological architecture that routinely examined histologically using hematoxylin and Eosin (H & E) stain, liver is composed of different histological elements including hepatocytes, sinusoidal capillaries and bile ducts [5]. Many pathological conditions affect the hepatic elements such as cirrhosis, fatty liver disease, hepatitis, benign and malignant tumors [6]. Traditionally the use of histological and histochemical stains was applicable but recently more specific and sensitive histopathological methods are used for reaching excellent diagnosis and from these methods is using immunohistochemical markers for different elements of hepatic tissue [7].

In this review, we will pass to discuss traditional histological and histochemical stains used for hepatic sections reaching to explaining the different immunohistochemical markers that are commonly used for identification of different histopathological liver conditions.

1.1 Histological and Histochemical Stains

Hematoxylin and Eosin (H & E) stain are considered a routine stain for most histological sections of tissue in human body, when it is used in liver section; it will give the routine architecture of liver structure showing hepatocytes cytoplasm, nuclei and the sinusoidal spaces [8].

Another connective tissue used stain is Masson Trichrome that stains collagen blue or green against red hepatocytes and this staining method is applied to staging and grading of liver fibrosis and cirrhosis [9]. Gömöri / Snook's Reticulin stain is also a special connective tissue stain that impregned the reticulin with silver which is considered as collagen type III protein to mark cell plates, this staining method is of benefit to assess liver structure and crucial in the diagnosing of hepatocellular carcinoma [10]. Sirius Red stain is also considered as a selective connective tissue stain to illustrate collagen fibers and mostly correlate strongly with trichrome stain for diagnosis of liver fibrosis [11]. Verhoeff Van-Gieson stain is a special stain for detection of elastic fibers within blood vessels wall of the large portal tract and also considered as a special connective tissue stain [12].

Another histochemical stain involved in detection of liver histopathology is the Periodic Acid-Schiff reagent with or without diastases, this histochemical procedure identifies glycogen content of liver which is digested by diastase enzyme and illustrate mucin or alpha-1 antitrypsin globules which is resistant to diastases [13]. Perls' Prussian Blue histochemical stain is used to detect ferric iron storage of hepatocytes and Kupffer cells that is important in the diagnosis of hemochromatosis and hemosiderosis [14]. Rhodanine or Orcein stains copper associated proteins and highlight copper accumulation in hepatic tissue specially seen in Wilson's disease or chronic cholestatic disease [15]. Oil Red O or Sudan Black special stains to detect lipid droplets and neutral lipids in cases of steatosis but it is used mainly with frozen sections of hepatic tissues [16].

Congo Red is one of special staining used for liver sections which highlights amyloid deposits as apple- green birefringence by using of polarized light [17]. Lastly, we consider Orcein / Victoria Blue stain that visualizes elastic fibers and copper protein over-accumulation and hepatitis B surface antigen in ground glass hepatocytes [18].

All the above-mentioned stains were commonly used in the diagnosis of many pathological conditions in liver but with the revolution in the diagnostic procedures that applied in the last decades, the use of only special and histochemical stains became diminished when it is compared to more sensitive and specific immunohistochemical techniques. Even so, the diagnosis of hepatic pathologies needs to combine the routine stain H & E with selected IHC antibody markers.

1.2 Immunohistochemistry

The selection of antibodies for immunohistochemical testing, which is based on their tissue specificity and the probability that they would react with the tissue under examination, is one of the key concepts of applying this approach [19]. One of several detection techniques is used to identify positive reactions (tissue antigen-antibody binding) following the incubation of tissue sections with the potential antibodies [20]. The most sensitive ones employ a secondary antibody that reacts with the primary antibody that is conjugated or connected to an enzyme marker [21]. Because it permits a comparatively large number of enzyme molecules, including peroxides, to attach at the antigen site, this system is typically particularly sensitive. The choice of precipitating chromogen determines the color of the reaction [22].

Here we will illustrate and discuss the most commonly used primary antibodies for detection of histological and pathological conditions related to hepatic sections.

2 HEPATOCYTE MARKERS

2.1 Hep Par 1

A mouse monoclonal antibody called Hepatocyte paraffin 1 (Hep Par 1) is frequently utilized in surgical pathology practice to identify the hepatic origin of tumors [23]. The target antigen is called Carbamoyl Phosphate Synthetase 1, this enzyme is located in the mitochondria of the hepatocytes [24]. This immunohistochemical marker is of benefit in distinguishing between primary liver carcinoma from metastatic secondary adenocarcinoma that its primary in colon, breast or lung and from bile duct cancer (cholangiocarcinoma) and also help in the differential diagnosis of primary liver carcinoma and clear cell renal cell carcinoma [25]. It is sensitive marker for diagnosis of hepatocellular carcinoma, hepatic adenomas and hepatoblastomas. However, it also gives positive results in normal liver tissue [26]. The positive results are determined by appearance of strong and coarse cytoplasmic staining due to reaction with mitochondrial enzyme Carbamoyl Phosphate Synthetase 1, but its sensitivity is decrease in a poorly differentiated hepatocellular carcinoma, therefore it is used with other markers like Arginase-1 and Glypican-3 [27].

2.2 Arginase-1 (ARG-1)

It is the enzyme in the final step of urea cycle which is regarded as a key cytosolic enzyme which converts L-arginine to urea and L-ornithine [28]. It is considered the most sensitive and specific marker for diagnosing hepatocellular tumors. ARG-1 is superior to Hep Par 1 and Glypican-3 in diagnosing hepatocellular carcinoma by 96% sensitivity reaction specially in well and moderately differentiated tumors [29]. This sensitivity is also higher in poorly differentiated tumors and those of high-grade hepatocellular carcinoma [30]. It is used in the differential diagnosis of hepatocellular carcinoma and hepatic adenomas from secondary metastatic adenocarcinoma of liver, intrahepatic cholangiocarcinoma and metastatic neuroendocrine tumors. Positive findings obtained when there were both cytoplasmic and nuclear staining of hepatocytes. It is expressed also in normal hepatocytes like Hep Par 1 antibody [31].

2.3 Glypican-3 (GPC3)

It is a cell surface heparan sulfate proteoglycan which is crucial for cellular growth, differentiation and morphogenesis [32]. GPC3 is considered an oncofetal protein because it is expressed in hepatic malignant tumors in fetal liver tissues and therefore it is unlike Hep Par 1 and ARG-1 antibodies that express positively in both normal and malignant hepatic tissues [33]. GPC3 is essential in distinguishing between hepatocellular carcinoma and benign hepatic diseases such as hepatic adenoma, dysplastic cirrhotic nodules and focal nodular hyperplasia. It is very sensitive in poorly differentiated hepatocellular carcinoma and to high-grade types [34]. In other hand, it is also expressed in non-hepatic neoplasia such as yolk sac tumor and choriocarcinoma. The antibody considered positive when there is cytoplasmic and rim like membranous staining appeared and sometime perinuclear canalicular staining confirms the positivity of the marker.70-90% sensitive in detecting hepatocellular carcinoma and mainly in high-grade types rather than well differentiated tumors [35].

2.4 Alpha-fetoprotein (AFP)

It is an oncofetal biomarker, a major plasma glycoprotein produced by the yolk sac and fetal liver tissue during embryonic period and its serum level drops down in adult and become neglectable [36]. It is specific marker for hepatocellular carcinoma but 30-50% sensitive to this tumor type so, negative expression of biomarker dose not exclude cancer. Positive expression is also obtained in hepatoblastoma. The mode of positive expression is heterogenous cytoplasmic within the tumor area [37].

2.5 Glutamine synthetase

The hepatic conversion of ammonia and glutamate to glutamine for nitrogen metabolism is catalyzed by glutamine synthetase [38]. Hepatocytes around the principal veins of a healthy liver express glutamine synthetase. β-catenin targets the gene glutamine synthetase, and activation of β-catenin is indicated by significant diffuse glutamine synthetase staining [39]. From precancerous lesions to early and advanced hepatocellular carcinoma, glutamine synthetase immunostaining progressively increases. About 13% of cases of early hepatocellular carcinoma and 39% of cases of advanced hepatocellular carcinoma express glutamine synthetase [40].

3 BILIARY AND DUCT MARKERS

3.1 Cytokeratin 7 (CK7)

It is a low molecular weight intermediate filament expressed primarily in simple glandular epithelium, ductal epithelium in transitional epithelium [41]. It is considered an important marker in detection of the primary origin of secondary cancers therefore it is used for subtyping of carcinomas of unknown primary alongside Cytokeratin 20

(CK20), it is positively expressed in pancreatobiliary adenocarcinoma and cholangiocarcinoma and negative in hepatocellular carcinoma and in normal hepatocytes. Positive reactions appeared as diffuse cytoplasmic and membranous expressions [42].

3.2 Cytokeratin 19 (CK19)

It is an intermediate filament of smallest known acidic (type 1) cytokeratin [43]. It is specifically expressed in simple, pseudostratified and ductal epithelial tissue and therefore it is considered an important biomarker for ductal differentiation especially in liver and pancreatobiliary tract. It is used to distinguish between cholangiocarcinoma of bile duct (which is CK19+) and hepatocellular carcinoma (CK19-), but 10-20% of hepatocellular carcinoma give CK19+, and this indicates an aggressive behavior with a high recurrence rate and therapy resistance progenitor cell phenotype tumor [44]. In histological section, a diffuse cytoplasmic and membranous expression of the marker is considered positive results. In normal liver tissue, it is positive in bile ducts and negative in hepatocytes [45].

3.3 Carbohydrate Antigen 19-9 (CA19-9)

It targets sialyl-Lewis A which is a mucinous glycoprotein present in the surface of epithelial cells. It is a tumor marker used both in serology and immunohistochemistry for gastrointestinal and pancreatobiliary tumors [46]. CA19-9 is expressed in intrahepatic and extrahepatic cholangiocarcinoma. Serum level of CA19-9 will be obviously raised in benign conditions associated with biliary system like cholangitis, choledocholithiasis and in cases of cirrhosis. Immunohistochemical positive expressions appeared as cytoplasmic and apical/luminal membranous staining [47].

3.4 CDX2

It is caudal-type homebox transcription factor-2. Primarily, it is a sensitive antibody for diagnosing adenocarcinoma of intestinal origin, but it is essential biomarker in distinguishing secondary metastatic tumors in distant body tissue like hepatic tissue to determine its gastrointestinal primary origin. Positive results obtained as a strong nuclear pattern, so the cytoplasmic distribution considered nonspecific result [48].

4 STELLATE CELLS AND FIBROSIS MARKERS

4.1 Alpha-Smooth Muscle Actin

It is an actin isoform present in vascular smooth muscle cells, myofibroblasts and pericytes. In liver, it is considered as biomarker of hepatic stellate cells activation and liver fibrogenesis [49]. In healthy liver, the hepatic stellate cells showed minimal expression of Alpha-Smooth Muscle Actin biomarker due to presence of vitamin A in these cells, in chronic hepatic injury due to alcohol consumption or by viral hepatitis, the expression of Alpha-Smooth Muscle Actin become strong positive in stellate cells [50]. In cases of fibrosis, different degrees of Alpha-Smooth Muscle Actin biomarker expression are detected, and this depends on the degree of collagen fibers deposited in extracellular matrix [51]. Portal hypertension could be detected by positive staining of Alpha-Smooth Muscle Actin marker in the area surrounding sinusoids. In cases of intrahepatic cholangiocarcinoma and hepatocellular carcinoma, Alpha-Smooth Muscle Actin stains the fibroblast in the stroma surrounding the tumor [52].

4.2 Desmin

It is class III intermediate filament which is present in z disc of the three types of muscle in the body. In healthy hepatic tissue, it is considering a marker of the hepatic stellate cells, so it is positively expressed in the cytoplasm of these cells located in the perisinusoidal area in the space of Disse [53]. When fibrosis is considered, a strong positive expression of desmin is obtained which mean an early stage of fibrosis is suggestive. In hepatic leiomyoma and leiomyosarcoma, a strong positive desmin expression is considered [54].

4.3 CD34

Endothelial cells contain CD34, a transmembrane phosphoglycoprotein involved in cell-cell adhesion. The sinusoids in a normal liver are highlighted by CD34, but the lobules are not further highlighted. For CD34, hepatocellular cancer usually has a prominent diffuse sinusoidal staining pattern [55]. Hepatocellular adenoma and localized nodular hyperplasia usually exhibit patchy CD34 positivity. Nonetheless, 27% of instances of hepatocellular adenoma have diffuse CD34 positivity [56].

5 INFLAMMATION AND IMMUNE MARKERS

5.1 CD68

It is a transmembrane glycoprotein localized mainly to endosomes and lysosomes (Macrosialin / KP1 clone). In liver, it is the biomarker of monocyte/macrophage linage represented as Kupffer cells in liver which stains the intrahepatic Kupffer cells positive by CD68 [57]. In cases of viral hepatitis, positive CD68 expressions are obtained due to accumulation of foamy macrophages and microgranulomas [58]. It is expressed strongly positively in Gaucher disease by staining lipid-laden macrophages within sinusoids and primary liver histiocytic neoplasms. Positive results obtained as granular cytoplasmic expression reflect lysosomal contents. CD68 is negative in normal hepatocytes and bile duct epithelial cells. It is crucial in diagnosing steatohepatitis and lysosomal storage disease [59].

5.2 CD3 and CD20

These markers are regarded as lymphoid markers to distinguish the inflammatory infiltrates and so they are important in autoimmune liver disease, hepatic lymphomas and in assessing allograph rejection [60]. Regarding CD3, this is considered as pan T-cell marker which stains T cell receptors on T lymphocytes; therefore, it is positive in normal liver cells especially in areas of portal tract and sinusoids [61]. On the other hand, CD20 is regarded as pan B cell marker, so stained B lymphocytes and plasma cells in healthy hepatic tissues [62]. Their diagnostic importance is summarized in the following conditions: autoimmune hepatitis where CD3 is positively expressed, chronic hepatitis with both CD3 and CD20 are positively expressed and CD3 positive staining in primary biliary cholangitis [63]. In acute cellular allograph rejection, T lymphocytes are aggregated around portal vein, bile ducts and endothelium and CD3 positive reaction will be expected [64]. CD20 is crucial in the differential diagnosis of defuse large B cell lymphoma (positive CD20 expression) from T cell lymphoma. Both CD3 and CD20 positive reactions are demonstrated as membranous expression of the biomarker [65].

All above discussed biomarkers are mainly specified for liver lesions diagnosis, but other immunohistochemical markers can be used as diagnostic tools specially in cases of cancerous hepatic lesions, from these were the cancer stem cell markers that detect the cancerous transformation as histopathological changes and positive expression of different types of these markers, CD44, CD24, EpCAM, CD90, CD133, CD56, K19, ALDH1 and many other immunohistochemical markers can be mentioned regarding this issue [66].

6 CONCLUSION

This review summarizes the available and commonly used different types of histochemical stains related to hepatic tissue histology and for detection of many pathological conditions either benign, inflammatory, infectious and cancerous lesions. Combination of histochemical stains with immunohistochemical markers sometimes is of benefit for confirming diagnosis, also the use of two or more immunohistochemical markers makes the identification of the hepatic problem more accurate. Although these stains and markers are useful for exploring hepatic tissue, there are many other tools and techniques used to explore the pathology of liver like in situ hybridization, immunofluorescent stains, electron microscopy and laser capture microdissection that can be discussed in detail in future studies.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

The authors affirm that they have no competing interests with regard to this manuscript's publication.

REFERENCES

[1] Kim SW, Roh J, Park CS. Immunohistochemistry for Pathologists: Protocols, Pitfalls, and Tips. J Pathol Transl Med. 2016 Nov;50(6):411-418. doi: 10.4132/jptm.2016.08.08. Epub 2016 Oct 13. PMID: 27809448; PMCID: PMC5122731.

[2] Matos LL, Trufelli DC, de Matos MG, da Silva Pinhal MA. Immunohistochemistry as an important tool in biomarkers detection and clinical practice. Biomark Insights. 2010 Feb 9;5:9-20. doi: 10.4137/bmi.s2185. PMID: 20212918; PMCID: PMC2832341.

[3] Aydin S, Aydin S, Ugur K, Sahin İ, Emre E, Gencer SY, Aksoy A. An overview of immunohistochemistry: Evidence and personal experience. Journal of International Medical Research. 2026. https://doi.org/10.1177_03000605261469824.

[4] Li B, Huang L, Huang J, Li J. An Update of Immunohistochemistry in Hepatocellular Carcinoma. Diagnostics. 2025; 15(17):2144. https://doi.org/10.3390/diagnostics15172144.

[5] Choi JH. Histological and Molecular Evaluation of Liver Biopsies: A Practical and Updated Review. Int J Mol Sci. 2025 Aug 10;26(16):7729. doi: 10.3390/ijms26167729. PMID: 40869049; PMCID: PMC12387026.

[6] Takahashi Y, Dungubat E, Kusano H, Ganbat D, Tomita Y, Odgerel S, Fukusato T. Application of Immunohistochemistry in the Pathological Diagnosis of Liver Tumors. Int J Mol Sci. 2021 May 28;22(11):5780. doi: 10.3390/ijms22115780. PMID: 34071338; PMCID: PMC8198626.

[7] Fallatah MH, Ahmad AM, Alabbas KA, Alhammad LA. An Overview of Histological Staining Techniques. JoPH. 2024 Dec. 21;4(3):1187–1193. https://doi.org/10.63332/joph.v4i3.3191.

[8] Noel KI. Hepatic Tissues under the Effect of Dexamethasone: Histological Study, Dose and Duration Related Changes. Iraqi Journal of Medical Sciences. 2016; 11(2) (2013): 113-118. https://iraqijms.net/index.php/jms/article/view/154.

[9] Balaha HM, Ali KM, Mahmoud A, Aboudessouki A, Azam MT, Giridharan GA, Gondim D, El-Baz A. From Hematoxylin and Eosin to Masson's Trichrome: A Comprehensive Framework for Virtual Stain Transformation in Chronic Liver Disease Diagnosis. Diagnostics. 2026; 16(5):764. https://doi.org/10.3390/diagnostics16050764

[10] Popescu, Roxana, et al. Endothelial Markers and Fibrosis in Alcoholic Hepatitis. Trends in Alcoholic Liver Disease Research - Clinical and Scientific Aspects, 11 Jan. 2012. https://doi.org/10.5772/26853.

[11] Huang Y, de Boer WB, Adams LA, MacQuillan G, Rossi E, Rigby P, Raftopoulos SC, Bulsara M, Jeffrey GP. Image analysis of liver collagen using sirius red is more accurate and correlates better with serum fibrosis markers than trichrome. Liver Int. 2013 Sep;33(8):1249-56. doi: 10.1111/liv.12184. Epub 2013 Apr 25. PMID: 23617278.

[12] Percival KR, Radi ZA. A modified Verhoeff's elastin histochemical stain to enable pulmonary arterial hypertension model characterization. Eur J Histochem. 2016 Feb 11;60(1):2588. doi: 10.4081/ejh.2016.2588. PMID: 26972717; PMCID: PMC4800253.

[13] Fu DA, Campbell-Thompson M. Periodic Acid-Schiff Staining with Diastase. Methods Mol Biol. 2017;1639:145-149. doi: 10.1007/978-1-4939-7163-3_14. PMID: 28752454.

[14] Iezzoni JC. Diagnostic histochemistry in hepatic pathology. Seminars in Diagnostic Pathology. 2018; 35 (6): 381-389. https://doi.org/10.1053/j.semdp.2018.10.003.

[15] Ludwig J, Moyer TP, Rakela J. The Liver Biopsy Diagnosis of Wilson's Disease: Methods in Pathology. American Journal of Clinical Pathology. 1994; 102(4), 443-446. https://doi.org/10.1093/ajcp/102.4.443.

[16] Riva G, Villanova M, Cima L, Ghimenton C, Bronzoni C, Colombari R, Crestani M, Sina S, Brunelli M, D'Errico A, Montin U, Novelli L, Eccher A. Oil Red O Is a Useful Tool to Assess Donor Liver Steatosis on Frozen Sections During Transplantation. Transplant Proc. 2018 Dec;50(10):3539-3543. doi: 10.1016/j.transproceed.2018.06.013. Epub 2018 Jun 22. PMID: 30577233.

[17] Howie AJ. Origins of a pervasive, erroneous idea: The "green birefringence" of Congo red-stained amyloid. Int J Exp Pathol. 2019 Aug;100(4):208-221. doi: 10.1111/iep.12330. Epub 2019 Sep 13. PMID: 31515863; PMCID: PMC6877999.

[18] Henwood AF. The Orcein Stain—A Versatile Stain for Histopathology. Journal of Histotechnology. 2002;25(1):29. doi:10.1179/HIS.2002.25.1.29.

[19] Noel KI, Khamees NH, Abdulateef HH. Assessment of the Effect of Glucocorticoid Injections on the Expression of Apoptotic Active CASP3 and ALDH1A1 Renal Cell Markers in New Zealand Rabbits. Eastern J Med. 2024 ;29(4):397-405. doi:10.5505/ejm.2024.39049.

[20] Noel KI, Al Hamdany MZ, Akkila SS, Khamees NH. Allocation of stem cell alterations in spermatogenesis of male rats affected by zymafluor and detection of reverse effect of vitamin E on testis histology using immunohistochemical techniques. Scripta Medica. 2026;57(2):277-85. doi: 10.5937/scriptamed57-65024.

[21] Noel KI, Khamees NH, Akkila SS. The Role of Fibroblast Growth Factor-2 and Caspase-3 in Nontoxic Multinodular Goiter versus Normal Thyroid Tissue Cases from Baghdad, Iraq. Al-Rafidain J Med Sci. 2026 Mar. 8;10(1):247-53. doi:10.54133/ajms.v10i1.2778.

[22] Noel KI, Abdulateef HH, Khamees NH. Pluripotency Stem Cell Marker Expression and Apoptotic Changes in Placental Tissues of Normal and Intra-Uterine Growth Restriction (IUGR) Babies of Iraqi Mothers: A Comparative Study. Al-Rafidain J Med Sci. 2025 Feb. 16;8(1):71-7. doi:10.54133/ajms.v8i1.1642.

[23] Choi JH, Thung SN. Pathology and diagnostic approaches to well-differentiated hepatocellular lesions: a narrative review. J Yeungnam Med Sci. 2025;42.5. DOI: https://doi.org/10.12701/jyms.2024.00766.

[24] Butler SL, Dong H, Cardona D, Jia M, Zheng R, Zhu H, Crawford JM, Liu C. The antigen for Hep Par 1 antibody is the urea cycle enzyme carbamoyl phosphate synthetase 1. Lab Invest. 2008 Jan;88(1):78-88. doi: 10.1038/labinvest.3700699. Epub 2007 Nov 19. PMID: 18026163.

[25] Wennerberg AE, Nalesnik MA, Coleman WB. Hepatocyte paraffin 1: a monoclonal antibody that reacts with hepatocytes and can be used for differential diagnosis of hepatic tumors. Am J Pathol. 1993 Oct;143(4):1050-4. PMID: 7692729; PMCID: PMC1887067.

[26] Visalsawadi P. A Study of Hep Par 1 Antibody in Differential Diagnosis of Hepatocellular Carcinoma from Other Hepatic Tumors. MNRHJ. 2025 Jan. 7;29(1):15-22. https://he04.tci-thaijo.org/index.php/MNRHJ/article/view/2516.

[27] Yeasmin F, Ali MA, Dewan RK, et al. Role of Hep Par1 Immuno marker for Cytological Differentiation between Primary and Metastatic Liver Cancer. American J Pathol Res. 2024; 3(1): 1-5. DOI: 10.33425/2836-3647.1009.

[28] Caldwell RW, Rodriguez PC, Toque HA, Narayanan SP, Caldwell RB. Arginase: A Multifaceted Enzyme Important in Health and Disease. Physiol Rev. 2018 Apr 1;98(2):641-665. doi: 10.1152/physrev.00037.2016. PMID: 29412048; PMCID: PMC5966718.

[29] S Clemente G, van Waarde A, F Antunes I, Dömling A, H Elsinga P. Arginase as a Potential Biomarker of Disease Progression: A Molecular Imaging Perspective. Int J Mol Sci. 2020 Jul 25;21(15):5291. doi: 10.3390/ijms21155291. PMID: 32722521; PMCID: PMC7432485.

[30] Wang C, Shao X, Zhang X, Xie C, Yu J, Xu X, Yang J, Li Y, Xu W. Diagnostic value of glypican-3, arginase-1 and hepatocyte paraffin antigen -1 in differentiating hepatocellular carcinoma from intrahepatic cholangiocarcinoma. Transl Cancer Res. 2020 Jan;9(1):128-136. doi: 10.21037/tcr.2019.11.20. PMID: 35117166; PMCID: PMC8797808.

[31] Timek DT, Shi J, Liu H, Lin F. Arginase-1, HepPar-1, and Glypican-3 are the most effective panel of markers in distinguishing hepatocellular carcinoma from metastatic tumor on fine-needle aspiration specimens. Am J Clin Pathol. 2012 Aug;138(2):203-10. doi: 10.1309/AJCPK1ZC9WNHCCMU. PMID: 22904131.

[32] Grozdanov PN, Yovchev MI, Dabeva MD. The oncofetal protein glypican-3 is a novel marker of hepatic progenitor/oval cells. Lab Invest. 2006 Dec;86(12):1272-84. doi: 10.1038/labinvest.3700479. Epub 2006 Oct 2. PMID: 17117158.

[33] Haruyama Y, Kataoka H. Glypican-3 is a prognostic factor and an immunotherapeutic target in hepatocellular carcinoma. World J Gastroenterol. 2016 Jan 7;22(1):275-83. doi: 10.3748/wjg.v22.i1.275. PMID: 26755876; PMCID: PMC4698492.

[34] Kandil DH, Cooper K. Glypican-3: a novel diagnostic marker for hepatocellular carcinoma and more. Adv Anat Pathol. 2009 Mar;16(2):125-9. doi: 10.1097/PAP.0b013e3181992455. PMID: 19550373.

[35] Devan AR, Nair B, Pradeep GK, et al. The role of glypican-3 in hepatocellular carcinoma: Insights into diagnosis and therapeutic potential. Eur J Med Res. 2024; 29, 490. https://doi.org/10.1186/s40001-024-02073-2.

[36] Ucdal M, Yazarkan Y, Sonmez G, Celtikci B, Balaban Y. Alpha-fetoprotein: A Multifaceted Player in Cancer Biology. Euroasian J Hepatogastroenterol. 2025 Jan-Jun;15(1):72-82. doi: 10.5005/jp-journals-10018-1458. Epub 2025 Jun 18. PMID: 40718612; PMCID: PMC12288575.

[37] Xiang D, Liu J, Wang Y, Hu D, Zhang C, Zeng T, Jiang W, Liang X, Dong W, Sun W, Xu L, Li H, Shi Y, Zhang J, Liu H, Ding J. Oncofetal MCB1 Is a Functional Biomarker for HCC Personalized Therapy. Adv Sci (Weinh). 2024 Dec;11(45):e2401228. doi: 10.1002/advs.202401228. Epub 2024 Oct 14. PMID: 39402741; PMCID: PMC11615823.

[38] Frieg B, Görg B, Gohlke H, Häussinger D. Glutamine synthetase as a central element in hepatic glutamine and ammonia metabolism: novel aspects. Biological Chemistry. 2021;402(9): 1063-1072. https://doi.org/10.1515/hsz-2021-0166.

[39] Delgado TC, Martínez-Chantar ML. Understanding gut-liver axis nitrogen metabolism in Fatty Liver Disease. Frontiers in Endocrinology. 2022; 13, 1058101. https://doi.org/10.3389/fendo.2022.1058101.

[40] Hakvoort TB, He Y, Kulik W, Vermeulen JL, Duijst S, Ruijter JM, Runge JH, Deutz NE, Koehler SE, Lamers WH. Pivotal role of glutamine synthetase in ammonia detoxification. Hepatology. 2017 Jan;65(1):281-293. doi: 10.1002/hep.28852. Epub 2016 Nov 12. PMID: 27641632.

[41] Karantza V. Keratins in health and cancer: more than mere epithelial cell markers. Oncogene. 2011 Jan 13;30(2):127-38. doi: 10.1038/onc.2010.456. Epub 2010 Oct 4. PMID: 20890307; PMCID: PMC3155291.

[42] Moll R, Divo M, Langbein L. The human keratins: biology and pathology. Histochem Cell Biol. 2008; 129, 705–733. https://doi.org/10.1007/s00418-008-0435-6.

[43] Pastuszak M, Groszewski K, Pastuszak M, Dyrla P, Wojtuń S, Gil J. Cytokeratins in gastroenterology. Systematic review. Prz Gastroenterol. 2015;10(2):61-70. doi: 10.5114/pg.2015.51182. Epub 2015 Jul 1. PMID: 26557935; PMCID: PMC4631267.

[44] Luft T, Conzelmann M, Benner A, et al. Serum cytokeratin-18 fragments as quantitative markers of epithelial apoptosis in liver and intestinal graft-versus-host disease. Blood. 2007;110:4535–42. doi: 10.1182/blood-2006-10-049817.

[45] Lavallard VJ, Bonnafous S, Patouraux S, et al. Serum markers of hepatocyte death and apoptosis are non invasive biomarkers of severe fibrosis in patients with alcoholic liver disease. PLoS One. 2011;6:e17599. doi: 10.1371/journal.pone.0017599.

[46] Ventrucci M, Pozzato P, Cipolla A, Uomo G. Persistent elevation of serum CA 19-9 with no evidence of malignant disease. Dig Liver Dis. 2009 May;41(5):357-63. doi: 10.1016/j.dld.2008.04.002. Epub 2008 Jul 3. PMID: 18602352.

[47] Benson KK, Sheel A, Rahman S, Esnakula A, Manne A. Understanding the Clinical Significance of MUC5AC in Biliary Tract Cancers. Cancers (Basel). 2023 Jan 9;15(2):433. doi: 10.3390/cancers15020433. PMID: 36672382; PMCID: PMC9856870.

[48] Ben Rejeb S, Bacha D, Rachdi H, Bellil K. The role of CDX2 immunohistochemical marker in colorectal adenocarcinoma « CDX2 in colorectal adenocarcinoma ». Tunis Med. 2025 Dec 27;103(10):1460-1465. doi: 10.62438/tunismed.v103i10.6093. PMID: 41879697.

[49] Rockey DC, Du Q, Weymouth ND, Shi Z. Smooth Muscle α-Actin Deficiency Leads to Decreased Liver Fibrosis via Impaired Cytoskeletal Signaling in Hepatic Stellate Cells. Am J Pathol. 2019 Nov;189(11):2209-2220. doi: 10.1016/j.ajpath.2019.07.019. Epub 2019 Aug 30. Erratum in: Am J Pathol. 2020 Jul;190(7):1580. doi: 10.1016/j.ajpath.2020.05.002. PMID: 31476284; PMCID: PMC6902116.

[50] Gressner OA, Weiskirchen R, Gressner, AM. Biomarkers of hepatic fibrosis, fibrogenesis and genetic pre-disposition pending between fiction and reality. Journal of Cellular and Molecular Medicine. 2007; 11: 1031-1051. https://doi.org/10.1111/j.1582-4934.2007.00092.x.

[51] Dewidar B, Meyer C, Dooley S, Meindl-Beinker aN. TGF-β in Hepatic Stellate Cell Activation and Liver Fibrogenesis—Updated 2019. Cells. 2019; 8(11):1419. https://doi.org/10.3390/cells8111419.

[52] Feng Y, Zhang X, Wang XJ, et al. Metabolic reprogramming in fibrosis-related diseases: underlying mechanisms and therapeutics. Mol Biomed. 2026; 7, 84. https://doi.org/10.1186/s43556-026-00490-9.

[53] Sufleţel RT, Melincovici CS, Gheban BA, Toader Z, Mihu CM. Hepatic stellate cells - from past till present: morphology, human markers, human cell lines, behavior in normal and liver pathology. Rom J Morphol Embryol. 2020 Jul-Sep;61(3):615-642. doi: 10.47162/RJME.61.3.01. PMID: 33817704; PMCID: PMC8112759.

[54] Kamm DR, McCommis KS. Hepatic stellate cells in physiology and pathology. J Physiol. 2022 Apr;600(8):1825-1837. doi: 10.1113/JP281061. Epub 2022 Mar 30. PMID: 35307840; PMCID: PMC9012702.

[55] Ohmori S, Shiraki K, Sugimoto K, Sakai T, Fujikawa K, Wagayama H, Takase K, Nakano T. High expression of CD34-positive sinusoidal endothelial cells is a risk factor for hepatocellular carcinoma in patients with HCV-associated chronic liver diseases. Hum Pathol. 2001 Dec;32(12):1363-70. doi: 10.1053/hupa.2001.29678. PMID: 11774170.

[56] Akter MM, Ahmed M, Afroze N, Amin M. Immunohistochemical expression of CD34 in hepatocellular carcinoma and non-malignant hepatic nodules: experience at a tertiary care hospital in Bangladesh. BIRDEM Med J. 2025; 15(1): 22-27. DOI: https://doi.org/10.3329/birdem.v15i1.79310.

[57] Ju C, Tacke F. Hepatic macrophages in homeostasis and liver diseases: from pathogenesis to novel therapeutic strategies. Cell Mol Immunol. 2016 May;13(3):316-27. doi: 10.1038/cmi.2015.104. Epub 2016 Feb 24. PMID: 26908374; PMCID: PMC4856798.

[58] Tsomidis I, Tsakou A, Voumvouraki A, Kouroumalis E. Liver Macrophages in the Pathogenesis of Viral Hepatitis. Current Issues in Molecular Biology. 2026; 48(7):687. https://doi.org/10.3390/cimb48070687.

[59] Borger DK, Sidransky E, Aflaki E. New macrophage models of Gaucher disease offer new tools for drug development. Macrophage (Houst). 2015;2(1):e712. PMID: 26090519; PMCID: PMC4469193.

[60] Lee EJ, Kim M, Kim HS, Kang HJ, Kim HJ, Min SK, Lee YK. CD3 and CD20 Immunohistochemical Staining Patterns of Bone Marrow-Infiltrating Malignant Lymphoma Cells. Ann Clin Lab Sci. 2017 Mar;47(2):136-143. PMID: 28442514.

[61] Liu D, Hu X, Chen Z, Wei W, Wu Y. Key links in the physiological regulation of the immune system and disease induction: T cell receptor -CD3 complex. Biochem Pharmacol. 2024 Sep;227:116441. doi: 10.1016/j.bcp.2024.116441. Epub 2024 Jul 17. PMID: 39029632.

[62] Pavlasova G, Mraz M. The regulation and function of CD20: an "enigma" of B-cell biology and targeted therapy. Haematologica. 2020 Jun;105(6):1494-1506. doi: 10.3324/haematol.2019.243543. PMID: 32482755; PMCID: PMC7271567.

[63] Kobayashi M, Kakuda Y, Harada K, Sato Y, Sasaki M, Ikeda H, Terada M, Mukai M, Kaneko S, Nakanuma Y. Clinicopathological study of primary biliary cirrhosis with interface hepatitis compared to autoimmune hepatitis. World J Gastroenterol. 2014 Apr 7;20(13):3597-608. doi: 10.3748/wjg.v20.i13.3597. PMID: 24707143; PMCID: PMC3974527.

[64] Ronca V, Wootton G, Milani C, Cain O. The Immunological Basis of Liver Allograft Rejection. Front Immunol. 2020 Sep 2;11:2155. doi: 10.3389/fimmu.2020.02155. PMID: 32983177; PMCID: PMC7492390.

[65] Wada N, Kohara M, Ogawa H, Sugiyama H, Fukuhara S, Tatsumi Y, Kanamaru A, Hino M, Kanakura Y, Morii E, Aozasa K. Change of CD20 Expression in Diffuse Large B-Cell Lymphoma Treated with Rituximab, an Anti-CD20 Monoclonal Antibody: A Study of the Osaka Lymphoma Study Group. Case Rep Oncol. 2009 Oct 21;2(3):194-202. doi: 10.1159/000249152. PMID: 20737037; PMCID: PMC2914382.

[66] Noel KI, Raoof RM, Khamees NH. Cancer stem cells and their detection using specific cancer stem cell markers- a new strategy for cancer therapies. GSC Biological and Pharmaceutical Sciences. 2021; 17(03), 094–099. https://doi.org/10.30574/gscbps.2021.17.3.0357