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REVIEW

ARTIFICIAL INTELLIGENCE IN HISTOLOGICAL PROFILING OF HEPATOCELLULAR CARCINOMA: STATE OF THE ART

Gavino **Faa** [1, 2, †], Matteo **Fraschini** [3, †], Pina **Ziranu** [4, *], Andrea **Pretta** [4], Flaviana **Cau** [1], Peter **Van Eyken** [5], Yukio **Gibo** [6], Ekta **Tiwari** [7], Andrea **Casadei Gardini** [8], Jasjit **S. Suri** [9, 10, 11, 12, 13], Luca **Saba** [14], Mario **Scartozzi** [4], Massimo **Rugge** [15]

[1] Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy
[2] Department of Biology, College of Science and Technology, Temple University, Philadelphia (PA), USA
[3] Department of Electrical and Electronic Engineering, University of Cagliari, Cagliari, Italy
[4] Medical Oncology Unit, University Hospital and University of Cagliari, Cagliari, Italy
[5] Department of Pathology, Regional Hospital Oost Limburg, Genk, Belgium
[6] Hepatology Clinic, 1-34-20 Muraimachiminami, Matsumoto, Nagano, Japan
[7] Department of Innovation, Global Biomedical Technologies, Inc., Roseville, USA
[8] Department of Oncology, IRCCS San Raffaele Scientific Institute Hospital, Vita-Salute San Raffaele University, Milan, Italy
[9] Department of ECE, Idaho State University, Pocatello (ID), USA
[10] Department of CE, Graphics Era Deemed to be University, Dehradun, India
[11] University Center for Research & Development, Chandigarh University, Mohali, India
[12] Symbiosis Institute of Technology, Nagpur Campus, Symbiosis International (Deemed University), Pune, India
[13] Stroke Diagnostic and Monitoring Division, AtheroPoint, Roseville (CA), USA
[14] Unit of Radiology, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy
[15] Department of Medicine, DIMED, General Anatomic Pathology and Cytopathology Unit, University of Padova, Padua, Italy
[†] Equal contribution
[*] Correspondence to: ✉ pi.ziranu@gmail.com; https://orcid.org/0000-0002-5659-7366

ABSTRACT: Hepatocellular cancer (HCC) is the fifth most common malignancy and the fourth leading cause of cancer-related deaths worldwide. Liver histology plays a crucial role in the biological profiling of HCC, informs cancer prognosis, and supports personalized treatment strategies. Over the past decade, machine learning, deep learning algorithms, and convolutional neural networks have emerged as powerful tools for the histological and molecular assessment of malignancies. Machine learning and deep learning algorithms applied to whole slide digital images (WSIs) of liver cancers have demonstrated significant accuracy in distinguishing non-cancer *versus* cancer liver tissue and histologically subtyping HCC phenotypes associated with different clinical outcomes. Generative Artificial Intelligence models applied to WSIs obtained from hematoxylin and eosin-stained (H&E) histology specimens have shown promising results in delivering crucial insights into the genetic HCC disarrangement, potentially providing the biological rationale for molecular-targeted therapeutic strategies. This review highlights the diagnostic advances in computational histology for primary liver cancer. The manuscript focuses on the state of the art in AI-based histotyping and molecular profiling for HCC. A critical evaluation of their current performance is essential for inspiring the clinical research priorities and promoting the safe employment of AI models in managing HCC patients.

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Impact statement: Histology-based AI applied to H&E whole-slide images improves HCC diagnosis, phenotyping, molecular inference and prognostication, strengthening risk stratification and personalized care, and accelerating integration of computational pathology into routine clinical workflows.

Key words: *Artificial intelligence; liver cancer; hepatocellular carcinoma; deep learning; machine learning.*

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INTRODUCTION

In adult populations, hepatocellular carcinoma (HCC) is the fifth most common liver malignancy and the fourth most prevalent cancer-related death worldwide (1, 2). Liver cirrhosis is the cancerization field for HCC, with varying etiologies in different epidemiological settings. The etiological impact of transmissible (HBV or HCV) and non-transmissible (toxic agents, autoimmunity) agents differs significantly according to the considered populations (3).

Assessing liver malignancies and delivering patient-tailored treatments involves combining clinical evaluation, imaging, histology, and molecular profiling (4). Artificial intelligence (AI) has emerged as an extraordinary opportunity in the clinical management of malignancies in the last decade. Gigantic datasets may collect and connect multiparametric information (histology, genomic, proteomic, and metabolomic data), resulting in a hyper-human integration of different analytic methods and ultimately shaping the patient management strategy (5-8). A schematic overview of this multimodal workflow and its potential clinical outputs is provided in **Figure 1**. Within this multimodal framework, liquid biopsy offers a minimally invasive, longitudinal source of biomarkers that can complement tissue-based AI for risk stratification and disease monitoring.

Machine learning (ML) supervised and unsupervised models, Deep algorithms (DL) and Convolutional Neural Networks (CNN) have been developed and tested for their effectiveness in enhancing human-based diagnostics performance (9).

In histologically profiling HCC (diagnosis and grading), generative artificial intelligence (GAI) performs close to that of trained pathologists, and deep learning (DL) models have shown promising potential in predicting HCC-associated genetic disarrangements that can be exploited for targeted therapies (5, 10, 11). GAI models based on whole slide images (WSIs) obtained from hematoxylin and eosin-stained (H&E) "traditional" histological slides may effectively assist pathologists in HCC diagnosis, molecular profiling, prognostication, and assessment of therapy efficacy (9). As already seen in diagnostic radiology, AI implementation in diagnostic pathology irreversibly modifies the landscape of pathology competencies and operational workflow.

This review critically analyzes the diagnostic performance of GAI algorithms applied to whole-slide digital images (WSIs) obtained from H&E-stained histological specimens of cancer liver lesions.

This is a narrative review based on a targeted search of peer-reviewed literature primarily in PubMed/MEDLINE, including studies published up to May 2025. Search terms combined disease and methodology keywords (*e.g.*, HCC/liver tumors, digital pathology/whole-slide images, machine learning/deep learning, generative AI, microvascular invasion, molecular prediction, recurrence/survival), and reference lists of key articles were screened for additional records. We prioritized original studies and high-quality reviews with clear methodology and clinical endpoints relevant to histology-based AI in liver tumors, excluding radiology-only papers and reports lacking sufficient technical detail.

THE GLOSSARY IN COMPUTATIONAL HISTOLOGY

Machine learning (ML) algorithms include supervised and unsupervised training procedures. Supervised ML models involve using labeled (*i.e.*, categorized) data sets to train algorithms to classify or categorize data. This can be applied to optimize diagnostic procedures or predict clinical outcomes in clinical settings (9).

Unsupervised training uses unlabeled (*i.e.*, non-pre-categorized) data sets to reveal potential associations or patterns of variables within the data set. This "unlabeled" approach may uncover clustering or associations of variables, which may require interpretation and validation trials for clinical plausibility (9).

Deep learning (DL) is a subset of ML models mimicking human neuroanatomy. DL technology can learn complex representations, and its algorithms include artificial neural networks (synonym: Convolutional neural network (CNN)). CNN can automatically learn multiple levels of features based on a network of interconnected computing units organized in layers (12, 13).

AI ALGORITHMS CURRENTLY TESTED IN HCC HISTOLOGICAL ASSESSMENT

Different AI algorithms have been employed in the computational histology of liver tumors.

The ChOWDER (Cooperative Workspace DrivER) system is web-scalable and does not require specialized software, hardware, or expert annotations. It oper-

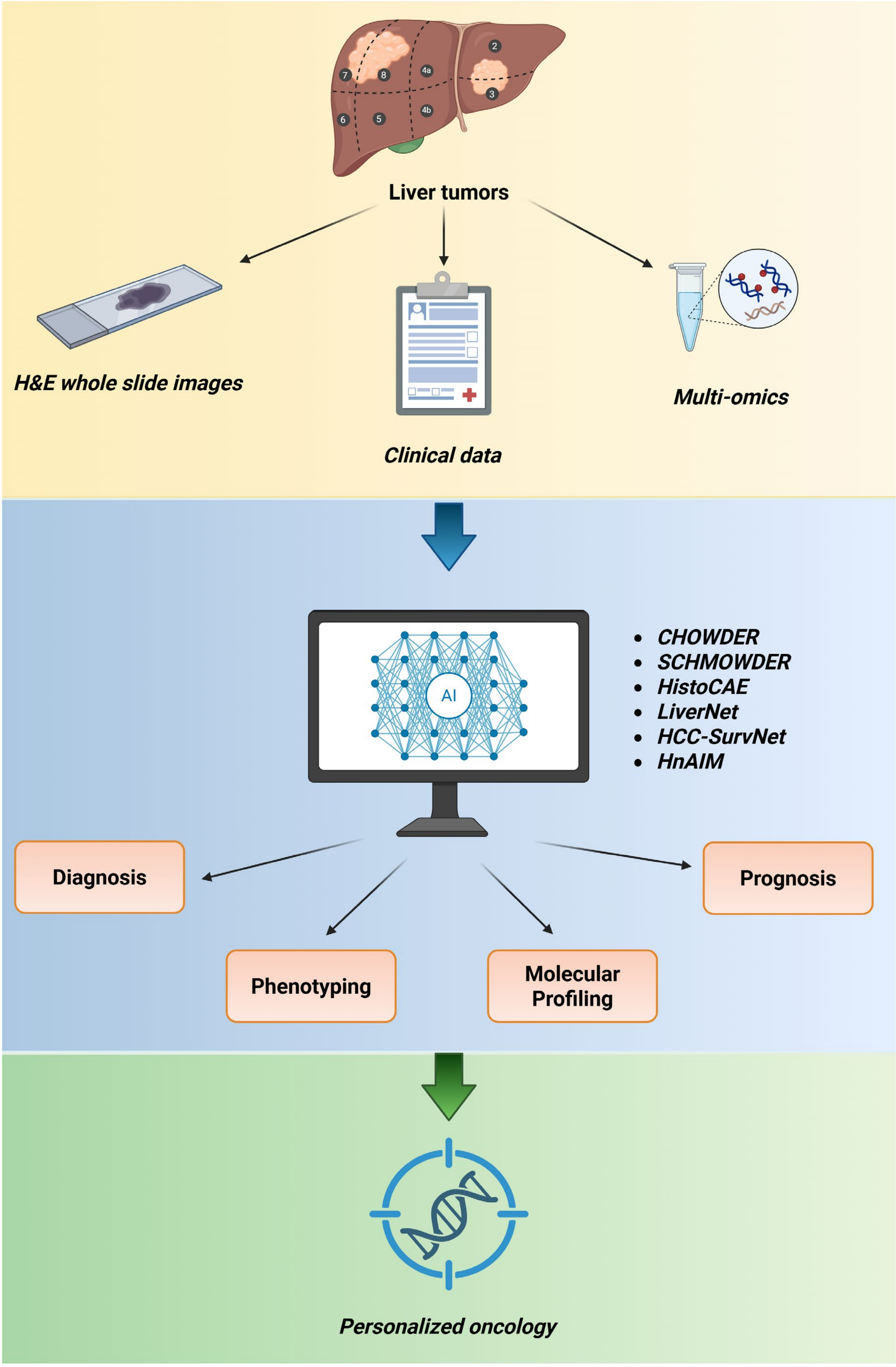

Figure 1. *Overview of an AI-enabled multimodal workflow for histological profiling of liver tumors.*
H&E whole-slide images, clinical data, and multi-omics features can be integrated to develop models supporting diagnosis, phenotyping, molecular profiling, and prognosis, ultimately enabling personalized oncology.

ates using multiple display devices, allowing a web browser to create a single large pixel space. Additionally, the ChWODER algorithm greatly enhances prognostic predictions based on HCC histology (14). The DL SCHMOWDER model has been used to predict patient survival by analyzing whole slide images (WSIs) of HCC. This algorithm calculates a prognostic risk score based on the histological cancer phenotype. Unlike the ChOWDER algorithm, SCHMOWDER requires human input to annotate the neoplastic areas that may be linked to the highest cancer aggressiveness levels, enhancing its prognostic accuracy (14). HistoCAE is a DL model developed for the segmentation of HCC in whole slide images. The model segments viable tumor areas, capturing fine spatial details missed by traditional histology (15).

Based on histological images (WSIs) of HHC samples, the MVI-DL (Microvascular Invasion-Deep Learning) algorithm focuses on detecting HCC microvascular invasion (16). This model has been successfully applied to the preoperative prognostic assessment of HCC patients (16).

The first-generation LiverNet deep learning model was developed to diagnose different subtypes of HCC based on H&E-stained whole slide images (WSIs) of tumor samples (17). In its original version, LiverNet classified HCC into three categories: low, intermediate, and high. This classification system helped pathologists make AI-assisted diagnoses of HCC. The improved second generation of the model (*i.e.*, LiverNet2) demonstrated a more than 97% diagnostic accuracy (18).

A recent, sophisticated deep convolutional neural network analyzes HCC histological images by capturing cellular modifications discarded by traditional assessment and effectively distinguishing high-grade HCC from cirrhosis (19).

A new deep learning model accurately predicts portal hypertension in HCC patients based on combined clinical variables and imaging, enabling timely therapeutic interventions (20).

AI IN HCC PHENOTYPING: WSIS ON H&E-STAINED HISTOLOGICAL SPECIMENS

Several studies have explored the performance of computational pathology (so-called “artificial” histology (21) in the biological profiling of different malignancies. These experimental experiences have provided essential insights into the diagnostic power of ML, DL, and CNN algorithms applied to H&E-stained, Whole Slide Digital Images (WSIs-H&E) obtained from “traditional” histological slides (22). These findings have consistently shown GAI’s potential to expand histology-based information on cancer’s phenotyping and clinical outcomes (23, 24). The AI algorithms extend the biological information on HCC far beyond the “traditional histology,” accurately classifying cancer histology, identifying molecular imbalances, and predicting cancer outcome (25, 26).

In 2017, an early study by Li and coauthors focused on AI-based nuclear grading of HCC. By joining multiple fully connected CNNs with a learning machine (MFC-CNN-ELM), a supervised algorithm achieved an overall grading accuracy of 0.811 ± 0.029 (27).

Lin and coauthors combined multiphoton microscopy with deep-learning algorithms. Convolutional neural networks combined with a pre-trained model (VGG-16) for image classification resulted in an accuracy of the HCC-grading over 90%. These findings documented the successful combination of multiphoton microscopy with deep learning models in realizing label-free, automated diagnostic assessment, potentially exploitable in clinical contexts (28).

In 2020, Kiani and coauthors specifically addressed the accuracy of AI models in the differential diagnosis of hepatocellular *versus* intrahepatic cholangiocellular cancers (7). Based on H&E-stained WSIs, the authors evaluated the diagnostic performance of a trained AI model *versus* 11 pathologists with variable levels of expertise. On a validation set (26 WSIs), the model achieved an accuracy of 0.885 *versus* 0.842 obtained from an independent test set of 80 WSIs. While no change in the mean accuracy of the 11 pathologists was detected ($p = 0.184$, OR = 1.281), it significantly improved the accuracy ($p = 0.045$, OR = 1.499) of a subset of nine pathologists considered to have “well-defined” experience levels.

A Chinese study by Liao *et al*. applied an AI-based diagnostic classifier (HCC *versus* non-cancer tissue) trained on 31 H&E-stained WSIs of HCC available from the Cancer Genome Atlas and tissue microarray images from a Chinese hospital (29). The diagnostic model successfully assessed HCC images in internal and external validation sets, with areas under the receiver operating characteristic curves (ROC curves) of 0.988 and 0.886, respectively. Moreover, the model consistently differentiated cancer from non-cancer tissue and discriminated long- from short-survival patients (see below).

More recently, a multicenter Chinese study achieved significant diagnostic consistency in the phenotypic assessment of nodular liver lesions applying an original ensemble of DL models (hepatocellular-nodular AI model: HnAIM) based on the integration of three different AI algorithms (ResNet50, InceptionV3, and Xception) (30). The trial involved surgical and biopsy tissue specimens representative of the full spectrum of nodular liver lesions, including focal nodular hyperplasia, cirrhosis, dysplastic nodules (high- and low-grade), hepatocellular adenoma, and H. The ROC curves and the AUC values on the testing database for models of Resnet50, Inception V3, Xception, and HnAIM demonstrated that the Xception and the HnAIM models performed the best, with AUC values of 0.9991. Moreover, the ensemble HnAIM model performed excellently in the external data set with an AUC value higher than 93%.

In a recent German study, the computational profiling of liver tumors achieved satisfactory prediction values in discriminating among histological classes (tile accuracy of 89%; case accuracy of 94%) and significantly distinguished liver metastasis from benign lesions at the case level (31).

The results obtained from both supervised and unsupervised models demonstrate the promising potential of (experimental) computational histology in distinguishing between cancer and non-cancer liver tissue. Additionally, they provide consistent information on cancer histotypes classification and grading, ultimately validating their potential to align with the diagnostic priorities in clinical practice (**Table 1**).

AI IN HCC PROGNOSIS AND PREDICTION OF TREATMENT OUTCOMES

Deep learning models, particularly CNN, have been extensively tested in liver cancer prognostication. Several studies focus on AI-driven imaging analyses, including CT scans, MRIs, and MRI radiomics (32-35). In some studies, CNN algorithms performed significantly well in prognostic prediction based on multiparametric data sets, including histology, among other clinical sources of information.

In 2020, a French study focused on the prognosis of HCC patients undergoing curative surgical resection. By applying the SCHMOWDER and CHOWDER DL algorithms, Saillard and colleagues obtained a "refined prediction" of their prognostic c-indices for both, with SCHMOWDER showing better performance due to expert pathologists' intervention in annotating neoplastic areas. Based on these results, the authors have emphasized the benefit resulting from pathologist-machine interactions in developing deep learning algorithms (14).

In 2021, two Japanese studies applied machine learning (36) and deep learning (37) algorithms to predict the risk of HCC recurrence after surgical treatment. In its conclusions, the study conducted by Saito and colleagues interpreted the "limitations" in the obtained prognostic estimates as stemming from the low number of cases considered (36). The deep learning model by Yamashita and coworkers obtained more satisfactory results (37). The risk score obtained by applying their original HCC-SurvNet DL achieved significant concordance indices (0.724 and 0.683) on the internal (0.724) and external (0.683) test cohorts, and both of them exceeded the prognostic performance of the "traditional" human-based TNM staging.

In 2021, a study by Jie-Yi Shi and coauthors applied a weakly supervised DL algorithm to explore the prognostic impact of HCC phenotypes computationally assessed on histological WSIs (38). The AI-based tumor risk score emerged as an independent prognostic factor with a predictive value superior to the clinical staging. Sinusoidal capillarization, macro-nucleoli, nucleus-to-cytoplasm ratio, and infiltrating inflammatory cells were identified as the main histological variables underlying the computational score of risk.

A recent 2025 study by Yixin Li and coauthors evaluated a deep learning model designed to predict the recurrence of HCC following surgical treatment (39). The model achieved an area under the receiver operating characteristic (AUROC) of 0.818 and 0.811 for predicting recurrence at 1 and 2 years, respectively, with external validation scores of 0.713 and 0.707. Additionally, the model effectively identified patients eligible for Sorafenib adjuvant therapy, enhancing its prognostic value by significantly recognizing candidates for targeted adjuvant treatment. Taken together, these histology-based deep learning models illustrate how AI can refine postsurgical risk stratification, recurrence prediction and treatment selection in HCC patients (**Table 2**).

HCC MOLECULAR PROFILING VIA AI ON H&E-STAINED WSIS

The AI models applied to liver cancer have been tested in their ability to provide information on

Table 1. *Histology-based and related AI models for diagnostic and phenotypic assessment of liver tumors.*

STUDY	AI MODEL / APPROACH	ENDPOINT	INPUT DATA	KEY FINDINGS
Li *et al.*, 2017 (27)	Joint multiple fully connected CNNs + extreme learning machine (MFC-CNN-ELM)	Automatic nuclear grading of HCC	H&E-stained histological images of HCC nuclei	Overall grading accuracy 0.811 ± 0.029 for HCC nuclear grading.
Lin *et al.*, 2019 (28)	CNN (VGG-16) applied to label-free multiphoton microscopy	Automated differentiation / grading of HCC	Label-free multiphoton microscopy images of liver tissue	High diagnostic accuracy (>90%) for HCC differentiation; demonstrates feasibility of label-free automated histological assessment.
Kiani *et al.*, 2020 (7)	Deep-learning assistant for differential diagnosis	Differential diagnosis between HCC and intrahepatic cholangiocarcinoma	H&E WSIs; stand-alone AI *vs* pathologists *vs* AI-assisted pathologists	Model accuracy 0.885 on validation set and 0.842 on independent test; AI assistance significantly improved accuracy in a subset of pathologists with "well-defined" experience (OR ≈ 1.5; p = 0.045).
Liao *et al.*, 2020 (29)	CNN-based diagnostic classifier	Classification of HCC *vs* non-cancer liver tissue and survival stratification	H&E WSIs from TCGA and an external Chinese cohort	AUC 0.988 (internal) and 0.886 (external) for HCC *vs* non-cancer; also discriminated long- *vs* short-survival patients.
Cheng *et al.*, 2022 (HnAIM) (30)	HnAIM ensemble (ResNet50, InceptionV3, Xception)	Phenotypic classification of nodular liver lesions (*e.g.*, FNH, cirrhosis, dysplastic nodules, HCA, HCC)	Surgical and biopsy H&E WSIs of nodular liver lesions	Best models (Xception and HnAIM) reached AUC up to 0.9991 on the test set; ensemble HnAIM maintained AUC >0.93 on external data.
Kriegsmann *et al.*, 2023 (31)	DL-based computational profiling of liver tumors	Classification of liver tumor histotypes; distinction of metastases *vs* benign lesions	H&E WSIs of primary and secondary liver lesions	Tile-level accuracy 89% and case-level accuracy 94%; significantly distinguished liver metastasis from benign lesions at case level.
HistoCAE, 2020 (15)	Convolutional autoencoder (HistoCAE)	Segmentation of viable HCC tumor regions	WSIs of liver cancer	Accurately segments viable tumor areas, capturing fine spatial details often missed by traditional visual assessment.
Wang *et al.*, 2023 (MVI-DL) (16)	Multimodal deep-learning model (MVI-DL)	Histological detection of microvascular invasion (MVI) and preoperative prognostic assessment	Histological WSIs of HCC (within a multimodal preoperative framework)	Deep-learning model focused on identifying MVI on histological images; successfully applied to preoperative prognostic assessment of HCC patients.
Aatresh *et al.*, 2021; Chanchal *et al.*, 2024 (LiverNet / LiverNet2.x) (17, 18)	LiverNet and LiverNet2.x CNN architectures	Automated grading and subtype classification of HCC	H&E WSIs of liver tumors	First-generation LiverNet enabled accurate AI-assisted grading and subtype classification; second-generation LiverNet2.x achieved >97% diagnostic accuracy.
Hang *et al.*, 2025 (19)	Deep CNN combined with hyperspectral imaging	Differentiation of high-grade HCC from cirrhosis	Hyperspectral histological images of liver tissue	Deep CNN captured subtle cellular modifications and effectively distinguished high-grade HCC from cirrhotic tissue.

It shows that most AI applications in liver tumor histopathology are H&E whole-slide image–based and mainly address diagnostic and phenotyping tasks, with promising performance but still heterogeneous validation across cohorts and settings. AI: Artificial Intelligence; DL: Deep Learning; CNN: Convolutional Neural Network; MFC: Multiple Fully Connected (layers); ELM: Extreme Learning Machine; CAE: Convolutional Autoencoder; HCC: Hepatocellular Carcinoma; H&E: Hematoxylin and Eosin; WSI / WSIs: Whole-Slide Image(s); TCGA: The Cancer Genome Atlas; HnAIM: Hepatocellular-Nodular Artificial Intelligence Model; FNH: Focal Nodular Hyperplasia; HCA: Hepatocellular Adenoma; MVI: Microvascular Invasion: AUC: Area Under the (ROC) Curve; OR: Odds Ratio.

Table 2. *AI models for prognosis, recurrence prediction and molecular profiling in hepatocellular carcinoma.*

STUDY (FIRST AUTHOR, YEAR)	AI MODEL / APPROACH	ENDPOINT	INPUT DATA	KEY FINDINGS (AS REPORTED IN THE REVIEW)
Saillard *et al.*, 2020 (CHOWDER / SCHMOWDER) (14)	CHOWDER web-scalable DL system and SCHMOWDER DL model	Post-resection prognosis (overall survival) in HCC	H&E WSIs of resected HCC; SCHMOWDER uses pathologist-annotated aggressive tumor areas	Both DL models provided refined survival prediction; SCHMOWDER outperformed CHOWDER thanks to expert annotation of aggressive neoplastic areas, highlighting the benefit of pathologist–AI interaction.
Saito *et al.*, 2021 (36)	Machine-learning model on digital pathology	Early recurrence of HCC after surgical resection	Digital histopathology images combined with clinicopathological variables	ML model predicted early recurrence of HCC; performance was promising but derived from a relatively limited dataset.
Yamashita *et al.*, 2021 (HCC-SurvNet) (37)	Deep-learning model (HCC-SurvNet)	Postsurgical recurrence risk and survival in HCC	Histological WSIs of resected HCC	Concordance indices 0.724 (internal cohort) and 0.683 (external cohort), both higher than the prognostic performance of traditional TNM staging.
Shi *et al.*, 2021 (38)	Weakly supervised DL model with AI-derived tumor risk score	Overall prognosis via histology-based tumor risk score	H&E WSIs of HCC with survival follow-up	AI-derived tumor risk score was an independent prognostic factor with predictive value superior to clinical staging; associated histologic features included sinusoidal capillarization, macro-nucleoli, high nucleus-to-cytoplasm ratio and inflammatory infiltrate.
Li *et al.*, 2025 (39)	Denoised recurrence-label deep-learning model	Postoperative recurrence risk and benefit from adjuvant Sorafenib	Histology-derived features integrated with clinical data	Model achieved AUROC 0.818 and 0.811 for 1- and 2-year recurrence (internal), and 0.713 and 0.707 in external validation; also identified patients most likely to benefit from Sorafenib as adjuvant therapy.
Wang *et al.*, 2023 (MVI-DL) (16)	Multimodal DL model (MVI-DL)	Presence of microvascular invasion and postoperative outcome	Histological images plus additional clinical/imaging variables	Novel multimodal DL model for preoperative prediction of MVI and patient outcome, supporting risk-adapted surgical planning.
He *et al.*, 2025 (20)	AI-based prediction model for portal hypertension	Clinically significant portal hypertension in HCC	Combined clinical variables and imaging features	Deep-learning model accurately predicted clinically significant portal hypertension, enabling earlier and better-targeted therapeutic interventions.
Fu *et al.*, 2020 (PC-CHiP) (41)	Pan-cancer computational histology (PC-CHiP)	Inference of molecular alterations from histology (including HCC, focus on TP53)	17,355 H&E slides from 10,452 patients (28 cancer types, including HCC)	Histology-derived features were quantitatively associated with multiple molecular alterations; in HCC, computational features were significantly associated with TP53 mutational status.
Liao *et al.*, 2020 (29, 42)	DL-based mutation-prediction models	Prediction of key gene mutations in HCC	H&E WSIs of HCC	Linked specific histologic patterns to mutations in TP53, MUC4, ALB, CSMD3, RYR2 and OBSCN, demonstrating the feasibility of mutation prediction directly from routine histology.

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STUDY (FIRST AUTHOR, YEAR)	AI MODEL / APPROACH	ENDPOINT	INPUT DATA	KEY FINDINGS (AS REPORTED IN THE REVIEW)
Chen *et al*., 2020 (11)	Inception V3a CNN	Prediction of recurrently mutated genes with potential therapeutic implications	H&E WSIs of liver cancer	Model trained on 10 frequently mutated genes (ARID1A, ASH1L, CSMD1, CTNNB1, EYS, FMN2, MDM4, RB1, TP53, ZFX4); external AUC 0.71–0.89, with particularly strong performance for CTNNB1, potentially useful to identify candidates for TTK inhibitors.W

It summarizes the rapid expansion of histology-based AI models for prognostic stratification (including recurrence/MVI-related endpoints) and molecular inference, highlighting clinically relevant outputs that nonetheless require robust external and prospective validation prior to routine adoption. AI: artificial intelligence; DL: deep learning; CNN: convolutional neural network; HCC: hepatocellular carcinoma; WSI: whole-slide image; MVI: microvascular invasion; AUROC: area under the receiver operating characteristic curve; TNM: tumor–node–metastasis.

molecular cancer profiles based on WSIs-H&E histological specimens (11, 40).

By applying a pan-cancer computational histology (PC-CHiP) analysis, Fu and coauthors tested the reliability of AI in associating histological cancer phenotypes with specific molecular disarrays (41). The algorithm was tuned on 17,355 H&E frozen tissue image slides, including 28 cancer histotypes from 10,452 individuals. In their study, the authors documented that "computational histopathological features" may infer quantitative associations with a spectrum of molecular disarrangements, and significantly associated *p53* mutations with HCC phenotype.

In the experience of Liao and coauthors, deep learning-based algorithms linked HCC histological specimens to specific molecular patterns involving TP53, MUC4, ALB, CSMD3, RYR2, and OBSCN (29, 42).

Chen and coauthors used whole-slide images WSIs-H&E liver tissue samples to train the Inception V3a CNN to predict HCC-associated genetic disarrangements with potential predictive impact (11). The DL model was trained and validated on ten of the most significantly mutated genes in HCC (ARID1A, ASH1L, CSMD1, CTNNB1, EYS, FMN2, MDM4, RB1, TP53, and ZFX4). Based on the WSIs-H&E histology, the model consistently revealed mutations involving CTNNB1, FMN2, TP53, and ZFX4, with external AUC values ranging from 0.71 to 0.89. In particular, the model highly predicted CTNNB1 mutations, identifying potential responders to targeted therapies with TTK inhibitors.

The findings above emphasize the potential of Deep Learning Convolutional Neural Networks (DL-CNN) for expanding the diagnostic message of histological phenotyping with valuable insights into the cancer molecular profile. This approach significantly simplifies the management of cancer patients and improves the efficiency and effectiveness of the diagnostic workflow.

Liquid biopsy can be integrated with histology-based AI to provide a minimally invasive and longitudinal source of information. In HCC, AI and ML approaches are currently being investigated for liquid biopsy signals, including circulating tumor DNA (ctDNA) and cell-free DNA (cfDNA) mutations, methylation patterns, and fragmentation or end-motif features, as well as circulating tumor cells and extracellular vesicles. These methods aim to support early detection, treatment monitoring, and assessment of recurrence or minimal residual disease (MRD) risk (43-45). Blood-based models can complement WSIs-derived predictors by capturing tumor dynamics over time and by facilitating the prioritization of confirmatory molecular testing when tissue samples are limited. Nevertheless, successful clinical translation requires rigorous standardization of pre-analytical procedures and robust external or prospective validation, especially in cirrhotic patients where tumor fraction may be low and confounding signals are prevalent (43-45).

CURRENT CHALLENGES IN AI EMPLOYMENT IN HCC HISTOLOGICAL ASSESSMENT

Pathologists' propensity to embrace the new vision of AI-based pathology is key to moving from traditional human-microscope-based pathology to the

WDS-GAI dimension. GAI was not part of the training of the previous generation of pathologists; fostering this profound innovation requires both personal aptitude and technical skills from mentors and residents, the latter are more receptive to digital innovation than their predecessors. Reluctance in novelty acceptance may be grounded in the "romantic" dimension of handcrafted work, but the current commitment to efficiency demands a timely, cost-effective, and more efficient "machine-made" dimension (46). While AI performance still needs nontrivial refinements, its rapid progress will quickly achieve the required operational levels (47).

In this context, the clinical value of AI for HCC histological assessment is best viewed in pragmatic terms: as decision support within a digital pathology workflow, rather than as a stand-alone diagnostic tool. The most credible near-term uses include slide/case triage, assistance in standardizing challenging diagnostic and grading scenarios, and objective quantification of relevant morphologic features (for instance, tumor segmentation and recognition of patterns that correlate with microvascular invasion or a higher likelihood of recurrence), which may complement routine reporting and multidisciplinary discussions. A further area of interest is the use of histology-based AI outputs to prioritize reflex molecular testing, helping to allocate limited tissue more efficiently and to support selection for targeted strategies or clinical trial enrollment.

From an implementation standpoint, supervised algorithms may further accelerate clinical translation because they rely on pathologist-labeled endpoints, which define clear targets for development and enable more straightforward validation and safer workflow integration (48). In this process, pathologists remain central: they define clinically meaningful labels and reference standards, curate representative cohorts (including borderline cases), guide annotation and error analysis, and oversee deployment through ongoing quality assurance, drift monitoring, and periodic re-validation.

Accordingly, successful clinical adoption requires outputs that are interpretable and auditable, with an appropriate governance framework that preserves the pathologist's central role in the diagnostic process.

Additionally, clinical translation comes at a cost, and converting microscope-based pathology to the digital format is expensive. Whole slide scanners require investments in high-performance machines and dedicated support technicians. Prioritizing, selecting, acquiring, and implementing diagnostic algorithms involves scientific, operational, marketing, and ethical challenges.

CONCLUSIONS

This review focused on the benefits and limitations of AI employment in the pathology setting of liver cancer diagnosis (49). Extraordinary progress has been made over the past decade, with paramount advancements covering AI-based HCC histological phenotyping (potentially overcoming the human-related diagnostic variability), molecular profiling (providing clinically crucial histology-based information), prognostication (enhanced by the multimodal assessment of the cancer disease), and prediction of the treatment outcomes for targeted therapies (supporting personalized oncology). However, this is the beginning of the journey. While current experimental algorithms are more than just promising, their performance needs to be reinforced by well-structured data collections, validated by robust clinical trials, and supported by a more defined regulatory framework (5, 50).

The safe implementation of GAI in HCC diagnostic (phenotyping and molecular) pathology requires further demonstrating its clinical advantages over "traditional" human approaches. Nevertheless, the already achieved evidence reveals a strong foundation and well-established potential for a near-bright future.

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Conflicts of interest

The authors declare no competing interests.

Availability of data and materials

All data generated or analyzed during this study are included in this article.

Authors' contributions

GF, MF, PZ: conceptualization. All authors: writing – original draft, writing – review & editing, final approval. GF, MF, AP, PZ: supervision, methodology.

Publications ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All the data corresponds to the real.

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