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Review

Application of biological big data and radiomics in hepatocellular carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC), one of the most common gastrointestinal cancers, has been considered a worldwide threat due to its high incidence and poor prognosis. In recent years, with the continuous emergence and promotion of new sequencing technologies in omics, genomics, transcriptomics, proteomics, and liquid biopsy are used to assess HCC heterogeneity from different perspectives and become a hotspot in the field of tumor precision medicine. In addition, with the continuous improvement of machine learning algorithms and deep learning algorithms, radiomics has made great progress in the field of ultrasound, CT and MRI for HCC. This article mainly reviews the research progress of biological big data and radiomics in HCC, and it provides new methods and ideas for the diagnosis, prognosis, and therapy of HCC.

1. Introduction

Hepatocellular carcinoma (HCC), one of the most common gastrointestinal cancers, has been considered a worldwide threat due to its high incidence and poor prognosis [1]. HCC has strong heterogeneity, resulting in difficult treatment [2]. The early diagnosis rate of HCC is low, and because HCC is often found in the late stage, the opportunity for surgery is lost. Even when patients receive surgery, there is a lack of hierarchical management and precise therapy. Most patients show a 5-year survival rate of merely 5%–14% [3].

HCC is an extremely complex disease involving multiple DNA, RNA, and protein abnormalities. In recent decades, with the continuous development of high-throughput sequencing technology, large-scale multiomics biological big data have been generated, providing multifaceted insights into biomarker discovery. Biological big data are crucial to reveal the high heterogeneity of HCC, improve the early diagnosis rate of HCC, and promote the hierarchical management and precise therapy of HCC.

In the clinic, HCC is usually diagnosed by cross-sectional liver imaging techniques, such as contrast-enhanced ultrasound, contrast-enhanced computed tomography (CT), and magnetic resonance imaging (MRI) [4–6]. However, some limitations of imaging methods, such as time consumption, low sensitivity, and subjective experience of physicians, determine the need to develop new screening methods and highly sensitive and specific radiomics models for the early diagnosis of HCC and prediction of patient prognosis.

In recent years, due to great progress in artificial intelligence (AI) technology, machine and deep learning methods are widely used in the field of radiomics [7]. Radiomics is a powerful tool for analyzing imaging data and is widely used in monitoring treatment response, biomarker determination, diagnosis, and prognosis prediction [8].

Therefore, it is necessary to mine multiomics biological big data and study radiomics to improve the early diagnosis rate of HCC, predict the prognosis of HCC, understand the heterogeneity of HCC, and realize precise therapy for HCC. This article reviews the research progress of biological big data and radiomics in the field of HCC, and it provides new methods and ideas for the diagnosis and treatment of HCC.

2. Biological big data

The summary of biological big data is shown in Table 1.

2.1. Genomics

Next-generation sequencing is providing a deeper understanding of cancer genetics. Genome sequencing not only promotes the study of tumor heterogeneity but also comprehensively illustrates the biological characteristics and

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Table 1
Biological big data.

	Biological big data	References
Genomics		
High frequency mutant genes	TERT, TP53, and CTNNB1	[14–25]
Liquid biopsy		[26–29]
Transcriptomics		
Immune-related gene/miRNA/lncRNA signature		
Immune-related genes	EZH2, FTL, CFHR3, ISM2, and CDK5	[33]
Immune-related microRNAs	microRNA-7702, microRNA-4772-3p, microRNA-141-3p, microRNA-346, microRNA-548f-3p, microRNA-509-3-5p, and microRNA-506-3p	[34]
Immune-related lncRNAs	AC145207.5, MSC-AS1, SNHG3, AL031985.3, NRAV, and AL365203.2	[35]
Metabolism-related gene/lncRNA signature		
Glycolytic related genes	CDCA8, RAB5IF, SAP30, and UCK2	[38]
Glycolysis-related lncRNAs	AL031985.3, AL365203.2, MIR4435-2HG, and AC015908.3	[39]
Lipid metabolism-related genes	ME1, MED10, and MED22	[41]
Amino acid metabolism-related genes	CYB5R3, B3GAT3, SEPHS1, HMGCS2, GNPDA1, HEXB, PLOD2, GOT2, and B4GALT2	[46]
Cell death-related gene/miRNA/lncRNA signature		
Ferroptosis-related gene/lncRNA signature		
Ferroptosis-related genes	SLC7A11, G6PD, CISD1, CARS, SLC1A5, ACACA, ACSL3, NQO1, NFS1, and GPX4	[49]
Ferroptosis-related lncRNA	AC015908.3, LINC01138, AC009283.1, Z83851.1, and LUCAT1	[50]
Pyroptosis-related lncRNA signature		
Pyroptosis-related lncRNAs	MKLN1-AS, LNCSRLR, AC023157.2, AP003392.4, AC007128.1, AL031985.3, AC019080.5, PCCA-DT, and AL445228.3	[55]
Pyroptosis-related lncRNAs	OSMR-AS1, AL031985.3, NRAV, MKLN1-AS, AL137186.2, AC073611.1, MIR44352HG, AL118511.1, and AL049840.4	[56]
Necroptosis-related miRNA/lncRNA signature		
Necroptosis-related miRNAs	miR-10b-5p, miR-592, miR-500a-3p, hsa-miR-326, and miR-139-5p	[61]
Necroptosis-related lncRNAs	HCG27, C2orf27A, BACE1-AS, SNHG4, MIR210HG, SNHG3, and HCG11	[62]
Autophagy-related gene/lncRNA signature		
Autophagy-related genes	HDAC1, RHEB, ATIC, SPNS1, and SQSTM1	[65]
Autophagy-related genes	SQSTM1, HSPB8, and BIRC5	[66]
Autophagy-related lncRNAs	LINC01138, PRRT3-AS1, RP11-324I22.4, RP11-73M18.8, CTD-2510F5.4, RP11-479G22.8, and CTC-297N7.9	[67]
EMT lncRNA signatures		
EMT-related lncRNAs	AC103760.1, AC015908.3, LINC02362, LINC02499, F11-AS1, LINC00942, PRRT3-AS1, AC012146.1, AC092171.2, AC099850.3, CASC19, and AL158206.1	[71]
EMT-related lncRNAs	AL031985.3, AC023157.3, AC099850.3, CYTOR, and AL365203.2	[72]
Hypoxia-related lncRNA signature		
Hypoxia-related lncRNAs	NRAV, AC099850.4, MIR210HG	[74]
Hypoxia-related lncRNAs	RHPN1-AS1, DUXAP8, CAHM, MKLN1-AS, and LINC00869	[75]
Proteomics		
Protein biomarkers	AFP, AFP-L3, DCP, OPN, glypican-3, and midkine (MDK)	[78–95]

clinical outcomes of cancer cells. The most prevalent driver gene mutations in HCC are in the telomerase reverse transcriptase (TERT) promoter, TP53, CTNNB1, AXIN1, ARID1A, and ARID2, which cause changes in the activation of several pathways, including telomere maintenance, P53 cell regulation, Wnt/β-catenin, Akt/mTOR, MAPK, and oxidative stress [9–15].

2.1.1. *TERT*

The most common somatic mutations (60%) in HCC are in the promoter region of the TERT gene, which is a major regulator of telomere length [14]. TERT promoter mutations are reported in dysplastic nodules or early HCC, suggesting that they may be driver genes in HCC [16].

2.1.2. *TP53*

The second most frequently altered gene in HCC is TP53. As a transcription factor, the p53 tumor suppressor protein regulates the expression of genes involved in a variety of processes, including DNA repair, cell cycle arrest, and cell apoptosis [17,18]. p53 mutations have been reported to be highly associated with HCC [19,20]. Studies have shown that long-term smoking can lead to an increase in p53 mutations, which can lead to HCC [21].

2.1.3. *CTNNB1*

The third most frequently mutated gene is CTNNB1. Notably, CTNNB1, which encodes β-catenin, has been recognized as one of the most frequently mutated genes in primary HCC [22]. It has been reported that HCC patients with CTNNB1 mutations have longer overall survival (OS), suggesting that CTNNB1 mutations are a favorable prognostic marker [23,24]. However, activation of the Wnt/β-catenin pathway reduces immune infiltration and is likely to be resistant to immune checkpoint inhibitors. A previous study has reported that Wnt/β-catenin pathway mutations are associated with poorer outcomes, including shorter median progression-free survival and shorter median OS, in patients receiving PD-1 inhibitors [25].

2.1.4. *Liquid biopsy*

Liquid biopsy has good clinical application prospects and is widely used in the study of tumor heterogeneity. Liquid biopsy refers to the analysis of tumors by circulating tumor cells (CTCs), which are cells from tumors that enter the circulation, or circulating tumor DNA (ctDNA), which is a fragment of DNA in the blood circulation that is derived from tumors [26]. Liquid biopsies offer many benefits over traditional needle biopsies. Needle biopsies are invasive and require sampling from the tumor, while liquid biopsies are relatively non-invasive and require only drawing blood. Liquid biopsies offer a non-invasive method to continuously monitor a patient's tumor changes over time without causing harm to the body. Moreover, needle biopsy samples come from a tumor lesion at a single point in time, and they may not reflect tumor burden or fully capture genomic changes throughout the tumor [27,28]. However, liquid biopsies reflect major tumor region genetic changes rather than a specific region by measuring CTCs or ctDNA entering the bloodstream. Cai et al. conducted a detailed analysis of the mutation profile of patients having HCC; they confirmed that ctDNA overcomes tumor heterogeneity, and they demonstrated that tumor stem somatic mutations dynamically reflect tumor burden. Cai et al. showed that genomic alterations related to drug targets can be detected in ctDNA, which suggests that analysis of the circulating mutation spectrum may provide detailed information for guiding drug treatment in addition to monitoring-gained mutations related to drug resistance [29].

However, due to the high cost of the technology and low detection sensitivity, liquid biopsy is still a long way from being used in clinical practice. With the improvement of detection technology, liquid biopsy technology may accelerate clinical development and build a bridge to precision medicine.

2.2. Transcriptomics

Gene expression is one of the most important biological processes in living organisms. Transcriptome sequencing is the most widely used high-throughput gene expression detection technology in biomedical research. Transcriptome sequencing not only analyses the differences in gene expression between tumors and normal tissues but also identifies novel cancer markers, constructs risk prediction models, and predicts cell composition and abundance. Transcriptome sequencing also promotes the development of a large number of biological information mining methods for transcriptome data. Transcriptome sequencing technology has been applied for more than 10 years, generating a large amount of transcriptome data. The most common public databases are The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO). TCGA is a landmark cancer genome plan led by the National Cancer Institute and the National Human Genome Research Institute. TCGA database contains transcriptome sequencing data (including mRNA, microRNA, and lncRNA) from nearly 20,000 samples from 33 cancers and partially matched adjacent samples. Moreover, TCGA database provides clinical information and survival times of these cancer samples. GEO is a gene expression database created by the National Center for Biotechnology Information, and it is also the largest gene expression data center.

In recent years, an increasing number of studies have been conducted to construct HCC risk prediction models based on transcriptome data. Cox proportional hazards regression is the most commonly used method in these studies. The Cox proportional hazards model, which was first proposed by Cox DR in 1972 [30], is a classical and widely used model in medical survival analysis. A Cox regression model has been used to study the influence of related factors on survival time and survival status. The dependent variables of the model are survival time and survival outcome, while the independent variables are factors related to survival.

We focused on summarizing the risk prediction models of HCC based on the immune gene signature, metabolism gene signature, cell death gene signature, autophagy gene signature, epithelial–mesenchymal transition (EMT) lncRNA signature, and hypoxia-related lncRNA signature to provide a new perspective for risk stratification, prognosis, and treatment optimization of HCC.

2.2.1. Immune-related gene/miRNA/lncRNA signature

In recent years, tumor immunity and immunotherapy have attracted great attention in the fields of oncology and immunology. Tumor immunotherapy, especially immune cell infiltration in the tumor microenvironment and immune checkpoint blockade therapy, has achieved remarkable results in cancer treatment, which provides an excellent opportunity to re-examine and explore the role of the immune system in tumors [31,32]. Huang et al. [33] identified five immune-related genes (IRGs) (EZH2, FTL, CFHR3, ISM2, and CDK5) by univariate Cox regression analysis-LASSO regression analysis-multivariate Cox regression analysis in TCGA database; they generated a risk score based on five IRGs, and according to the median risk score, patients with higher risk scores had lower OS at 1, 2, 3, and 5 years in both the training and validation groups. In addition, IRGs signature are associated with the infiltration of immune cells. The risk prediction model based on IRGs and clinical characteristics can predict the OS of patients at 1, 3, and 5 years with area under the curve (AUC) of 0.8. Li et al. [34] constructed an immune signature based on seven immune-related microRNAs (microRNA-7702, microRNA-4772-3p, microRNA-141-3p, microRNA-346, microRNA-548f-3p, microRNA-509-3-5p, and microRNA-506-3p), and according to the median risk score, patients were divided into high- and low-risk groups. The Kaplan-Meier (KM) curve analysis showed that the low-risk group had better OS than the high-risk group in different ages, different genders, different grades and different tumor staging, and the 1-, 3-, and 5-year AUC values of the risk prediction model based on immune-related microRNAs were 0.692, 0.703, and 0.687, respectively. In addition, the results showed that the infiltration of immune cells and the expression of immune checkpoint genes were different between the high-risk and low-risk groups. Zhou et al. [35] constructed a prognosis signature based on six immune-related lncRNAs (AC145207.5, MSC-AS1, SNHG3, AL031985.3, NRAV, and AL365203.2), and they confirmed that the signature was an independent risk factor in patients having HCC. The risk prediction model had good prediction ability, and the AUC of the model reached 0.775. Gene set enrichment analysis (GSEA) suggested that the immune-related six-lncRNA signature was associated with the infiltration of immune cells. Furthermore, the immune-related six-lncRNA signature can predict the outcomes and immunotherapy response in patients with HCC.

2.2.2. Metabolism-related gene/lncRNA signature

Accumulating evidence suggests that reprogramming of energy metabolism plays an important role in the initiation and progression of tumors [36]. Aerobic glycolysis rapidly produces enough adenosine triphosphate to meet the energy demand of tumor growth and proliferation under hypoxic conditions, and aerobic glycolysis plays an important role in tumor proliferation, growth, invasion, and treatment [36,37]. Chen et al. [38] constructed a model based on four glycolytic-related genes (CDCA8, RAB5IF, SAP30, and UCK2) related to the prognosis of HCC with 1, 3, and 5-year AUC values of 0.815, 0.726, and 0.725, respectively, and they reported that the signature was an independent prognostic factor. These results suggested that the gene signature may contribute to individual risk estimation, survival prognosis, and clinical management. Bai et al. [39] constructed a prognostic model based on four glycolysis-related lncRNAs (AL031985.3, AL365203.2, MIR4435-2HG, and AC015908.3) with good prediction ability and significantly different OS in the high-risk and low-risk groups. The AUC of the model reached 0.763 in the training cohort and 0.728 in the validation cohort. In addition, the signature based on the four glycolysis-related lncRNAs was significantly associated with infiltrating immune cells and expression of immune checkpoint genes in patients having HCC.

Lipids are important substances for energy storage and the energy supply of the body, and they are also important structural components of biofilms. Abnormal lipid metabolism is also an important cause of cancer. Changes in fatty acid synthesis, β-oxidation, and cellular lipid composition contribute to the occurrence and development of HCC [40]. Wang et al. [41] identified three genes (ME1, MED10, and MED22) related to lipid metabolism with prognostic value for HCC, and they calculated the risk score of each HCC patient based on these genes and showed that the survival rate of patients having HCC in the high-risk group was significantly lower than that in the low-risk group. Multivariate Cox regression analysis showed that the risk score based on this gene was an independent prognostic factor for HCC. The AUC of the model reached 0.74 in the training cohort and 0.762 in the validation cohort.

Amino acid metabolism in the human body plays the following roles: (a) synthesis of tissue protein; (b) translation into acids, hormones, antibodies, creatine, and other ammonia-containing substances; (c) conversion to carbohydrates and fats; (d) oxidation into carbon dioxide, water, and urea to produce energy [42–44]. Amino acid metabolism mainly occurs in the liver [45]. Zhao et al. [46] constructed a prognostic risk prediction model for HCC based on nine amino acid metabolism-related genes (CYB5R3, B3GAT3, SEPHS1, HMGCS2, GNPDA1, HEXB, PLOD2, GOT2, and B4GALT2). According to the risk score, the patients were divided into a high-risk group and a low-risk group. KM analysis showed that high-risk patients had shorter OS than low-risk patients, and the AUC values of the signature for predicting the 1-, 2-, 3-, and 5-year survival rates of patients having HCC were 0.813, 0.770, 0.744, and 0.702, respectively.

2.2.3. Cell death-related gene/miRNA/lncRNA signature

Cell death mainly includes ferroptosis, pyroptosis, necroptosis, intrinsic apoptosis, extrinsic apoptosis, autophagy-dependent cell death,

lysosome-dependent cell death, immunogenic cell death, and cellular senescence [47]. Many new mechanisms have been discovered to regulate cell death pathways, and we will discuss the effects of ferroptosis, pyroptosis, and necroptosis on the prognosis of HCC.

2.2.3.1. Ferroptosis-related gene/lncRNA signature. Ferroptosis is a novel form of iron-dependent cell death characterized by excessive iron accumulation and lipid peroxidation, which is recognized to differ from other well-known types of cell death. Due to the susceptibility of the liver to oxidative damage, excessive iron accumulation is a major feature of most liver diseases. In recent years, ferroptosis has rapidly attracted attention in the field of liver diseases [48]. Lian et al. [49] identified ten ferroptosis-related genes (SLC7A11, G6PD, CISD1, CARS, SLC1A5, ACACA, ACSL3, NQO1, NFS1, and GPX4), and they divided patients into a high-risk group and low-risk group based on these genes. KM analysis showed that patients in the high-risk group had a worse prognosis than those in the low-risk group. The 1, 2, and 3-year AUC values of the risk prediction model were 0.8, 0.69, and 0.668, respectively. Xiong et al. [50] constructed a signature with five ferroptosis-related lncRNAs (AC015908.3, LINC01138, AC009283.1, Z83851.1, and LUCAT1) to enhance the prognosis prediction of patients having HCC. The five ferroptosis-related lncRNA signature was an independent risk factor according to multivariate Cox regression analysis with 1-, 2-, and 3-year AUC values of 0.818, 0.738, and 0.79, respectively, for the risk prediction model. According to GSEA, the high-risk group was enriched in tumorigenesis and immune-related pathways. Additionally, immune cell infiltration, immune checkpoint molecules, and half-inhibitory concentrations of drugs were different in the high-risk and low-risk groups, indicating that the signature may be used to predict the clinical efficacy of chemotherapy and immunotherapy.

2.2.3.2. Pyroptosis-related lncRNA signature. Pyroptosis, also known as inflammatory necrosis of cells, is a type of programmed cell death in which cells continuously expand until the cell membrane bursts, resulting in the release of cell contents and the activation of a strong inflammatory response. Pyroptosis is activated by dying cells through the following two main approaches: (a) gasdermin D (GSDMD)-dependent activation regulated by caspases 1, 4, 5, and 11 and (b) GSDME-dependent activation regulated by caspase 3 [51–54]. Zhang et al. [55] constructed a prognostic model based on nine pyroptosis-related lncRNAs (MKLN1-AS, LNCSRLR, AC023157.2, AP003392.4, AC007128.1, AL031985.3, AC019080.5, PCCA-DT, and AL445228.3). In the training cohort, the AUC values were 0.8043, 0.7878, and 0.8118 at 1, 2, and 3 years, respectively; in the validation cohort, the AUC values were 0.7315, 0.7372, and 0.7222 at 1, 2, and 3 years, respectively. The expression of multiple immune checkpoint genes (including PD-1, PD-L1, and CTLA4) was increased in the high-risk group. These results suggested that the signature may be used as a predictor of immunotherapy response, which can accurately predict the prognosis of patients having HCC. Wu et al. [56] constructed a prognostic model based on nine pyroptosis-related lncRNAs (OSMR-AS1, AL031985.3, NRAV, MKLN1-AS, AL137186.2, AC073611.1, MIR44352HG, AL118511.1, and AL049840.4). The KM analysis showed that the low-risk group had a better survival than the high-risk group. The AUC of the model reached 0.795 in the training cohort and 0.747 in the validation cohort. These results also suggested that the risk score was closely related to the sensitivity of different drugs. Patients in the high-risk group were more sensitive to bortezomib, cisplatin, gemcitabine, imatinib, and paclitaxel, whereas patients in the low-risk group were more sensitive to docetaxel. Thus, this signature may be useful in predicting patient outcomes and optimizing treatment.

2.2.3.3. Necroptosis-related miRNA/lncRNA signature. Necroptosis has long been considered passive death caused by physical or chemical damage factors, such as hypoxia and malnutrition. Cell swelling, organelle deformation, organelle enlargement, and cell rupture are caused by an increase in the membrane permeability of necrotic cells. When dead cells are dissolved, they release their inclusions, causing an inflammatory response [57–59]. An increasing number of studies have reported that necrosis is closely related to tumor immune cell infiltration and drug sensitivity [60]. Meng et al. [61] constructed a prognostic model based on five necroptosis-related miRNAs (miR-10b-5p, miR-592, miR-500a-3p, hsa-miR-326, and miR-139-5p) with high AUC values at 1, 3, 5, and 7 years (AUC >0.7), and survival analysis showed that the high-risk group had low survival probabilities. Chen et al. [62] established a prognostic model based on seven necroptosis-related lncRNAs (HCG27, C2orf27A, BACE1-AS, SNHG4, MIR210HG, SNHG3, and HCG11) with 1-, 3-, and 5-year AUC values of 0.745, 0.727, and 0.653, respectively, for the risk prediction model. Patients in the low-risk group had a significantly better survival than those in the high-risk group, and the IC50 analysis of chemotherapy showed that the signature was closely associated with the sensitivity of commonly prescribed drugs.

2.2.4. Autophagy-related gene/lncRNA signature

Autophagy is an evolution-conserved process for the turnover of intracellular substances in eukaryotes. In tumors, autophagy may play an inhibitory role in the early stages of tumorigenesis. However, there is increasing evidence that autophagy can help formed tumors cope with changes in intracellular environmental stress, such as hypoxia, nutrient deficiency, and other environments, thereby promoting tumor survival [63,64]. Huo et al. [65] identified five autophagy-related genes (ARGs) (HDAC1, RHEB, ATIC, SPNS1, and SQSTM1) associated with OS in patients having HCC. Importantly, the risk score based on ARGs is an independent risk factor for HCC prognosis. In addition, the AUC of the prognostic risk model was 0.747, indicating that the model had a high accuracy in predicting the prognosis of HCC. Yang et al. [66] constructed a prognostic model based on three ARGs (SQSTM1, HSPB8, and BIRC5), and patients having HCC and higher risk scores in TCGA and GEO validation cohorts had worse prognosis. In TCGA and GEO cohorts, the area under the ROC curve was 0.756 and 0.672, respectively, which had a good accuracy in predicting patient survival. In addition, the corrected curves and C-index indicated that the risk prediction model based on ARGs had a good predictive ability and may be a promising tool for predicting the prognosis of patients having HCC. Yang et al. [67] constructed a prognosis model based on seven autophagy-related lncRNAs (LINC01138, PRRT3-AS1, RP11-324I22.4, RP11-73M18.8, CTD-2510F5.4, RP11-479G22.8, and CTC-297N7.9). KM analysis showed that patients in the low-risk group had a better prognosis than those in the high-risk group, and the prognostic prediction accuracy of the risk score (AUC = 0.786) was significantly higher than that of ALBI (0.532), Child-Pugh (0.573), alpha-fetoprotein (AFP, 0.5751), and AJCC stage (0.631).

2.2.5. EMT lncRNA signature

Epithelial–mesenchymal transition (EMT) is a cellular conversion process in which cells lose their epithelial characteristics and acquire mesenchymal features. EMT has been associated with various tumor functions, including tumor initiation, malignant progression, tumor stemness, tumor cell migration, metastasis, and resistance to therapy [68–70]. EMT is often defined by the loss of the epithelial marker, E-cadherin, and the gain of the mesenchymal marker, vimentin. Huang et al. [71] constructed a prognostic model based on 12 EMT-related lncRNAs (AC103760.1, AC015908.3, LINC02362, LINC02499, F11-AS1, LINC00942, PRRT3-AS1, AC012146.1, AC092171.2, AC099850.3, CASC19, and AL158206.1) with AUC values of 0.825 and 0.736 for the risk prediction model in the training and validation sets, respectively. KM analysis showed that the prognosis of patients in the low-risk group was significantly better than that in the high-risk group. In addition, the results revealed that the signature was related to drug sensitivity and may be used to guide individualized therapy. Xu et al. [72] constructed a prognostic model based on five EMT-related lncRNAs (AL031985.3, AC023157.3, AC099850.3, CYTOR, and AL365203.2) with 1-, 2-, 3-, and 5-year AUC values of 0.754, 0.720, 0.704, and 0.662, respectively, for the risk

prediction model. Bioinformatics analysis showed that the signature was involved in the regulation of EMT and migration in HCC.

2.2.6. Hypoxia-related lncRNA signature

Many studies have reported that hypoxia is significantly associated with the tumor microenvironment, apoptosis, autophagy, DNA damage, mitochondrial activity, drug efflux proteins, p53, and chemotherapy [73]. Zhou et al. [74] constructed a prognostic model based on three hypoxia-related lncRNAs (NRAV, AC099850.4, and MIR210HG), and KM analysis demonstrated that the high-risk group was associated with worse survival. The 1-, 3-, and 5-year AUC values of the model were 0.805, 0.672, and 0.63, respectively. GSEA showed that immune-related pathways were enriched in the high-risk group, while metabolism-related pathways were enriched in the low-risk group. In addition, the results showed that the signature was associated with immune checkpoints and immune cell infiltration, and the signature may guide personalized immunotherapies. Tang et al. [75] constructed a prognostic model based on five hypoxia-related lncRNAs (RHPN1-AS1, DUXAP8, CAHM, MKLN1-AS, and LINC00869) with a 5-year AUC of 0.705, which was better than that of histopathological grade, AJCC stage, and age. Patients with low-risk scores had better OS than those with high risk scores. The number of activated CD8+ T cells and activated B cells in the low-risk group was higher than that in the high-risk group. These results suggested that the low-risk group was predicted to be more responsive to immunotherapy and targeted therapy than the high-risk group. This signature may provide new insights into immunotherapy and targeted therapy.

2.3. Proteomics

The concept of the proteome was first described by Wilkins and Williams in 1994 [76]. Proteomics mainly studies all proteins expressed in cells or organs, and it achieves the purpose of protein separation, identification, and analysis through gel electrophoresis, biomass profiling, and bioinformatics technology [77]. Proteins are the executive agents of human life activities. Therefore, proteomics is expected to discover specific proteins related to tumor pathology, which can be used to discover key sites that can be combined with drugs and to determine the activity of tumor cells, thus providing clues for tumor research, diagnosis, and pharmaceuticals. We focused on the analysis of protein biomarkers that have guiding significance for the diagnosis and prognosis of HCC.

2.3.1. AFP

In 1956, Czar and Bergstrand identified a new human protein fraction in fetal blood serum (AFP) [78]. To date, AFP is the most widely used serum marker for the diagnosis and efficacy monitoring of HCC [79].

2.3.2. AFP-L3

AFP-L3, an isoform of AFP, is highly and specifically expressed in tumors. In early HCC detection, AFP-L3 has better specificity than AFP, and it can accurately identify patients having high-risk HCC [80]. A meta-analysis has shown that high levels of AFP-L3 before treatment are associated with poor OS [81].

2.3.3. DCP

DCP, also known as PIVKA-II, is an aberrant prothrombin [82]. Aberrant prothrombin is a non-clotting prothrombin produced abnormally by the liver in the absence of vitamin K in the body. It has been reported that DCP expression is correlated with tumor size and angiogenesis in HCC [83]. In addition, serum DCP levels are closely related to poor prognosis and aggressiveness of HCC [84]. In the detection of HCC, DCP is more specific than AFP, and it is considered to be a reliable indicator for predicting HCC recurrence and survival [85]. Other studies have shown that DCP is better than AFP in detecting large tumors [86], and DCP is considered to be a good predictor for both OS and recurrence-free survival in HCC patients who are treated with radiofrequency ablation [87].

2.3.4. Osteopontin

In 2012, osteopontin (OPN), a new promising biomarker, was identified by mass spectrometry from patients with cirrhosis and HCC [88]. The expression of OPN in HCC tissues is significantly higher than that in adjacent tissues, and its high level is significantly related to tumor metastasis and poor prognosis [89,90]. Studies have shown that the serum OPN level is significantly increased in HCC, even in tumors less than 2 cm. Regarding the diagnostic performance of OPN, the AUC reaches 0.851, which is higher than that of AFP. In AFP-negative samples, serum OPN also performs well with an AUC of 0.838. The combination of AFP and OPN significantly improves diagnostic performance compared to AFP alone [90].

2.3.5. Glypican-3

Glypican 3 (GPC-3) is a heparan sulfate proteoglycan that plays an important role in cell proliferation and differentiation, and it was first identified as a diagnostic and prognostic biomarker for HCC in 2003 [91]. Some studies have shown that the expression of GPC3 in HCC tissues is significantly higher than that in hepatitis and liver cirrhosis tissues [92], and GPC3 levels are significantly different between patients without HCC and those with early HCC. However, more studies are needed to evaluate the potential of serum GPC3 as a non-invasive diagnostic marker for HCC [93].

2.3.6. Midkine

Midkine (MDK) is a 13 kDa small heparin-binding growth factor that is detected in most HCC tissues but is rarely expressed in surrounding non-tumor tissues. MDK is more accurate than AFP in diagnosing HCC, especially for early-stage HCC and AFP-negative HCC [94]. Patients with elevated MDK levels have more CTCs, a significantly higher recurrence rate, and shorter RFS [95].

Although other candidate markers, including squamous cell carcinoma antigen (SCCA) [96], apelin [97], β2 microglobulin [98], dickkopf-1 [99], GATA zinc finger domain containing 1 [100], OPN [101], and squalene epoxidase [102], have been reported as sensitive biomarkers for HCC prediction, these markers have not been used clinically or recommended by major professional liver societies, which may be due to insufficient sample sizes and lack of multicenter validation. Therefore, a large number of prospective studies are needed to further validate the role of candidate markers in the diagnosis and prognosis of HCC.

3. Radiomics model

As the core technology of radiomics models, machine learning algorithms, especially deep learning, have made significant progress in recent years. Radiomics models use various computer algorithms to extract data features and rules from a large amount of historical data, which are used to analyze the existing data to make intelligent predictions [7]. The main body of machine learning is algorithm research, and commonly used algorithms include artificial neural networks, random forests (RFs), support vector machines, Bayesian neural networks, and neighborhood classification algorithms [103]. Deep learning is a machine learning algorithm. Compared to traditional machine learning, deep learning is a type of a multilayer neural network structure, and deep learning better selects features of data by adding network layers. Therefore, deep learning better simulates the signal transmission mechanism of the human brain and has been widely used in image analysis in recent years. The differential diagnosis of benign and malignant focal liver lesions (FLLs) is a key and difficult point in clinical work. FLLs include liver cysts, hemangiomas, adenomas, focal nodular hyperplasia (FNH), HCC, and metastatic carcinoma (MET). The differential diagnosis of benign and malignant FLLs is of great significance for the selection of treatment and the prediction of prognosis. At present, the clinical application of

radiomics models in the field of medical imaging is in the link of image diagnosis, mainly focusing on the detection and recognition of lesions as well as the determination of benign and malignant lesions. The perception and cognitive performance of the radiomics model can be used to identify medical images and mine important information to provide help for inexperienced imaging doctors, thus improving the film reading rate. Moreover, by integrating and training a large amount of image data and clinical information through machine learning, the radiomics model is equipped with the ability to diagnose diseases, which is conducive to reducing the rate of missed diagnosis by imaging doctors. Compared to the existing working mode of the imaging department, the radiomics model is free from interference from external factors and maintains an efficient and continuous working state at all times, which helps to improve the efficiency and quality of the imaging department. We focused on the application of radiomics models based on ultrasound (US), CT, and MRI images in the differential diagnosis of HCC (Table 2).

3.1. US images

US, as one of the most commonly used imaging modalities, has become an essential screening and diagnostic tool in clinical practice. Ultrasound has the advantages of relative safety, low cost, real-time imaging, non-invasiveness, and convenience, and it is widely used in clinical diagnosis and disease surveillance [104]. Li et al. [105] selected contrast-enhanced ultrasound images of 226 FLL patients, including 107 cases of atypical HCC and 119 cases of FNH, and they extracted a total of 3132 features from greyscale ultrasound, arterial phase (AP), and portal phase images. Using LASSO regression, they selected 14 features to construct an ultrasound model and demonstrated that the machine learning support vector machine had a good ability to distinguish FNH from atypical HCC with an AUC of 0.86 (0.80–0.89), a sensitivity of 76.6% (67.5%–84.3%), and a specificity of 80.5% (70.6%–85.9%). Yang et al. [106] selected B-mode ultrasound images of 2143 FLL patients and constructed an US model based on a deep convolutional neural network to help US physicians distinguish benign and malignant FLLs. The AUC of the model in the externally validated cohort was 0.924 (0.889–0.959), and the sensitivity and specificity of the model were better than those of 15-year experienced sonographers (86.5% vs. 76.1% and 85.5% vs. 76.9%, respectively). The deep convolutional neural network deep learning model based on ultrasound images had high sensitivity and specificity in the diagnosis of FLLs, which may assist inexperienced sonographers in improving the diagnosis level.

Table 2
Image model.

	Image model	References
US image		
	Atypical HCC and FNH	[105]
	Benign and malignant FLLs	[106]
CT image		
	HCC, metastasis carcinoma, benign non-inflammatory FLLs, and abscesses	[108]
	Hepatic cyst, hepatic hemangioma, liver metastasis, hepatoblastoma, focal nodular hyperplasia, and primary liver cancer	[109]
MRI image		
	Hepatic cyst, focal nodular hyperplasia (FNH), hemangioma (HEM), hepatic abscess (HEP), hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and metastasis carcinoma (MET)	[111]
	Hepatic epithelioid angiomyolipoma (HEAML), hepatocellular carcinoma (HCC), and focal nodular hyperplasia (FNH)	[112]
	Fat-poor angiomyolipoma (FP-AML), hepatocellular carcinoma (HCC)	[113]
WSIs		
	WD-HCC, HGDN, low-grade DN, focal nodular hyperplasia, hepatocellular adenoma	[117]
	Hepatocellular carcinoma, and cholangiocarcinoma	[118]

3.2. CT images

In comparison to MRI, CT is a well-tolerated examination and less prone to motion artefacts, even in elderly or noncooperative patients who are unable to hold their breath. The main disadvantages include radiation exposure, relatively low contrast resolution, and tissue differentiation [107]. Cao et al. [108] extracted CT image features of 517 FLLs (including 111 HCCs, 112 metastatic carcinomas, 162 benign noninflammatory FLLs, and 132 abscesses) in the precontrast phase, AP, portal vein phase (VP), and delayed phase (DP). A multiphase convolutional dense network was used for the classification of FLLs. The classification system had a strong ability to distinguish between different lesion types. The AUC values for HCCs, metastases, benign non-inflammatory FLLs, and liver abscesses were 0.92, 0.99, 0.88, and 0.96, respectively. Zhang et al. [109] discussed the application value of a deep learning model based on CT images in the diagnosis of liver lesions. A total of 58 patients (6 hepatic cysts, 9 hepatic hemangiomas, 12 liver metastases, 10 hepatoblastomas, 3 FNHs, and 18 primary liver cancers) were selected, and the convolutional neural network (CNN) algorithm was used to segment the tumor region in the CT images. The DICE similarity coefficient (DSC), precision, and recall were used to quantitatively evaluate the segmentation results. The models showed that the DSC of the CNN algorithm reached 0.987 with an accuracy of 0.967 and a recall of 0.954. The results of the enhanced delayed CT scan were consistent with the pathological diagnosis in 58 patients with a total diagnostic coincidence rate of 96.55%. In summary, the CNN algorithm performed accurate and efficient segmentation, providing a more scientific basis for the segmentation of liver tumors in CT images. The radiomics model has a good effect on the segmentation and differential diagnosis of liver lesions, and it is worthy of clinical application.

3.3. MRI images

MRI is an excellent modality for lesion detection and characterization due to its higher contrast resolution and ability to assess more tissue properties than vascularization alone [110]. Wang et al. [111] extracted 557 FLLs, including hepatic cyst, FNH, hemangioma (HEM), hepatic abscess, HCC, intrahepatic cholangiocarcinoma, and metastasis carcinoma (MET) multiple sequence MRI images. The CNN of RESNET-18 was used to classify benign and malignant tumors as well as seven types of FLLs. The AUC values of the two- and seven-way classification models were 0.969 and from 0.919 to 0.999, respectively. The accuracy of the seven-way classification model was higher than that of the radiology residents and general radiologists but lower than that of the academic radiologists. Liang et al. [112] extracted the preoperative enhanced MRI images of 137 patients and used the RF algorithm to construct a radiomics model for preoperative differentiation of hepatic epithelioid angiomyolipoma, liver cancer (HCC), and FNH. The results showed that the radiological model based on the RF algorithm had a good discrimination function for liver lesions, and the AUC values of the training set and test set were 0.999 and 0.925, respectively. Zhao et al. [113] extracted CE-MRI image features of 165 patients in the AP, VP, and DP. A logistic regression classifier was used to differentiate fat-poor angiomyolipoma (FP-AML) from HCC before surgery. In the internal validation, the AUC of the combined model (AP + VP + DP) reached 0.789, and it reached 0.730 in the external validation, which was higher than the AP model (AUC values of 0.711 and 0.638, respectively) and significantly higher than the VP model (AUC values of 0.594 and 0.610, respectively) and the DP model (AUC values of 0.547 and 0.538, respectively). The AUC values of the two radiologists' diagnoses were 0.656 and 0.594 in the internal validation cohort and 0.643 and 0.500 in the external

validation cohort. In both the internal and external validation cohorts, the AUC of the combined model was higher than that of the two radiologists and significantly higher than that of the single sequence model.

In addition, the increasing popularity of whole-slide images (WSIs) for histopathological diagnosis has facilitated the development of digital pathology, which provides a more objective and quantitative examination [114,115]. However, it remains a challenge how to provide efficient, accurate, and automated image analysis in WSIs. In recent years, deep learning, as a subset of AI, has shown great application prospects in pathological image analysis [116]. Hepatocellular nodular lesions constitute a heterogeneous group of disorders. The differential diagnosis of these lesions, especially high-grade dysplastic nodules and well-differentiated hepatocellular carcinoma, is difficult. Thus, it is necessary to develop a system to improve the histopathological diagnosis of hepatocellular nodular lesions (well-differentiated hepatocellular carcinoma, high-grade dysplastic nodules, low-grade DN, FNH, and hepatocellular adenoma) and background tissues (nodular cirrhosis and normal liver tissue). Cheng et al. [117] obtained 213,280 patches from 1115 whole-slide images of 738 patients, and they used four deep neural networks (ResNet50, InceptionV3, Xception, and Ensemble) to establish the model. The optimal model was selected according to the F1 score and the AUC, which was named the hepatocellular nodule AI model (HnAIM). In the independent external validation cohort, the overall AUC of the seven categories was 0.935. For biopsy specimens, the agreement rate with subspecialists' majority opinion was higher for HnAIM than for the nine pathologists on both the patch level and whole-slide image level. Kiani et al. [118] developed a deep learning auxiliary tool based on a CNN with DenseNet architecture to help pathologists distinguish HCC and cholangiocarcinoma on hematoxylin and eosin-stained whole-slide images (WSIs). The model achieved accuracies of 0.885 on a validation set of 26 WSIs and 0.842 on an independent test set of 80 WSIs. Although the use of the assistant did not change the mean accuracy of the 11 pathologists, it significantly improved the accuracy of a subset of 9 pathologists who fell within well-defined experience levels.

4. Conclusions and perspectives

Biological big data generated by multiomics technology have revealed changes in the molecular characteristics of tumors. DNA sequencing technology, especially whole genome sequencing technology, comprehensively reflects tumor heterogeneity. The results of genome sequencing confirmed that TERT, TP53, and CTNNB1 were the top three high-frequency mutated genes in HCC. Liquid biopsy refers to the analysis of tumors by CTCs or ctDNA, and it offers a non-invasive method to continuously monitor a patient's tumor changes over time without causing harm to the body. Liquid biopsy has great prospects for clinical application in the future. Transcriptome sequencing is the most widely used high-throughput gene expression detection technology in biomedical research. Researchers have used machine learning to construct prognostic risk prediction models for HCC with different features (IRG/miRNA/lncRNA signature, metabolism-related gene/lncRNA signature, cell death-related gene/miRNA/lncRNA signature, ARG/lncRNA signature, EMT lncRNA signature, and hypoxia lncRNA signature) based on transcriptome data. These models provide a new perspective for the prognosis, risk stratification, and treatment optimization of HCC. In proteomics, we focused on the analysis of traditional protein biomarkers (AFP, AFP-L3, DCP, OPN, glypican-3, and midkine) that have guiding significance for the diagnosis and prognosis of HCC. Tumors are a complex systemic disease. Biological big data comprehensively and systematically clarify the mechanism of tumor initiation and development, which is conducive to the transformation from symptom-oriented traditional medicine to molecular-based precision medicine.

In recent years, with the continuous development of machine learning and deep learning algorithms, radiomics has played an increasingly important role in image analysis. Radiomics technology is used to extract valuable information from large-scale data of ultrasound, CT, and MRI images, and the model is trained by machine learning or deep learning algorithms to output the final prediction results. The radiomics model not only quickly outputs the region and category of diseases but also improves the diagnostic level of doctors and solves the problems of insufficient medical resources and lack of senior doctors.

Although biological big data and radiomics models have achieved remarkable progress in cancer research, there are still many challenges. First, the cost of multiomics sequencing is high, and research funding is scarce. Second, the biological big data of different omics methods lack collation, and it is difficult to solve the interconnection problem of biological big data in different hospitals and sequencing centers. Third, as an emerging technology, radiomics is still in its infancy. Medical-related algorithm models are still not mature and carry the risk of system failure and algorithm error. These errors will lead to misjudgment of clinical evaluation, diagnosis, treatment selection, and other work, which may mislead clinicians to make incorrect decisions, ultimately leading to medical accidents. The safety of the radiomics model needs to be further improved. Therefore, clinicians still need to maintain a clear and objective understanding while making use of radiomics models for convenience. The final decision assisted by the radiomics model still needs medical experts to strictly review and adjudicate manually. In conclusion, in the era of big data, a liver cancer model should be established by combining clinical big data and multiomics biological big data, and it should be applied to basic research, diagnosis, treatment, prognosis prediction, drug development, and other aspects of liver cancer to promote individualized, refined, and intelligent diagnosis and treatment of liver cancer. The improvement of the radiomics model will make medical treatment more convenient and accurate. The appropriate combination of radiomics and biological big data will prevent patients from suffering from diseases and improve their lives.

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Author contributions

Fang GX and Zeng YY designed the study; Fang GX, Fan JH, and Ding ZR wrote the manuscript; Fang GX and Zeng YY revised the manuscript; and all authors made final approval of the version of the manuscript.

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Declaration of competing interest

The authors declare no competing interests.

Data available statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Ethics statement

Ethics approval was waived for this study because no patients' data were reported.

Informed consent

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