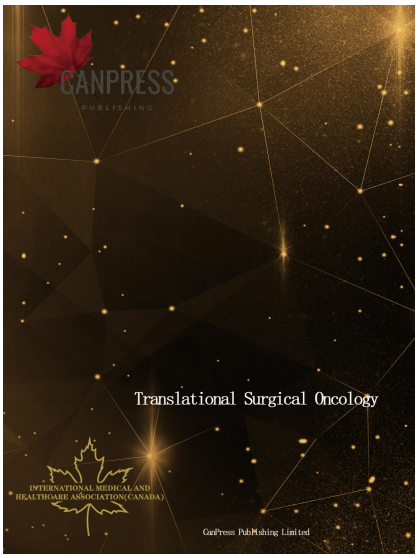
Accurate prediction of the expression of Ki-67 marker in hepatocellular carcinoma based on AI radiomic model



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Abstract

Ki-67 is an important tumor marker. Therefore, the development of Ki-67 based model for predicting the prognosis of hepatocellular carcinoma (HCC) is crucial for successful management of HCC patients in the clinic. With rapid advance in artificial intelligence, machine learning models have been developed recently to incorporate the features of radiomics, tumor surrounding areas, and clinical factors to accurately predict Ki-67 expression in HCC. These breakthroughs provide novel insight into the development of machine learning model based on Ki-67 to guide personalized treatment for HCC patients. In conclusion, the combination of radiomics, genomics, histological data, and demographic information will enhance the accuracy and precision of predictive models for cancer patients.

Keywords: ki-67; hepatocellular carcinoma; radiomics; machine learning; predictive model

Introduction

Ki-67 is a nuclear protein that is expressed in proliferating cells. Ki-67 has been used as a marker to assess the rate of cell proliferation in various physiological and pathological conditions, especially in the context of cancer1, 2. In particular, Ki-67 is expressed in all phases of cell cycle (G1, S, G2, and M), but is absent in cells that are not actively dividing (G0 phase). Moreover, the expression level of Ki-67 is proportional to the rate of cell proliferation, and becomes the index of cell proliferation. Therefore, Ki-67 can be applied as a prognostic marker of cancer because high Ki-67 level usually indicates rapid tumor growth and poor prognosis3, 4. Furthermore, Ki-67 can monitor the efficacy of cancer therapy because a decrease of Ki-67 level after therapy suggests the efficacy of cancer treatment5, 6. Therefore, accurate and timely assessment of Ki-67 level will be important to monitor the progression of cancer and the remission of cancer after treatment.

While immunochemical detection of ki-67 is the most common method for the assessment of ki-67 expression, recent studies suggest that radiological prediction of Ki-67 plays an important role in determining clinical outcomes of cancer patients, including patients with hepatocellular carcinoma (HCC)7-9. HCC is known as a highly aggressive cancer with high morbidity and mortality, especially in China where the population has a high risk of HCC10. HCC patients usually have poor prognosis after surgery therapy, chemotherapy and immunotherapy 11-14. Therefore, the development of Ki-67 based model for predicting the prognosis of HCC is crucial for successful management of HCC patients in the clinic.

Interestingly, a recent study showed that a long noncoding

RNA called Kinesin Family Member 9-Antisense RNA 1 (KIF9-AS1) was associated with the prognosis of HCC patients and it regulated stem cell behaviors of HCC via a novel mechanism [13]. In detail, the authors found that KIF9-AS1 level was significantly higher in HCC patients than controls, and KIF9-AS1 level was correlated with poor prognosis of HCC patients. Moreover, the expression of m6A writer METTL3 was higher in HCC cells, which could promote m6A modification of KIF9-AS1. Consequently, IGF2BP1 as an m6A reader stabilizes m6A-marked KIF9-AS1 to increase the stability of KIF9-AS1 in HCC cells.

Furthermore, the authors revealed that KIF9-AS1 upregulated ubiquitin-specific peptidase 1 (USP1) to enhance the stability of short stature homeobox (SHOX2). SHOX2 is a significant transcriptional factor that regulates development. Recently, SHOX2 has been proposed as a marker for the diagnosis and prognosis of various types of cancer, including HCC [14-16]. Mechanistically, SHOX2 promotes tumorigenesis via Wnt/β-catenin and TGFβ pathways [17,18]. Therefore, this study provides novel insight into the role of METTL3/KIF9-AS1/SHOX2 axis in the regulation of stem cell behaviors of HCC (Figure 1). METTL3 promotes the m6A methylation of KIF9-AS1 to stabilize it in IGF2BP1 dependent manner. The stabilized KIF9-AS1 then upregulates USP1 in an unclear mechanism. The upregulated USP1 then inhibits the ubiquitination and degradation of SHOX2. The stabilized SHOX2 then drives the transcription of key genes involved in Wnt/β-catenin pathway, TGFβ signaling pathway and other unclear pathways to promote stem cell behaviors of HCC, including but not limited to cell stemness and resistance to chemotherapy. Further studies are needed to explore the unclear mechanism or pathways highlighted in Figure 1 to get better understanding of the role of METTL3/KIF9-AS1/SHOX2 axis in HCC.

The development of machine learning models to predict Ki-67 expression in HCC

A recent study provided novel insight into the development of machine learning model based on Ki-67 to guide personalized treatment for HCC patients 15. First, the authors constructed predictive radiomic models based on optimal radiomic features extracted from intratumoral, peritumoral, and combined regions of samples from HCC patients, and found that fusion model had the highest predictive capability, compared to intratumoral model and the peritumoral model. Next, the authors analyzed independent predictors for high Ki-67 expression and found that Radscore, alanine aminotransferase (ALT), hepatitis B virus (HBV) infection and cirrhosis were positively associated with high Ki-67 expression. Therefore, the authors incorporated ALT, HBV infection and cirrhosis, and developed a combined model by integrating the Radscore from the fusion model with clinical characteristics from the clinical model. The combined clinical-radiomic nomogram demonstrated superior predictive performance of Ki-67 expression compared with radiomic fusion model and clinical model.

Although this study has several limitations as the authors acknowledged, such as single-center retrospective study design, limited number of cases and the uncertainty of peritumoral region as the most advantageous region, the findings by the authors have significant implications for clinical practice. With the development of artificial intelligence enhanced imaging tools, the integration of radiomic features with clinical data could improve predictive performance of Ki-67 expression in HCC patients and provide guidance for personalized treatment strategies for HCC 16-20. However, we have to acknowledge that Ki-67 expression is not a perfect predictor of cancer behavior. Other clinical factors can affect the prognosis of HCC. Therefore, further studies are needed to integrate additional demographic information, differential gene expression patterns and potential prognostic factors into the clinical-radiomic nomogram to provide accurate prediction of prognosis of HCC (Figure 1).

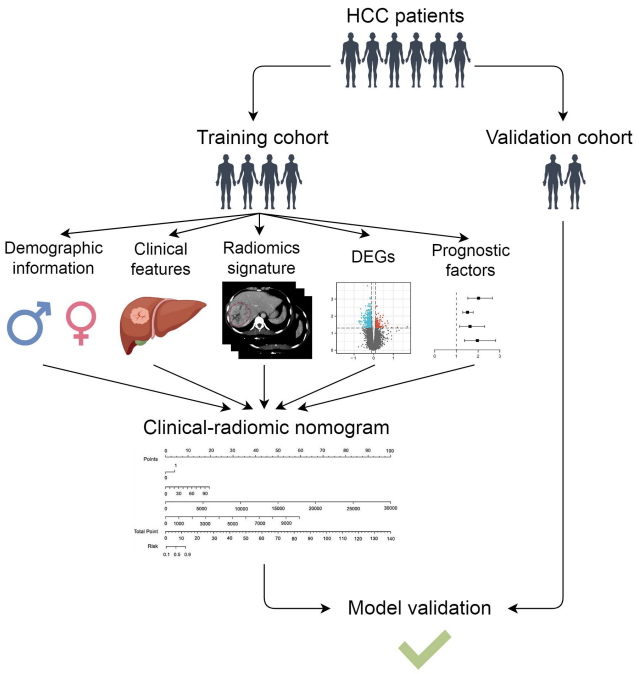

Figure 1. The development of clinical-radiomic nomogram for prediction of prognosis of HCC patients. For training cohort, demographic information, clinical features, radiomics signature, differentially expressed genes (DEGs), and prognostic factors are integrated to develop clinical-radiomic nomogram, which will be then validated in validation cohort.

Conclusion

This study sets up an excellent example for the combination of radiomics, genomics, histological data, and demographic information to enhance the accuracy and precision of predictive models for cancer patients.

Acknowledgement

Supported by the National Natural Science Foundation of China, 82103173 and 82460461; Medical Subject Leader of Yunnan Province (General Surgery), D-2024029; Yunnan Fundamental Research Project for Excellent Young Scholars, 202401AW070003; and the Young and Mid-aged Academic and Technical Leader Reserve Talent Program of Yunnan Province, 202205AC160063.

Conflict of interest

The authors declare that they have no conflict of interest.

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