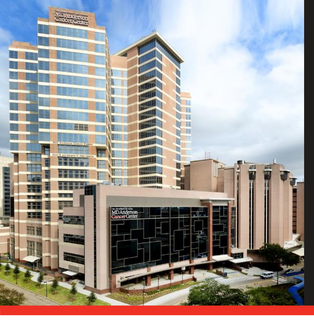

Analysis and Prediction of Patient Survival After Radiotherapy For Liver Cancer Based On Volumetric Segmental Response and Clinically Relevant Factors

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Introduction

Primary liver cancer is one of the leading causes of cancer fatalities globally, with over 905,000 people diagnosed and over 830,000 deaths in 2020[1]. The three major types of adult liver cancer are hepatocellular carcinoma (HCC), cholangiocarcinoma (CC), and colorectal metastasis (CRM).

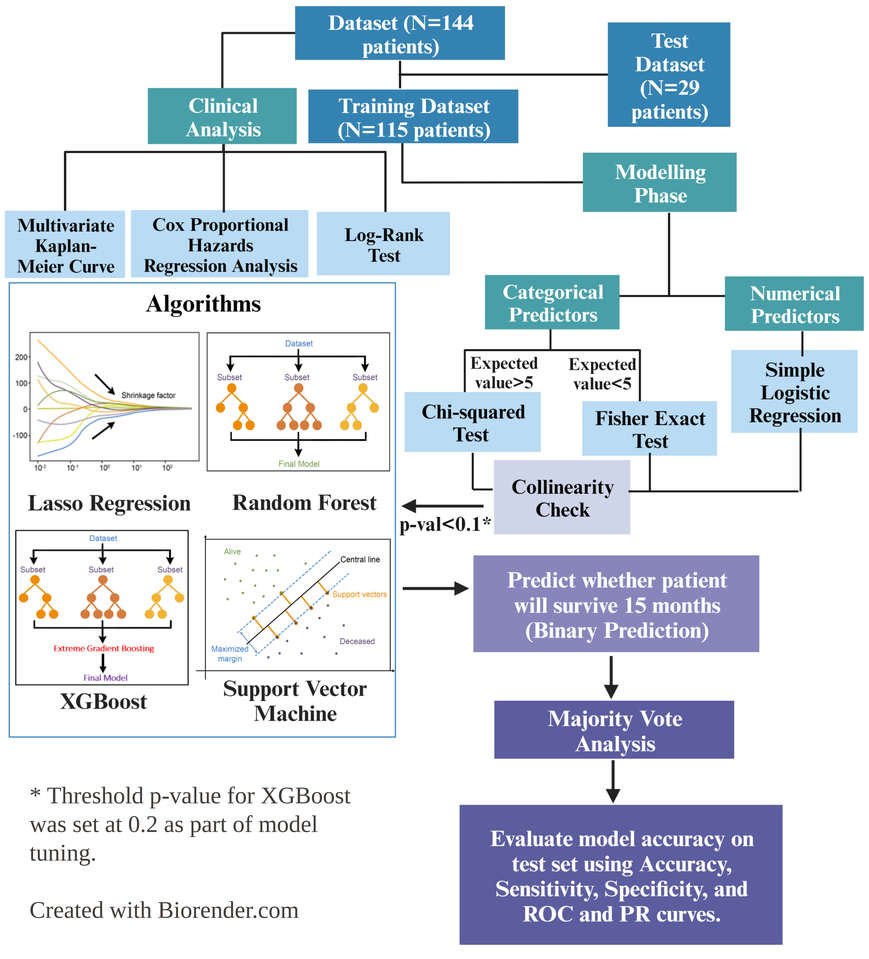
The liver's unique capability to regenerate functional tissue allows for significant recovery following loss of liver function due to cancer-associated damage. Namely, marked increases in normal tissue volume following external beam radiotherapy[2] (RT) and contralateral hypertrophy after radioembolization[3] have been documented. However, **there is limited literature documenting liver segment-specific hypertrophy due to RT and its hypothesized connection with liver cancer patient survival.**

Thus, the **goals of the study** include:

1. To analyze the relationship between post-RT liver segment hypertrophy in HCC, CC, and CRM patients **and survival outcomes**.

2. To build a binary risk prediction model to forecast liver cancer patient survival, incorporating data on liver segment hypertrophy, radiation dosimetrics, and other relevant predictors.

Methods: Clinical Analysis & Predictive Modeling



* Threshold p-value for XGBoost was set at 0.2 as part of model tuning.

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Fig 1. Flowchart of study, including clinical analysis, predictive modeling, and model validation.

Results: Survival Analysis

Kaplan Meier Curves

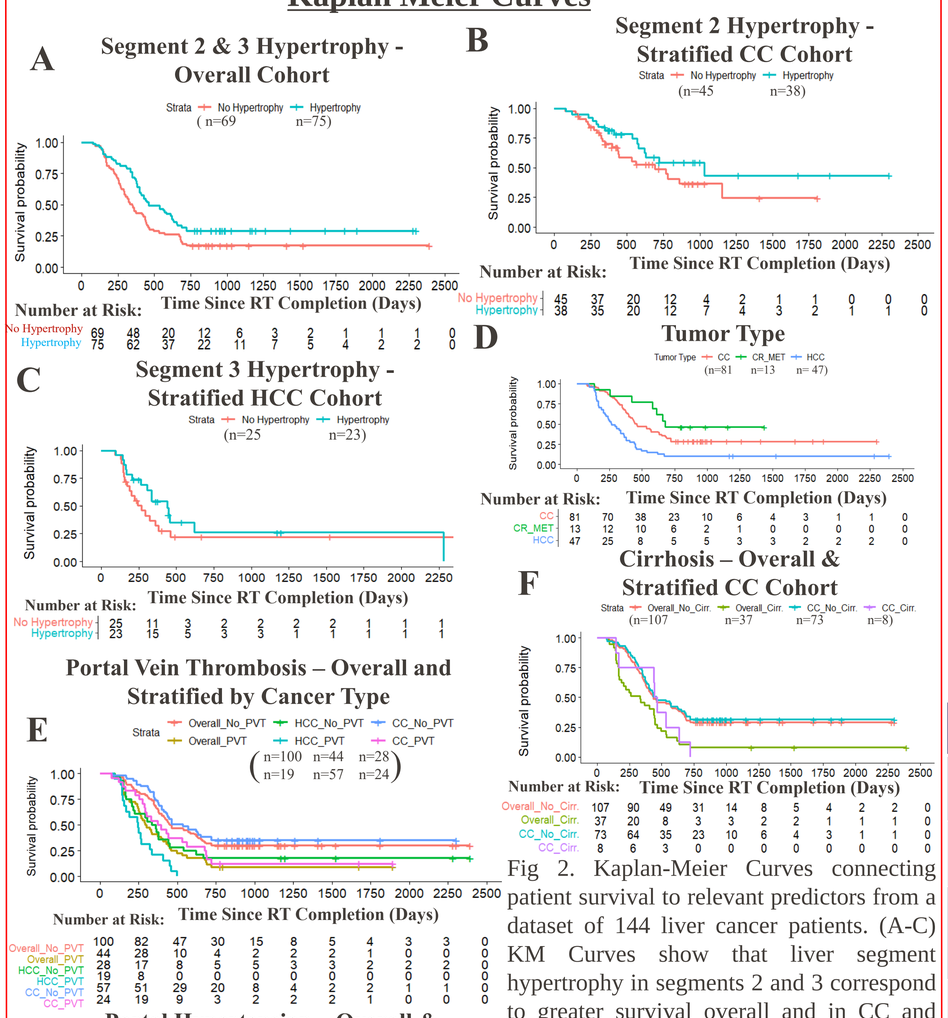

Fig 2. Kaplan-Meier Curves connecting patient survival to relevant predictors from a dataset of 144 liver cancer patients. (A-C) KM Curves show that liver segment hypertrophy in segments 2 and 3 correspond to greater survival overall and in CC and HCC patient cohorts, respectively. (D) KM Curve by tumor type shows that HCC is the most fatal liver cancer subtype and CRM corresponds to the greatest survival probability. (E) KM Curves show that portal vein thrombosis leads to greater fatality overall and in both HCC and CC patient cohorts. (F) KM Curves show that cirrhosis in overall and CC patient cohorts may lead to greater fatality. (G) KM curves show that portal hypertension corresponds to greater mortality overall and markedly so in HCC patients.

Statistical Metrics

(A) Predictor	Cox Hazard Ratio	Log Rank Test (p-value)
Segments 2 & 3 Hypertrophy - Overall	0.43	0.02*
Segment 2 Hypertrophy - CC	0.64	0.2
Segment 3 Hypertrophy - HCC	0.39	0.3
§Tumor Type – HCC	2.25	7.1×10^{-4}*** (Relative to CC)
§Tumor Type – CRM	0.59	7.4×10^{-3}** (Relative to HCC)
Portal Vein Thrombosis - Overall	2.02	3×10^{-4}***

(B) Predictor	Cox Hazard Ratio	Log Rank Test (p-value)
Portal Vein Thrombosis - CC	1.88	0.02*
Portal Vein Thrombosis - HCC	2.07	0.02*
Cirrhosis - Overall	2.02	6×10^{-4}***
Cirrhosis - CC	2.30	0.2
Portal Hypertension - Overall	1.39	0.09
Portal Hypertension - HCC	2.09	0.05*

§ Benjamini-Hochberg adjusted p-values. *p-value ≤ 0.05 ** p-value ≤ 0.01 *** p-value ≤ 0.001

Table 1 (A and B). Hazard ratios (HR) depicting differential patient survival between positive and negative groups, or subgroups, for each predictor. HR greater than 1 indicates comparatively higher probability of death in the positive group relative to the negative group (or between comparative subgroups) at any given time point and HR lesser than 1 indicates comparatively lesser probability of death [at any given time point]. Log-rank test results (α = 0.05) indicate whether there is a significant difference in the effect on patient survival between positive and negative groups, or subgroups, for each predictor.

Key Points: Figure 2 and Table 1

1. Liver cancer patients in the overall patient cohort with hypertrophy in segments 2 and 3 have a 56.67% greater probability of surviving relative to those who do not at any given time point.

2. Patients in all cohorts with PVT, with cirrhosis in the overall cohort, and with PHT in the HCC patient cohort, respectively, are approximately 2 times as likely to die at any given time point [compared to the negative group].

Results: Predictive Modeling

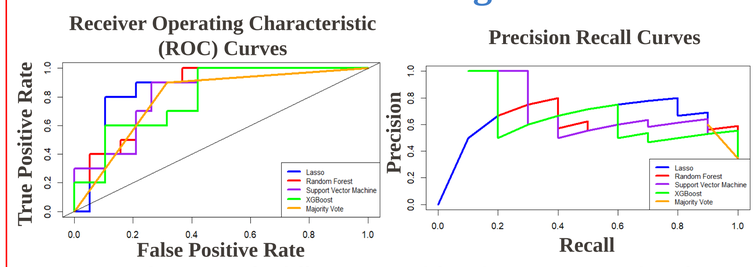

Fig 3. ROC and PR curves for different ML models and majority vote analysis for binary classification of 15-month patient survival.

	Accuracy	Specificity	Sensitivity	AUROC	AUPRC
Lasso Regression	0.76	0.68	0.90	0.87	0.71
Random Forest	0.72	0.63	0.90	0.84	0.75
Support Vector Machine	0.76	0.68	0.90	0.83	0.75
XGBoost	0.72	0.58	1.00	0.80	0.71
Majority Vote	0.76	0.68	0.90	0.79	0.61

Table 2. Relevant metrics for evaluation of ML models and majority vote analysis.

Conclusions & Future Steps

1. Liver hypertrophy in segments 2 and 3 significantly correlates with better survival, with PVT, PHT, and cirrhosis significantly associated with greater mortality in certain liver cancer patient cohorts.

2. We developed binary risk prediction ML models to predict patient survival 15 months following the end of RT treatment. In the future, we aim to expand the prediction model to predict survival as a continuous outcome, in days survived after the end of radiotherapy.

3. All model accuracies, AUROC, and sensitivities were equal to or above 0.72, 0.79, and 0.90, respectively, demonstrating strong performance. Further steps include to integrate additional clinical and radiomic factors and increase the number of patients included in the survival analysis and predictive modeling.

4. Lasso regression seems to be the most robust model due its relatively greater AUROC and comparatively similar accuracy, specificity, and sensitivity, although Random Forest and Support Vector Machine also exhibit relatively high predictive power.

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