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The Predictive Value of the Proliferation Marker Ki-67 in Patients with Fulminant Hepatic Failure

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INTRODUCTION

In the United States, acute liver failure (ALF) affects an estimated 2,000 people per year and accounts for 6% of all liver transplants. Without transplantation, however, less than 50% of patients survive with medical management alone. Early identification of patients with survivable AFL is important to guiding their management and early referral to transplantation.

Studies have shown that the current prognostic scoring systems used for FHF, including the King's College Criteria (KCC) and the Model for End-Stage Liver Disease (MELD), have poor sensitivity and negative predictive value for predicting outcome, highlighting a need for more accurate predictive models.

Ki-67 is a well-established marker of cellular proliferation but its expression in FHF as a surrogate marker of liver regeneration has not been studied as a tool to predict outcome in these patients.

In this pilot study, we sought to determine the predictive value of Ki-67 expression in patients with FHF and its potential for improving the accuracy of current predictive models.

METHODS

A retrospective analysis was performed on patients admitted to Thomas Jefferson University Hospital (Philadelphia, PA) with ALF between 2000 and 2014 who underwent liver biopsies as part of their management. Under IRB approval, the surgical pathology database at TJUH was searched for biopsies with the keywords "confluent", "submassive", or "massive hepatic necrosis". The identified liver biopsies and medical records were reviewed, and all patients with confirmed confluent hepatic necrosis and acute liver failure were selected. Thirty patients were identified as meeting inclusion criteria and constituted the study.

The medical records of all 30 patients were reviewed and the demographic, laboratory, and clinical outcome data (survival with or without liver transplantation) were obtained.

The liver biopsies were sectioned and immunohistochemical staining for Ki-67 was performed. Ki-67 expression was assessed by an independent pathologist and categorized as either proliferative (numerous Ki-67 positive hepatocytes) or non-proliferative (few if any positive cells).

The clinical information obtained was used to calculate MELD scores and determine if KCC were met. Ki-67 expression, MELD score and KCC were correlated with the patient outcomes.

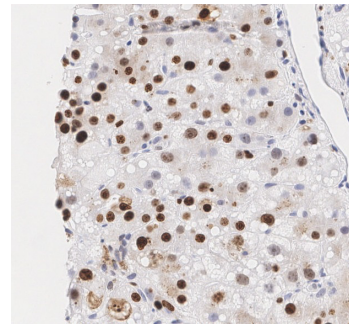


Figure 1. Proliferative liver biopsy by Ki-67 stain in patients with ALF

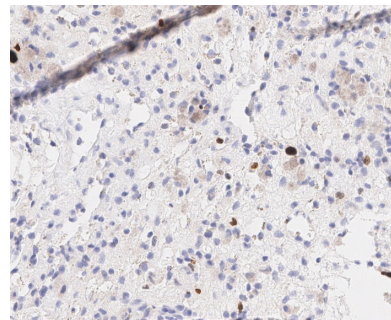


Figure 2. Non-proliferative liver biopsy by Ki-67 stain in patients with ALF

RESULTS

Demographic	n (%)
Mean Age	46.7 ± 16
Male/Female	12 (40%)/18 (60%)
Etiology of FHF:	
Acetaminophen	3 (10%)
Viral Hepatitis	7 (23%)
Drug-Induced	5 (17%)
Autoimmune	10 (33%)
Unknown	5 (17%)
Outcome:	
Spontaneous Survival	13 (43%)
Transplant	13 (43%)
Death	4 (13%)

Table 1. Demographic Profile of the Study Population

RESULTS

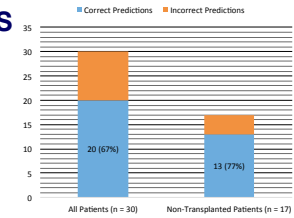


Figure 3. Overall Diagnostic Accuracy of Ki-67 for Outcome in FHF

Group	Proliferative Biopsy	Non-Proliferative Biopsy	Total	Sensitivity	Specificity	PPV	NPV
Non-Transplanted Patients							
Survival	9	4	13	100%	69%	50%	100%
Death	0	4	4				
Total	9	8	17				
All Patients							
Survival	9	4	13	65%	69%	73%	60%
Death/Transplant	6 (0/6)	11 (4/7)	17				
Total	15	15	30				

Table 2. Predictive Accuracy of Ki-67 for Outcome in Patients with FHF

- Among non-transplanted patients, Ki-67 had a sensitivity of 100% and a specificity of 69%. A proliferative biopsy had a 100% predictive value for survival.
- For all patients, Ki-67 had a sensitivity and specificity of 65% and 69% respectively. A non-proliferative biopsy had a predictive value for death or transplant of 73%.

Model	Sensitivity	Specificity	PPV	NPV	Overall Diagnostic Accuracy
King's College Criteria	53%	92%	90%	60%	70%
MELD > 32	88%	69%	79%	82%	80%
Non-Proliferative Biopsy by Ki-67	65%	69%	73%	60%	67%
2 or 3 Criteria (KCC, MELD > 32, Non-Proliferative Biopsy by Ki-67)	88%	92%	94%	86%	90%

Table 3. Predictive Accuracy of Various Prognostic Models for FHF

- A composite score requiring at least 2 of the 3 prognostic criteria resulted in a predictive value of 94% for death or transplantation and an overall diagnostic accuracy of 90%, both greater than any one of the criteria alone.

CONCLUSION

The results of this study show that the evaluation of liver biopsies for Ki-67 expression provides a useful adjunct to established criteria in determining the prognosis of patients with fulminant liver failure.

Larger studies should be performed to determine the true import of Ki-67 activity in such patients.