Recurrence of Hepatocellular Carcinoma (HCC) After Liver Transplantation: Patterns And Prognostic Factors in a Single Center Experience, King Faisal Specialty Hospital and Research Center (KFSH&RC)

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BACKGROUND

Liver transplant is the gold standard for hepatocellular carcinoma (HCC)[8]. Intention to treat is the drive use of living donors for the prolonged waiting time on the deceased donor list[2], considering actuarial survival rates of 73 % and recurrence-free survival rate of 83 % as reported by[9]. Transplantation outside the Milan criteria is possible using morphology-based extended criteria, e.g., University of California San Francisco (UCSF) criteria[12], Hangzhou criteria[15], Up-to-seven criteria[10] and others. Predicting HCC recurrence after liver transplant is an important topic that relies predominantly on pre-liver transplantation tumor morphology and explant histopathology. Imaging predictor post-chemoembolization for hepatocellular carcinoma showed a poor correlation with pathological findings, as reported by[5]. Our study aim is to identify perioperative recurrence predictors in transplanted hepatocellular cases by analyzing a cohort of liver transplant cases at KFSH&RC.

METHOD

The study is a retrospective observational study on post-liver transplantation adult patients who were reported to have hepatocellular carcinoma on explanted liver between 1st January 2011 and 30th November 2016. Operative & histopathology reports were used for case recruitment. The minimum follow-up period was 23 months. We excluded early death of less than two months and cases outside the pre-liver transplantation workup protocol. The analysis was descriptive and inferential, using Excel and S.P.S.S. programs. Processing identified variable, the following data mining tools (Figure 2) were used: binary regression analysis was conducted at a P value of 0.25 for clinically plausible predictive factors such as pre-liver transplant tumor morphology, alpha feta protein level, pre-liver transplantation loco-regional treatments, type of liver transplant, the timing of liver transplantation and post-liver transplantation histopathology findings. The statistically significant variables were subjected to Categorical Principal Components Analysis (C.A.T.P.C.A.). Then, multivariant Cox regression analysis was conducted, reporting hazard ratio (H.R.).

RESULTS & DISCUSSION

P.R.I.S.M.A. flow diagram demonstrated patients' inclusion/exclusion processing, (Figure 1). The median follow-up period was 52.5 months for included cases. Three patients' histopathology variables were recorded as missing values because the number of tumors was reported as numerous**,** so the total size and number cannot be assessed. We preferred to include these cases in the analysis because the imputation technique using Little's M.C.A.R. test gave the evidence that the missing data is at random (sig 0.542), which will not have a significant impact on the analysis.

Split liver was used in 15% of the cases, while most transplanted livers were living donors 68%. The recurrence rate was 8.9%. Half of these cases had multi-organ recurrence. The international recurrence rate is 10% and 40% for transplanted and hepatectomy cases, respectively[1]. The liver was one of the recurrence sites 50% of the time. 60% of the recurrences were within two years of follow-up.

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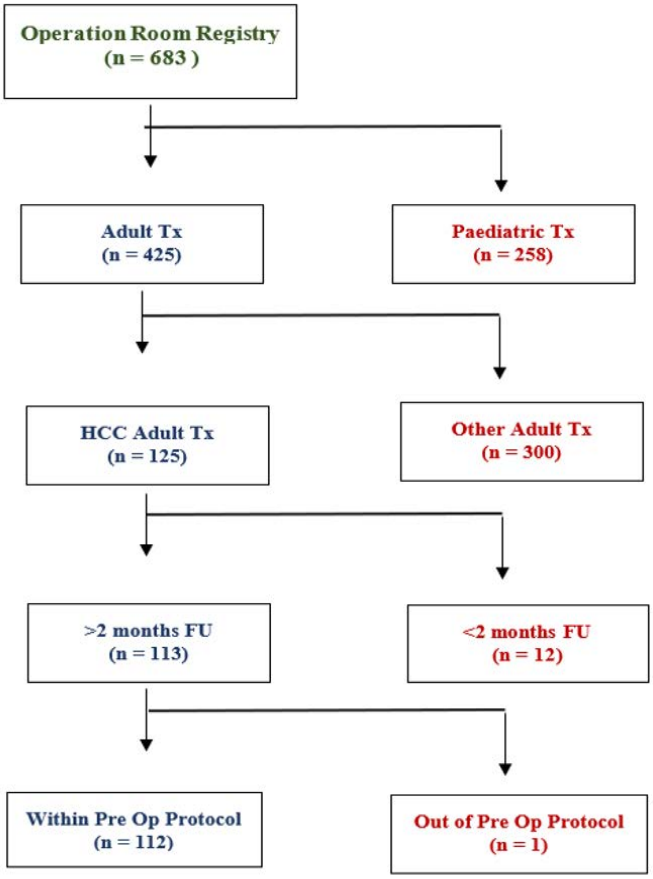

Figure 1. P.R.I.S.M.A. flow diagram demonstrated patients' inclusion/exclusion processing

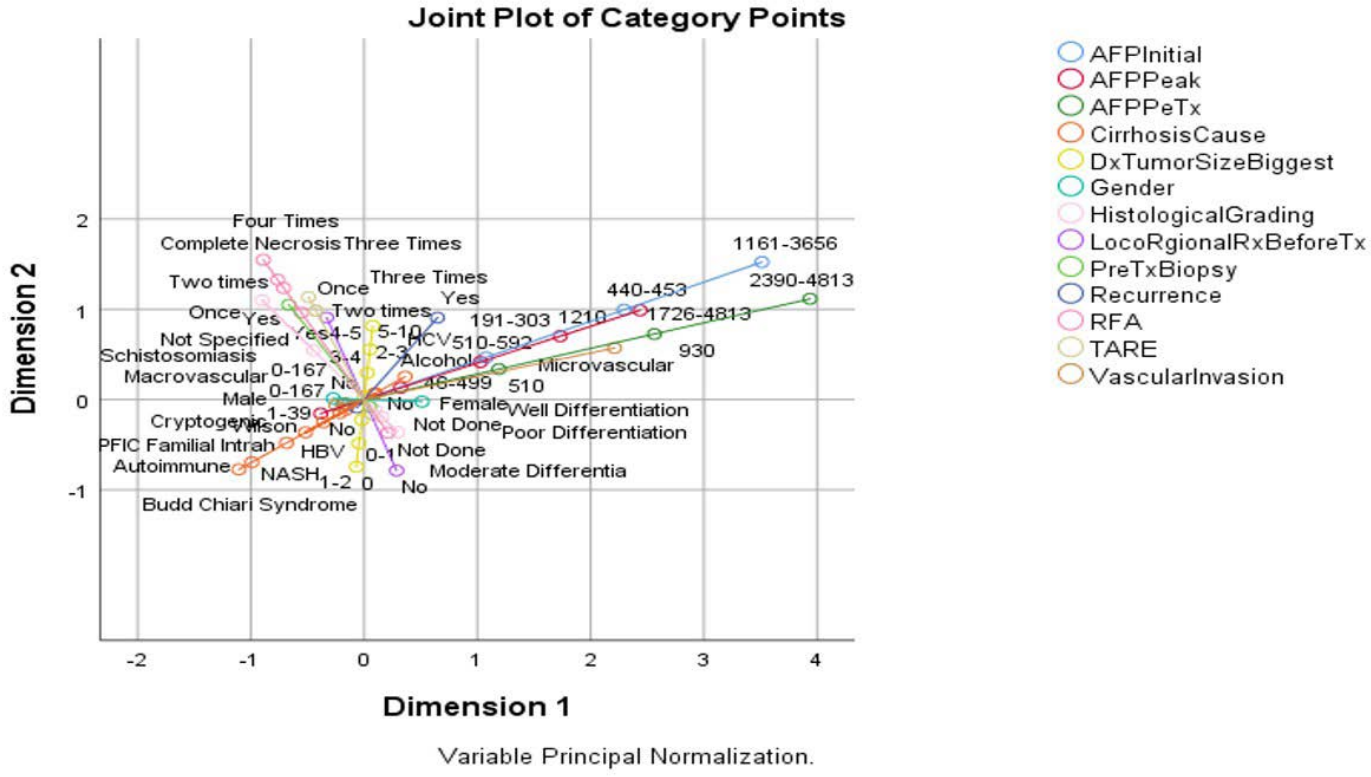

Figure 2. Categorical Principal Components Analysis (CATPCA) All 38 variables

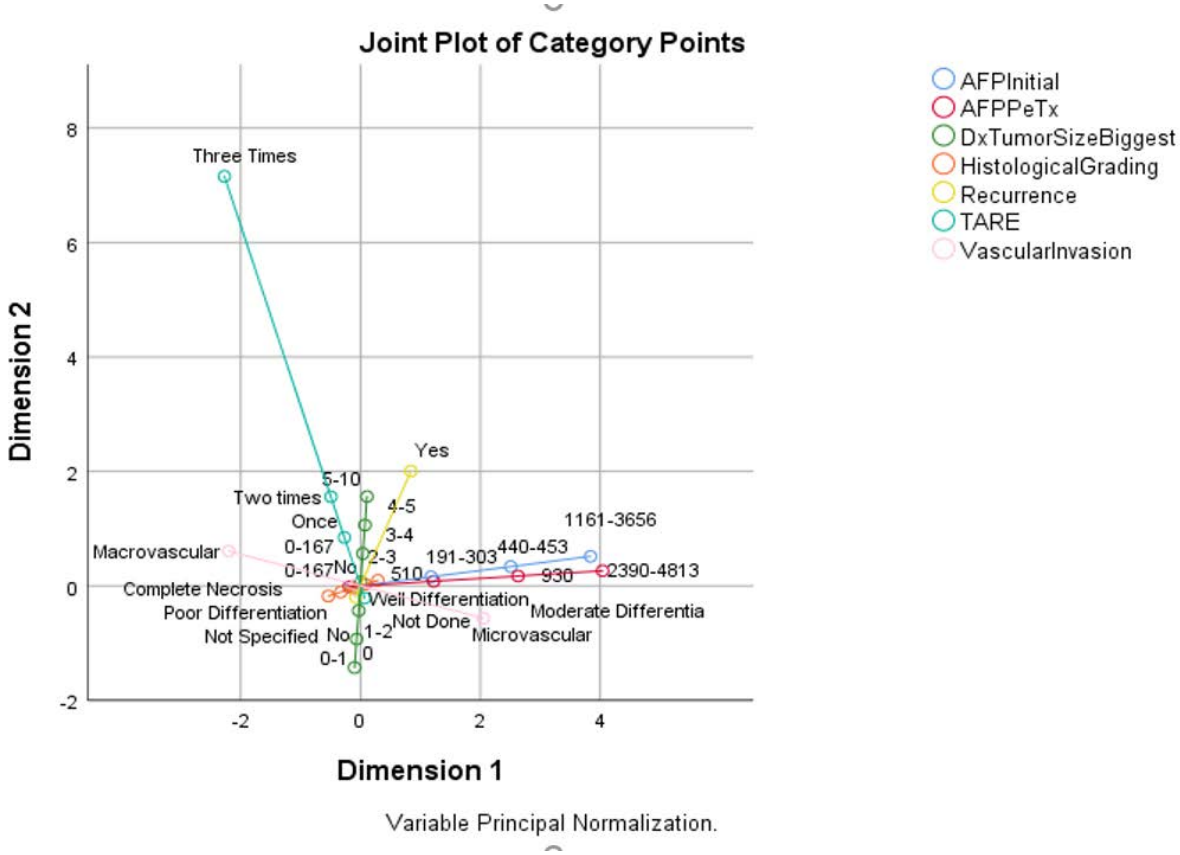

Figure 3. Categorical Principal Components Analysis (CATPCA) of 7 variables after binary regression analysis

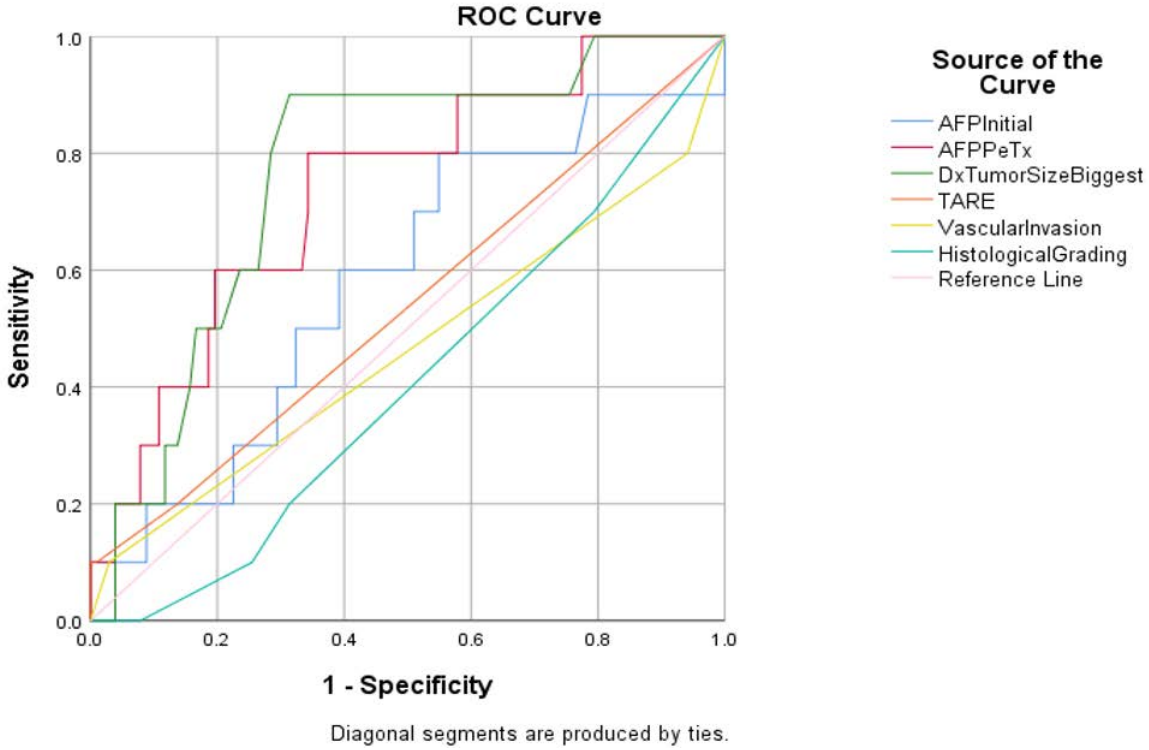

Figure 4. Receiver Operating Characteristic Curve for Type 2 Error

Clinical plausibility for different predictive factors based on literature evidence is as follows: radiological/morphological parameters, e.g., Milan Criteria[9], University of California San Francisco (UCSF) criteria[12], Hangzhou criteria[15] and up-to-seven criteria[10], tumor differentiation[14], vascular invasion[14], pretransplant locoregional treatment[13], Living donor vs diseased donor transplant[6], AFP[3], and biochemical markers[7]. Accordingly, we identified 38 variables that underwent binary regression analysis to end up with 6 variables, as shown in (Figure 2) & (Figure 3).

The recurrence rate for Beyond Millan within UCSF cases was 25% after pre-transplant loco-regional downstaging. Five years survival rate was 89% (+/- 15.2). Internationally, the biochemical markers used to assess HCC recurrence are alpha-fetoprotein (AFP), lens culinaris agglutinin-Reactive Glycoform of AFP (AFP-L3), Des-γ-Carboxy Prothrombin (DCP), serum proteins, e.g., Gypican 3, Osteopontin, and Golgi Protein 73, and liquid biopsy in term of circulating DNA/ RNA, circulating tumor cells (CTC) and exosomes[7]. Studying the biochemical markers in this detail was not possible in our setting. However, the initial AFP at diagnosis (Mean 385.47 ng/ml) was the most statistically significant predictive variable with an equivalent hazard ratio (HR1.001, Sig 0.001).

The biggest tumor diameter at diagnosis variable (Mean 3.72 cm) had a 30% increase in the risk of recurrence (HR 1305, Sig 0.052). According to the R.O.C. curve, the vascular invasion and histopathology grading have no statistical significance in H.C.C. recurrence rate, (Figure 4).

According to the cross-table analysis using the S.P.S.S. program, the observed more than expected for vascular invasion and histopathology grading indicates confounder factors in H.C.C. recurrence for these predictors. This contradicts most of the new publications highlighting the importance of vascular invasion[11]. One of the explanations for this finding is that the accuracy of vascular invasion reporting in hepatocellular carcinoma improved after implementation of subspecialty surgical pathology sign-out[4]. Subspecialty surgical pathology sign-out was implemented in our hospital six years ago, which means this implementation covered only three years of our study duration.

CONCLUSION

Although Milan criteria are considered too conservative for liver transplantation selection criteria in HCC cases, our study confirms that HCC morphological characteristic is the most clinically and statistically significant predictor of HCC recurrence post-liver transplantation. According to our local data, AFP has a second level of impact in predicting HCC recurrence. In future studies, we may need more input on the biochemical markers that have more significance with distal metastasis and circulating tumor principle.

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Potential Conflict of Interest: None

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