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Multi-Omics Integration and Artificial Intelligence for Dynamic Risk Stratification of Hepatocellular Carcinoma in MASLD: Toward Precision Surveillance and Personalized Immunotherapy

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and remains a major cause of cancer-related mortality worldwide. Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as an important driver of hepatocarcinogenesis, characterized by heterogeneous disease progression and the development of HCC even in non-cirrhotic patients, thereby challenging conventional surveillance strategies. **Objectives:** This review aimed to evaluate the role of multi-omics integration and artificial intelligence (AI) in the early detection and dynamic risk stratification of MASLD-related HCC, synthesize evidence regarding the association between multi-layer biomarkers, biological heterogeneity, and immunotherapy response prediction, and formulate a conceptual framework for dynamic risk stratification based on longitudinal molecular trajectories as a foundation for precision surveillance and personalized therapeutic strategies. **Methods:** A structured narrative literature review using a conceptual synthesis approach was conducted. Literature searches were performed in PubMed, Scopus, ScienceDirect, and Google Scholar for studies published between 2021 and 2026. Studies investigating genomics, transcriptomics, proteomics, metabolomics, or epigenomics integrated with AI-based approaches for HCC detection, risk stratification, or therapeutic response prediction were qualitatively synthesized. **Discussion:** Current evidence suggests that multi-omics integration provides a more comprehensive understanding of molecular heterogeneity and hepatocarcinogenic trajectories than single-biomarker approaches. AI facilitates the integration of multidimensional data through complex modeling, enabling dynamic risk stratification, improving early detection, and predicting immunotherapy response. **Conclusion:** Multi-omics and AI have the potential to transform risk-based surveillance and personalized management of MASLD-related HCC. However, prospective multicenter validation, standardized integration strategies, and adequate healthcare infrastructure are required for broader clinical implementation.

Keyword: artificial intelligence; hepatocellular carcinoma; MASLD; multi-omics; precision hepatology

ABSTRAK

Latar Belakang: Karsinoma hepatoseluler (*hepatocellular carcinoma*/HCC) merupakan keganasan hati primer tersering dan masih menjadi penyebab utama mortalitas terkait kanker di seluruh dunia. *Metabolic dysfunction-associated steatotic liver disease* (MASLD) telah berkembang sebagai determinan penting dalam hepatokarsinogenesis dengan karakteristik progresi penyakit yang heterogen serta kemampuan berkembang menjadi HCC bahkan pada pasien tanpa

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sirosis, sehingga menantang strategi surveilans konvensional. **Tujuan**: Tinjauan ini bertujuan mengevaluasi peran integrasi multi-omics dan kecerdasan buatan (*artificial intelligence*/AI) dalam deteksi dini dan stratifikasi risiko dinamis HCC terkait MASLD, mensintesis bukti mengenai hubungan biomarker multi-lapis dengan heterogenitas biologis dan prediksi respons imunoterapi, serta merumuskan kerangka konseptual stratifikasi risiko dinamis berbasis trajektori molekuler longitudinal sebagai dasar pengembangan surveilans presisi dan strategi terapi yang dipersonalisasi. **Metode**: Tinjauan literatur naratif terstruktur dengan pendekatan sintesis konseptual dilakukan melalui pencarian literatur pada PubMed, Scopus, ScienceDirect, dan Google Scholar terhadap studi yang dipublikasikan pada tahun 2021–2026. Studi yang mengevaluasi integrasi genomik, transkriptomik, proteomik, metabolomik, atau epigenomik dengan pendekatan berbasis AI untuk deteksi HCC, stratifikasi risiko, atau prediksi respons terapi dianalisis secara kualitatif. **Pembahasan:** Bukti terkini menunjukkan bahwa integrasi multi-omics memberikan pemahaman yang lebih komprehensif mengenai heterogenitas molekuler dan trajektori hepatokarsinogenesis dibandingkan pendekatan biomarker tunggal. AI memungkinkan integrasi data multidimensi melalui pemodelan kompleks untuk mendukung stratifikasi risiko dinamis, meningkatkan deteksi dini, serta memprediksi respons imunoterapi. **Kesimpulan:** Integrasi multi-omics dan AI berpotensi mentransformasi surveilans berbasis risiko dan tata laksana personalisasi HCC terkait MASLD. Namun, validasi prospektif multisenter, standardisasi strategi integrasi data, serta kesiapan infrastruktur kesehatan masih diperlukan untuk implementasi klinis yang lebih luas.
Kata kunci: kecerdasan buatan; karsinoma hepatoseluler; MASLD; multi-omics; hepatologi presisi

1. Introduction

Hepatocellular carcinoma (HCC) accounts for approximately 75–85% of all primary liver cancers and remains one of the leading causes of cancer-related mortality worldwide.[1-3] Epidemiologically, liver cancer ranks among the three leading causes of cancer-associated death globally, with hundreds of thousands of newly diagnosed cases and deaths reported annually.[2-3] The burden of disease continues to increase, particularly in Asia and low- and middle-income countries, largely driven by the high prevalence of chronic liver diseases that serve as major predisposing factors for hepatocarcinogenesis.[1]

The etiological landscape of HCC has undergone a profound shift over the past two decades. Whereas chronic infections with hepatitis B virus and hepatitis C virus historically represented the predominant drivers of hepatocarcinogenesis, metabolic dysfunction-associated steatotic liver disease (MASLD) has increasingly emerged as a major determinant of HCC development.[4-7] The global epidemic of obesity, type 2 diabetes mellitus, and metabolic syndrome has contributed to an exponential rise in MASLD prevalence.[5-7] Consequently, MASLD is projected to become the leading underlying cause of HCC in the coming decades.[5,7] Importantly, this transition represents not merely a change in disease etiology but also a paradigm shift in hepatocarcinogenesis, as MASLD exhibits substantially greater heterogeneity in disease progression compared with viral-associated liver diseases.[4]

Unlike virus-related HCC, which typically arises in the setting of advanced cirrhotic liver injury, MASLD-associated HCC may develop in a considerable proportion of patients without established cirrhosis.[4] This phenomenon challenges conventional surveillance strategies that have traditionally focused on cirrhotic populations as the primary high-risk group.[8-10] Consequently, many high-risk individuals with MASLD remain unidentified by current screening programs and are often diagnosed at advanced stages when curative interventions, including surgical resection, locoregional ablation, or liver transplantation, are no longer feasible.[1,10] This diagnostic gap substantially contributes to the persistently high global mortality associated with HCC.[1-3]

The limitations of early detection are further compounded by the suboptimal performance of currently available surveillance modalities. Ultrasonography and alpha-fetoprotein (AFP) remain the standard surveillance tools recommended by several clinical guidelines; however, AFP demonstrates relatively low sensitivity for detecting early-stage HCC.[8-11] Furthermore, the biological heterogeneity of HCC, encompassing genetic, epigenetic, metabolic, and tumor immune microenvironmental variations, limits the ability of single-biomarker approaches to capture the full complexity of the disease.[12-16]

This complexity is also reflected in the variable responses to modern systemic therapies, including immune checkpoint inhibitor-based immunotherapy. Although immunotherapy has improved clinical outcomes in a subset of patients, a considerable proportion still fails to achieve meaningful therapeutic benefit.[17-18] Such variability is driven by intricate multi-level interactions among tumor molecular characteristics, the immune microenvironment, and patients' metabolic backgrounds, particularly in MASLD, which is characterized by chronic inflammation, insulin resistance, mitochondrial dysfunction, and lipid dysregulation.[12-16] These observations underscore that the major challenge in HCC management lies not only in improving early detection but also in tailoring therapeutic strategies according to individual biological profiles.[14,19]

Multi-omics approaches have emerged as promising strategies for achieving a more comprehensive understanding of hepatocarcinogenesis. The integration of genomics, transcriptomics, proteomics, metabolomics, and epigenomics enables the identification of biomarkers that more sensitively and specifically reflect tumor biological activity.[14-15,20] Technologies such as circulating tumor DNA (ctDNA) analysis and DNA methylation profiling have demonstrated considerable potential for detecting molecular alterations during preclinical stages, even before lesions become detectable through conventional imaging modalities.[14,20] Furthermore, multi-omics approaches facilitate the characterization of temporal tumor evolution, thereby providing opportunities for the development of dynamic risk stratification models.[13,15]

However, the integration of multi-omics data generates high-dimensional datasets characterized by intricate nonlinear interactions, rendering conventional statistical approaches inadequate for comprehensive analysis.[14-15] Artificial intelligence (AI), particularly machine learning and deep learning techniques, has emerged as a critical enabling technology in this context. AI algorithms can integrate molecular, clinical, and radiological data to construct predictive models with enhanced accuracy and generalizability.[17,19,21-22] These advances have fostered the emergence of a novel paradigm in modern hepatology, termed systems precision hepatology, which advocates for disease management based on the integration of multidimensional datasets to support more precise and individualized clinical decision-making.[14,19]

Despite the rapidly expanding body of research investigating multi-omics technologies and AI applications in HCC, most studies remain fragmented, focusing on individual omics layers or employing cross-sectional designs with relatively small cohorts.[14-15,20] To date, relatively few studies have integrated longitudinal multi-layer omics data to establish dynamic risk stratification models specifically for patients with MASLD while simultaneously incorporating predictions of immunotherapy responsiveness.[14,19] This knowledge gap is becoming increasingly relevant given the growing burden of MASLD-associated HCC and the pressing need for surveillance systems that are more precise, adaptive, and biologically informed.[4-7]

Therefore, this literature review aimed to: (1) evaluate the role of multi-omics integration and artificial intelligence in the early detection and risk stratification of HCC among patients with MASLD; (2) synthesize current evidence regarding the association between multi-layer biomarkers, biological heterogeneity, and immunotherapy response prediction; and (3) propose a conceptual framework for dynamic risk stratification based on longitudinal molecular trajectories as a foundation for developing precision surveillance and personalized therapeutic strategies for HCC. Collectively, these approaches are expected to provide a conceptual basis for transforming HCC surveillance and treatment paradigms from conventional static risk models toward adaptive, data-driven, and precision-oriented frameworks that leverage multidimensional biological information.[14,19-20,23]

2. Method

This study was conducted as a structured narrative literature review employing a conceptual synthesis approach to identify, evaluate, and integrate current evidence regarding the application of multi-omics technologies and artificial intelligence (AI) in the management of hepatocellular carcinoma (HCC). This approach was selected to facilitate exploration of the interplay among multiple molecular biomarker layers and to support the development of a conceptual framework for dynamic risk stratification aimed at improving early detection and predicting immunotherapy response. Beyond summarizing existing evidence, this review sought to establish a conceptual basis for incorporating multidimensional molecular data into the emerging framework of systems precision hepatology to enable individualized risk-based clinical decision-making.

The review question was formulated according to the Population–Intervention–Comparison–Outcome (PICO) framework. The population comprised patients with hepatocellular carcinoma arising in the setting of

metabolic dysfunction-associated steatotic liver disease (MASLD), with cirrhotic populations included as comparators to contextualize differences in pathogenesis and risk profiles within biologically heterogeneous high-risk groups. The intervention/exposure of interest consisted of multi-omics platforms, including genomics, transcriptomics, proteomics, metabolomics, and epigenomics, integrated with artificial intelligence or machine learning approaches. Comparator strategies included conventional screening and risk stratification methods based on serum biomarkers, clinical parameters, or traditional imaging modalities. Outcomes of interest encompassed improvements in early-stage HCC detection, optimization of disease risk stratification, and enhanced prediction of immunotherapy response.

Literature selection was conducted using a transparent and reproducible process without adopting a formal systematic review protocol. The identification and screening process was reported descriptively using a modified literature selection flowchart to enhance transparency and minimize selection bias. A structured literature search was performed in PubMed, Scopus, ScienceDirect, and Google Scholar to identify studies published between 2021 and 2026. Restricting the search period to the most recent five years was intended to capture advances in multi-omics technologies, artificial intelligence, and translational applications of precision hepatology. PubMed, Scopus, and ScienceDirect were selected to ensure comprehensive coverage of high-quality biomedical and multidisciplinary literature, whereas Google Scholar was used as a supplementary source to identify potentially relevant interdisciplinary studies that might not have been indexed in conventional databases.

The search strategy combined keywords and Boolean operators, including "*hepatocellular carcinoma*," "*multi-omics*," "*genomics*," "*transcriptomics*," "*proteomics*," "*metabolomics*," "*circulating tumor DNA*," "*DNA methylation*," "*artificial intelligence*," "*machine learning*," and "*immunotherapy response prediction*." Literature screening was performed through sequential stages of study identification, title and abstract screening, and full-text eligibility assessment using Rayyan to improve transparency and reduce selection bias during study curation.

Studies were considered eligible if they were original investigations or review articles addressing the application of multi-omics and artificial intelligence in HCC screening, risk stratification, or therapeutic response prediction, were published in English or Indonesian, and were available in full text. Articles deemed irrelevant to the scope of the review, unavailable in full text, or representing non-scientific opinion pieces were excluded to maintain the validity of evidence synthesis.

All eligible studies were analyzed qualitatively using thematic synthesis by categorizing evidence according to omics platforms, artificial intelligence methodologies, and reported clinical applications. The robustness of the synthesis was strengthened through triangulation of evidence sources by comparing findings across studies, assessing consistency of results, and identifying differences in study design and population characteristics. In addition, the strength of evidence was qualitatively appraised based on study design, sample size, predictive model validation methods, and population generalizability.

To ensure analytical consistency, operational definitions were established as follows: (1) integration level was classified as single-omics, multimodal non-omics (e.g., radiomics combined with clinical variables), or true multi-omics (defined as the computational integration of at least two omics layers); (2) a dynamic model was defined as a longitudinal or time-to-event model incorporating temporal trajectories; and (3) validation was categorized as internal validation, external validation, or the absence of independent validation. The literature identification and selection process is summarized in a modified PRISMA 2020 flow diagram (Figure 1).

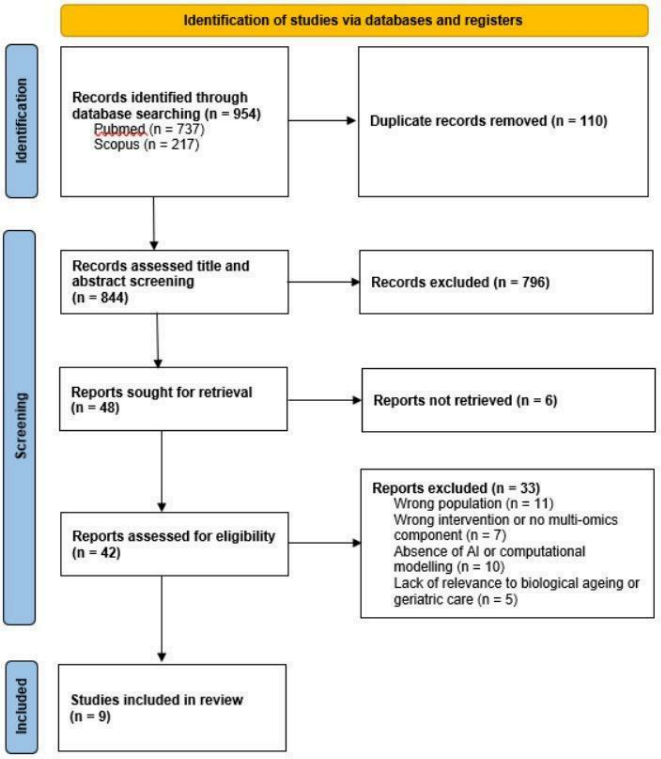

Figure 1. Modified PRISMA 2020 flow diagram of literature identification, screening, eligibility assessment, and inclusion.

3. Discussion

3.1 Clinical and Biological Heterogeneity of HCC Across the MASLD–Cirrhosis Spectrum

Hepatocellular carcinoma (HCC) remains one of the leading causes of cancer-related mortality worldwide, with more than 900,000 new cases diagnosed annually and a continuously increasing global incidence.[2-3] The changing epidemiology of chronic liver diseases has led to a substantial shift in the etiological landscape of HCC, with metabolic dysfunction-associated steatotic liver disease (MASLD) increasingly replacing viral hepatitis as a major driver of hepatocarcinogenesis.[5,7] The growing prevalence of obesity, type 2 diabetes mellitus, and metabolic syndrome has contributed significantly to the escalating global burden of MASLD, thereby increasing the risk of HCC development.[6-7]

Unlike classical etiologies such as hepatitis B or hepatitis C infection, MASLD-associated HCC exhibits greater clinical heterogeneity. In a substantial proportion of patients, HCC may develop even in the absence of established cirrhosis, posing a major challenge to current surveillance strategies that predominantly target cirrhotic populations.[4,10] Consequently, many patients with MASLD remain excluded from existing HCC surveillance programs, ultimately contributing to delayed diagnosis and reducing opportunities for curative interventions.[8-9]

From a biological perspective, hepatocarcinogenesis in MASLD is a multifactorial process involving complex interactions among metabolic dysfunction, chronic inflammation, oxidative stress, and alterations in the tumor microenvironment.[1,24] Insulin resistance and hepatocellular lipid accumulation can induce lipotoxicity, resulting in DNA damage, activation of inflammatory signaling pathways, and extracellular matrix remodeling that collectively facilitate malignant transformation of hepatocytes.[24-25] In addition, epigenetic modifications, genomic instability, and activation of molecular pathways associated with cellular proliferation and angiogenesis further contribute to tumor progression.[1,14]

The biological heterogeneity of HCC has been increasingly elucidated through multi-omics approaches, which have revealed substantial variations at the genomic, transcriptomic, proteomic, and tumor immune landscape levels.[12,14] Integrative analyses suggest that distinct molecular subtypes of HCC exhibit markedly different biological characteristics, therapeutic responses, and prognostic outcomes.[15,26] Moreover, interactions between tumor cells and the immune system, including T-cell exhaustion and dynamic

remodeling of the tumor immune microenvironment, play critical roles in determining responsiveness to systemic therapies, particularly immunotherapy.[27-28]

Although numerous candidate biomarkers have been identified through multi-omics studies, their clinical implementation remains limited due to the complexity of integrating large-scale biological datasets and the inherent limitations of conventional analytical approaches.[26,29] Consequently, artificial intelligence (AI)-based methodologies are increasingly being developed to integrate multi-omics, radiological, and clinical data in order to enhance risk stratification and improve prediction of therapeutic response in patients with HCC.[19,30]

Taken together, the clinical and biological heterogeneity observed across the MASLD–cirrhosis spectrum underscores the need for more comprehensive and precision-oriented diagnostic strategies. The integration of multi-omics technologies with AI-driven analytical frameworks may represent a promising avenue for elucidating the mechanisms underlying hepatocarcinogenesis while simultaneously improving early detection and enabling personalized therapeutic approaches in patients with HCC.

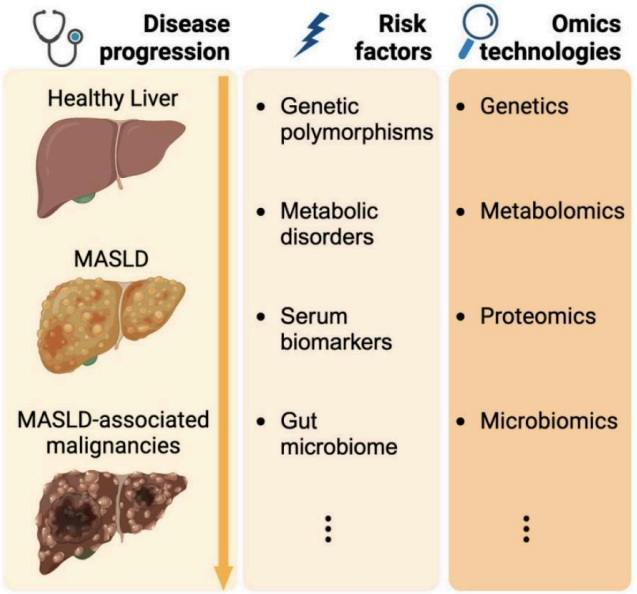

Figure 2. Spectrum of MASLD progression toward malignancy, illustrating risk factors and multi-omics platforms capturing the clinical and biological heterogeneity of MASLD-related HCC (adapted from Lan and Tacke).[24]

3.2 Limitations of Conventional Diagnostic and Risk Stratification Models

Despite recommendations from multiple clinical guidelines advocating surveillance strategies for high-risk populations, early detection of hepatocellular carcinoma (HCC) remains a significant challenge in routine clinical practice. Conventional surveillance approaches primarily rely on imaging modalities, particularly ultrasonography, with or without serum biomarkers such as alpha-fetoprotein (AFP). However, the sensitivity of these modalities for detecting early-stage HCC remains suboptimal, especially among patients with metabolic dysfunction-associated steatotic liver disease (MASLD).[8-11]

Beyond their limited sensitivity, current surveillance strategies predominantly target cirrhotic populations, potentially overlooking patients with MASLD who may develop HCC in the absence of established cirrhosis.[4,10] This limitation creates a substantial diagnostic gap, as a considerable proportion of individuals with MASLD are not eligible for routine HCC surveillance under existing recommendations. Consequently, many of these patients are diagnosed at advanced stages, when curative treatment options become increasingly restricted.[8-9,24,30]

Moreover, contemporary risk stratification models continue to rely heavily on conventional clinical and radiological parameters that do not adequately capture the biological complexity underlying hepatocarcinogenesis.[1,14] HCC development is increasingly recognized as a multidimensional process involving intricate interactions among genomic alterations, transcriptomic signatures, proteomic profiles, and

dynamic changes within the tumor microenvironment, features that cannot be comprehensively characterized using traditional diagnostic paradigms.[14,20]

These shortcomings become particularly evident when considering the pronounced molecular heterogeneity of HCC, which may substantially influence therapeutic response, disease progression, and patient prognosis.[15,31] In the absence of deeper biological integration, conventional prediction models possess limited capability to identify high-risk individuals accurately or to facilitate personalized treatment strategies.

With the rapid advancement of omics technologies and computational analytics, multi-omics integration has emerged as a promising avenue for uncovering novel biomarkers and clinically relevant molecular signatures.[26,29,32] Nevertheless, the resulting high-dimensional biological datasets necessitate more sophisticated analytical methodologies, particularly artificial intelligence (AI)-based approaches capable of extracting latent predictive patterns that are often inaccessible to conventional statistical methods.[19,22,30,33]

Taken together, the convergence of multi-omics technologies, liquid biopsy platforms, and AI-driven analytics may constitute the next generation of diagnostic strategies for HCC, offering the potential to improve early detection, refine individualized risk assessment, and ultimately support precision-oriented surveillance programs.

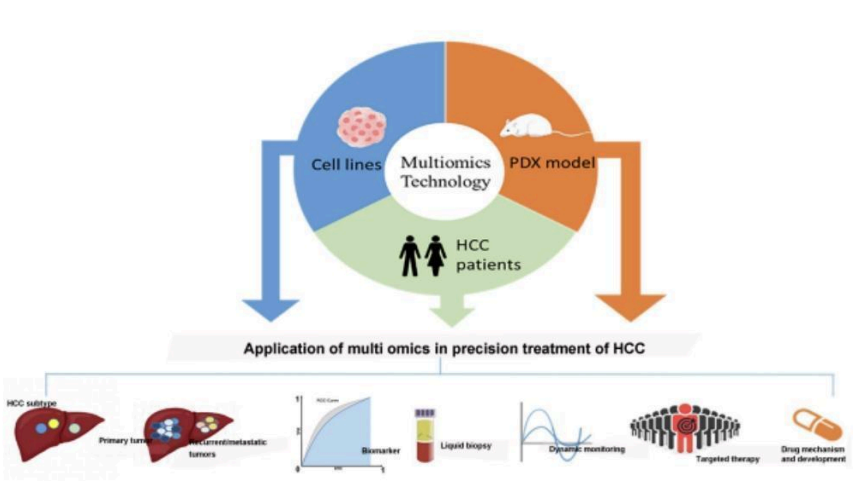

Figure 3. Conceptual model of dynamic risk stratification for MASLD-related HCC based on multi-omics integration and artificial intelligence (adapted from He et al.).[14]

3.3 Systems Precision Hepatology as an Emerging Paradigm

The biological complexity of hepatocellular carcinoma (HCC), coupled with the limitations of conventional diagnostic approaches, has fostered the emergence of a new paradigm in modern hepatology, namely systems precision hepatology. This framework seeks to characterize liver diseases as dynamic biological systems through the integration of multiple layers of molecular information, including genomics, transcriptomics, proteomics, metabolomics, and features of the tumor microenvironment.[14-15,20,23]

In contrast to traditional diagnostic strategies that rely predominantly on single biomarkers or isolated clinical parameters, systems precision hepatology emphasizes multidimensional analyses to capture the complexity of molecular networks underlying hepatocarcinogenesis.[9,14-15,24] Such an approach facilitates the identification of molecular HCC subtypes characterized by distinct biological features, pathogenic mechanisms, therapeutic susceptibilities, and clinical outcomes.[13,15,31,34]

Recent advances in multi-omics profiling have created unprecedented opportunities to integrate large-scale biological datasets and elucidate the interplay among genomic alterations, transcriptional regulation, protein expression, and metabolic reprogramming occurring throughout HCC progression.[13-14,20,35] Integrative analyses have further enabled the discovery of prognostic biomarkers and novel therapeutic targets that may remain undetectable through conventional single-layer analytical approaches.[26,29,32]

Nevertheless, the scale and complexity of multi-omics datasets pose considerable analytical challenges. To address these limitations, artificial intelligence (AI) and machine learning techniques have increasingly been

adopted to simultaneously integrate molecular, radiological, and clinical information.[19,22,30,33] These computational approaches enable the development of predictive models with improved performance for early detection, individualized risk stratification, and therapeutic response prediction in patients with HCC.

Taken together, systems precision hepatology provides a conceptual framework that combines multi-omics integration, advanced computational analytics, and liquid biopsy-derived biomarkers to characterize HCC heterogeneity more comprehensively. Beyond enhancing biological understanding, this paradigm has the potential to serve as the foundation for next-generation diagnostic and therapeutic strategies aimed at delivering more precise and personalized management of liver cancer.

3.4 Multi-Omics in Mapping Hepatocarcinogenic Trajectories

The development of hepatocellular carcinoma (HCC) is a multistep process characterized by the accumulation of molecular alterations across the spectrum of chronic liver disease, ranging from steatosis and metabolic inflammation to fibrosis and ultimately malignant transformation of hepatocytes. Multi-omics approaches provide an opportunity to delineate these hepatocarcinogenic trajectories more comprehensively by integrating multiple layers of biological information, including genomic, transcriptomic, proteomic, and metabolomic data. In HCC research, multi-omics strategies encompass genomic analyses of driver mutations, such as TP53 and CTNNB1, transcriptomic profiling through RNA sequencing, mass spectrometry-based proteomics, and metabolomic characterization reflecting metabolic reprogramming during MASLD-associated hepatocarcinogenesis.[14,17,20,24,36]

Genomic studies have identified a wide range of genetic alterations involved in hepatocarcinogenesis, including mutations affecting cell proliferation regulators, oncogenic signaling pathways, and DNA repair mechanisms.[14] In parallel, transcriptomic and proteomic analyses provide insights into alterations in gene and protein expression associated with cellular proliferation, angiogenesis, and extracellular matrix remodeling throughout tumor progression.[13,15,31]

Importantly, multi-omics integration facilitates the reconstruction of complex molecular interaction networks, including the interplay among metabolic pathways, immune responses, and the tumor microenvironment. Recent studies have demonstrated that alterations within the tumor immune landscape, including T-cell exhaustion and evolving interactions between malignant and immune cells, play critical roles in determining disease progression and responsiveness to immunotherapeutic interventions.[27-28]

Beyond elucidating biological mechanisms, multi-omics approaches are increasingly being employed to identify biomarkers capable of predicting prognosis and therapeutic response in patients with HCC.[13,27,34] The integration of large-scale biological datasets enables the development of molecular classification systems that more accurately distinguish tumor subtypes while uncovering clinically actionable therapeutic targets.[20,26,29]

Despite these advances, interpretation of multi-omics data remains challenging because of their high dimensionality and the complexity of molecular networks underlying hepatocarcinogenesis. Consequently, computational approaches powered by artificial intelligence are increasingly required to integrate multi-omics information with clinical and radiological data, thereby enabling more accurate modeling of disease trajectories and supporting the development of precision-based diagnostic and therapeutic strategies.[19,22,30,33]

To provide a structured overview of the available evidence, Table 1 summarizes selected omics- and AI-based approaches relevant to HCC detection, risk stratification, and therapeutic-response prediction. Because the intended outcomes and analytical designs differed across studies, model performance is presented using the metrics reported in each original study, including sensitivity, specificity, accuracy, area under the curve, or concordance index.

Study	Population/data source	Modality and parameter	Clinical purpose	Sensitivity	Specificity	Other reported performance	Relevance to MASLD-related HCC
Das et al., 2024 [12]	Hispanic patients with HCC; paired tumor and adjacent non-tumor tissues	Integrated genomics, transcriptomics, proteomics, metabolomics, and serum lipidomics	Molecular characterization and identification of HCC subtypes and candidate biomarkers	NA	NA	Two molecular subtypes identified and evaluated using an external HCC dataset	Indirect; HCC cohort with heterogeneous etiologies and not specifically MASLD
Hu et al., 2024 [13]	Public HCC transcriptomic, single-cell, spatial-transcriptomic, and clinical datasets	Mitochondria-associated cell-death gene signature	Prognostic and therapeutic-response stratification	NA	NA	Survival- and risk-model performance; sensitivity and specificity were not applicable to the prognostic outcome	Indirect; relevant to molecular heterogeneity but not MASLD-specific
Min et al., 2025 [18]	55 patients with HCC receiving immunotherapy	Pretreatment CT radiomics integrating liver and viable-tumor features	Prediction of immunotherapy response	70%	94%	Accuracy: 86% for the combined liver-tumor model	Indirect; relevant to personalized treatment, but radiomics rather than true multi-omics and not MASLD-specific
Feng et al., 2025 [17]	175 patients with advanced HCC receiving immunotherapy and targeted therapy, with or without radiotherapy	Clinical variables integrated using machine-learning models	Prediction of overall survival	NA	NA	Validation C-index: 0.65; validation AUCs: 0.72, 0.75, and 0.73 for 1-, 2-, and 3-year survival	Indirect; advanced-HCC prognostic model, not an early-detection or MASLD-specific model
Matboli et al., 2025 [35]	Patients assessed for metabolic dysfunction-associated steatohepatitis	EP300 and CPN60 expression integrated with biochemical and metabolic variables using machine learning	Noninvasive classification of MASH/NASH	NR	NR	Classification accuracy: 97%	Contextual; relevant to the MASLD-MASH continuum but did not evaluate HCC
Varghese et al., 2026 [34]	Egyptian HCC and cirrhosis cohort	Machine-learning integration of proteomic and metabolomic profiles	Differentiation of HCC from cirrhosis and multi-omics biomarker identification	NR	NR	Classification performance was evaluated, but separate sensitivity and specificity were not provided in the accessible abstract	Directly relevant to HCC classification, but the cohort was not MASLD-specific

Table 1. Selected omics- and AI-based approaches relevant to HCC detection, risk stratification, and therapeutic-response prediction.

Abbreviations: AI, artificial intelligence; AUC, area under the receiver operating characteristic curve; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; NA, not applicable to the study outcome; NR, not reported separately in the original study.

The summarized evidence demonstrates substantial heterogeneity in study populations, data modalities, clinical purposes, and performance metrics. Only a limited number of studies reported sensitivity and specificity because several models were developed for prognostic or therapeutic-response outcomes rather

than diagnostic classification. Furthermore, most studies involved mixed-etiology HCC cohorts and were not specifically developed or validated in patients with MASLD. Therefore, although these findings support the potential contribution of omics and AI to precision hepatology, their direct application to MASLD-specific HCC surveillance requires prospective longitudinal validation in etiologically defined populations.

3.5 Artificial Intelligence as an Orchestrator of Multi-Omics Integration for Risk Prediction and Early Detection

The rapid advancement of multi-omics technologies has generated vast amounts of high-dimensional biological data encompassing genomic, transcriptomic, proteomic, metabolomic, and tumor microenvironmental information. The complexity of these datasets presents substantial analytical challenges, as conventional statistical methods often fail to capture the intricate molecular interactions underlying hepatocarcinogenesis.[14-15,20,26]

In this context, artificial intelligence (AI) has emerged as a powerful computational framework capable of simultaneously integrating multiple layers of biological information to identify clinically relevant predictive patterns.[19,22] A variety of machine learning algorithms, including random forest, support vector machine, and deep neural network architectures, have been employed to integrate multi-omics and radiomics data for developing predictive models of HCC risk and immunotherapy responsiveness. These computational approaches enable the interrogation of multidimensional datasets to identify molecular signatures associated with HCC development, disease progression, and treatment outcomes.[30,34,37]

In addition to molecular data integration, AI has increasingly been utilized in radiological and radiomics analyses to improve the early detection of HCC. Deep learning models can extract quantitative features from medical images that are not visually discernible to humans, thereby enhancing the sensitivity of early-stage tumor lesion detection.[17-19,36] The integration of radiological data with molecular information derived from multi-omics approaches provides a more comprehensive understanding of tumor biological characteristics and their potential progression.

Furthermore, AI-based predictive models have demonstrated considerable potential in developing risk stratification systems that are more adaptive to the heterogeneity of HCC.[17] By combining clinical, molecular, and radiological parameters, this approach enables the development of a precision hepatology framework focused on early detection and the personalization of disease management strategies.

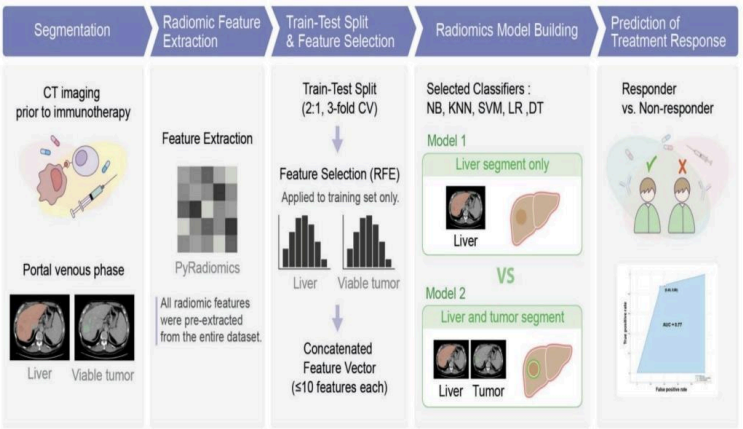

Figure 4. Schematic workflow of a pretreatment CT-based radiomics model for predicting treatment response in patients with HCC.[18]

3.6 Challenges in Clinical Translation and Healthcare System Implementation

To ensure that the integration of multi-omics and artificial intelligence (AI) has a tangible impact on outcomes in patients with hepatocellular carcinoma (HCC), predictive models need to be translated into clinical decision support systems (CDSSs) integrated with electronic health records and clinical workflows.[19,22,30,33] Effective CDSSs should generate practical outputs, such as dynamic HCC risk scores to determine surveillance intervals, prioritize imaging modalities, and guide the selection of systemic or locoregional therapies based on individual risk profiles.[8,11,14-15] To enhance clinicians' trust, these models also require an adequate level of interpretability through the identification of key clinical or omics features

driving predictions, for example, by using feature importance analysis or SHAP methods, thereby allowing system recommendations to be biologically traceable.[22,30,38-39]

On the other hand, the widespread implementation of these technologies is highly dependent on economic feasibility and healthcare system readiness. The costs associated with multi-omics sequencing, computational infrastructure, and bioinformatics expertise should be balanced against their potential benefits, including improved early-stage HCC detection, reduced use of ineffective and costly therapies, and optimization of diagnostic and therapeutic resources.[8-9,20,24] In developing countries, disparities in infrastructure between tertiary referral centers and peripheral healthcare facilities necessitate phased implementation strategies through pilot centers, centralized analytical platforms, and approaches such as federated learning to facilitate cross-institutional model development without transferring raw data.[9,24,30,32]

In addition to technical and economic considerations, data governance and equitable access represent critical factors in the implementation of precision hepatology. The integration of genomic and clinical data raises concerns regarding genomic privacy, cybersecurity, algorithmic fairness, and the potential for bias against specific populations.[22,26,29-30] Without robust regulatory frameworks and standardized bioinformatics pipelines, AI applications may result in predictive models with limited generalizability or may even exacerbate existing healthcare disparities. Therefore, the integration of multi-omics and AI requires strengthening clinical bioinformatics capacity, standardizing data protocols, and establishing healthcare policies that support the sustainable implementation of precision surveillance in high-risk populations, such as patients with MASLD-related HCC.[8-9,24,30,35]

3.7 Future Research Horizons

The advancement of multi-omics integration and artificial intelligence (AI) opens opportunities for the development of a digital twin liver, a dynamic computational representation of the liver that integrates genomic, transcriptomic, proteomic, metabolomic, radiomic, and longitudinal clinical data to simulate disease progression and therapeutic responses at the individual level. This concept is rooted in multi-layer integrative approaches and AI-based predictive modeling, which have demonstrated potential in the molecular classification and prognostic stratification of HCC but have not yet been fully developed into longitudinal simulation systems capable of adapting to patients' biological changes.[13-15,31,34]

Furthermore, the development of real-time omics monitoring through dynamic liquid biopsy approaches has the potential to revolutionize the HCC surveillance paradigm, particularly in patients with MASLD who may develop HCC in the absence of cirrhosis. The integration of circulating tumor DNA, methylation profiles, and proteomic signatures with machine learning models enables the detection of molecular alterations before radiological manifestations become apparent, while also facilitating more precise monitoring of clonal evolution and immunotherapy resistance.[20,23,31,34] Conceptually, this approach expands the role of surveillance from static detection toward the mapping of progressive molecular trajectories.

From a methodological perspective, the application of federated learning in hepatology represents a strategic direction for overcoming the limited generalizability of AI models trained on homogeneous single-center datasets. By enabling cross-institutional model training without sharing raw data, this approach has the potential to improve external validity, preserve patient data security, and accelerate the adoption of AI in global hepatology practice.[3,12,19,22] This strategy is particularly relevant in the context of the genetic and epidemiological heterogeneity of HCC across different populations, including those in Southeast Asia.

Overall, future research directions necessitate a transition from static predictive models toward adaptive systems based on longitudinal data that are capable of integrating molecular dynamics, immune responses, and clinical factors within a unified framework for precision surveillance and personalized therapy that is applicable in real-world clinical settings.

4. Conclusion

The integration of multi-omics and artificial intelligence represents a fundamental shift from single-biomarker approaches toward a systems precision hepatology framework in the management of hepatocellular carcinoma (HCC), particularly within the spectrum of metabolic dysfunction-associated steatotic liver disease (MASLD). The literature synthesis indicates that the combination of genomics, epigenomics, transcriptomics, proteomics, metabolomics, and liquid biopsy can reveal molecular heterogeneity and tumor evolutionary dynamics more comprehensively than conventional reductionist

approaches. When integrated with machine learning and deep learning algorithms, these multidimensional datasets have the potential to establish dynamic risk stratification systems that not only improve the accuracy of early detection but also support more precise prediction of immunotherapy response.

However, the majority of existing studies remain retrospective in nature, with limited external validation, cross-sectional analyses, and relatively homogeneous cohorts. Longitudinal integration across multiple omics layers, as well as the translation of AI models into real-world clinical practice, continues to face methodological, regulatory, and infrastructural challenges. Therefore, although the paradigm of dynamic risk stratification based on molecular trajectories from MASLD to hepatocarcinogenesis appears promising, its implementation still requires stronger evidence and methodological harmonization before widespread clinical adoption can be achieved.

5. Recommendations

Future efforts should focus on longitudinal study designs that characterize the molecular evolution from MASLD to HCC over time, thereby enabling risk stratification models to be developed based on biological trajectories rather than static molecular snapshots. Multicenter and multiethnic validation studies are essential to ensure the generalizability of AI models, particularly in populations with diverse etiological backgrounds. In addition, standardization of multi-omics data integration, algorithm transparency, and improved model interpretability should be prioritized to strengthen clinicians' confidence in AI-based systems.

Beyond technical considerations, evaluations of cost-effectiveness and healthcare system readiness should also be considered before widespread implementation. The transition toward precision surveillance will only be meaningful if it can be translated into adaptive screening strategies that are practical, safe, and sustainable within real-world clinical settings.

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