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Utility of liver biopsy in transplantation - What is practical?

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Patient-centred. Independent. Academic.

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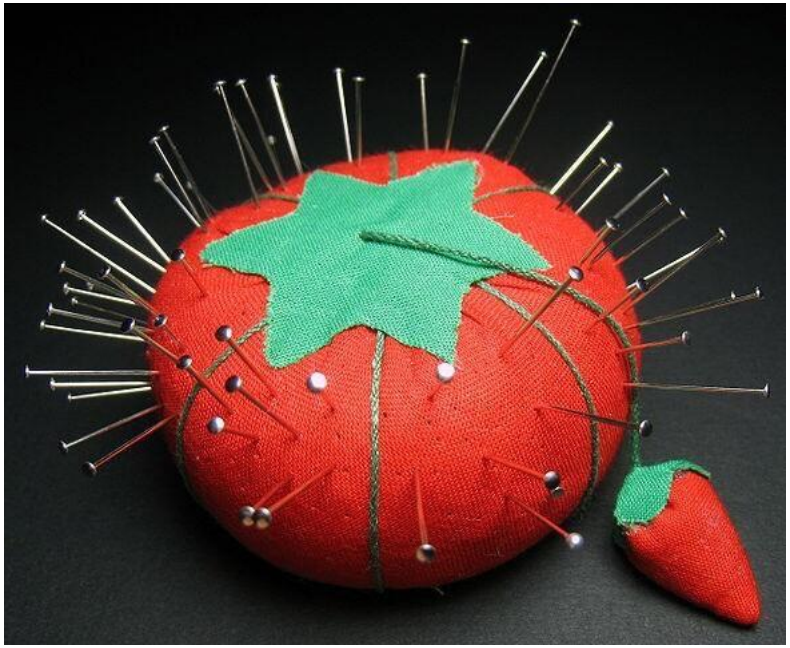
History

1923
Percutaneous Biopsy

1883
1st Documented biopsy
Paul Ehlrich

1970
Transjugular
Approach



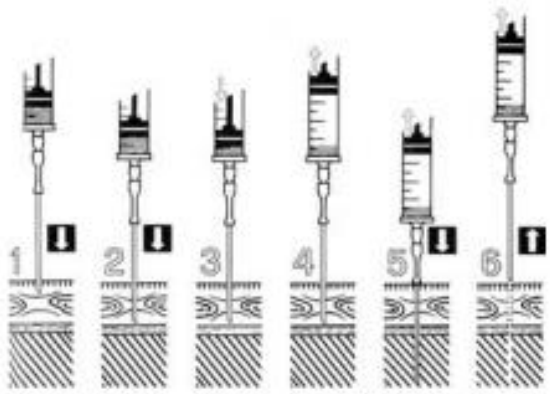
Utility

- 20 year survival of 50%
- Graft survival affected by
    - Rejection
    - Recurrence of disease
    - Infection
    - Ischaemic Injury
    - Biliary complications

Background

- Risk - 2-3% Morbidity
- Mortality: 0.01-0.03%

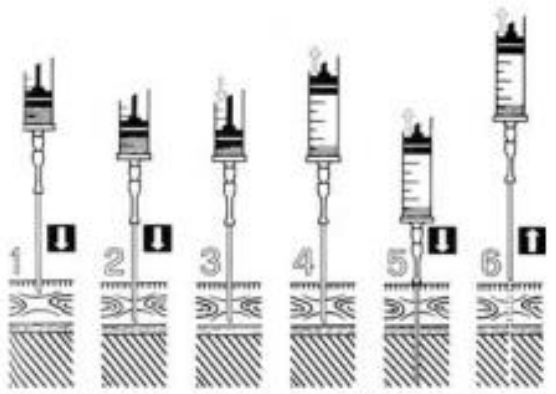
- Platelets >50 x 10^9
- INR >1.5
- Consented patient



- Percutaneous
- Transjugular
- Surgical

Background

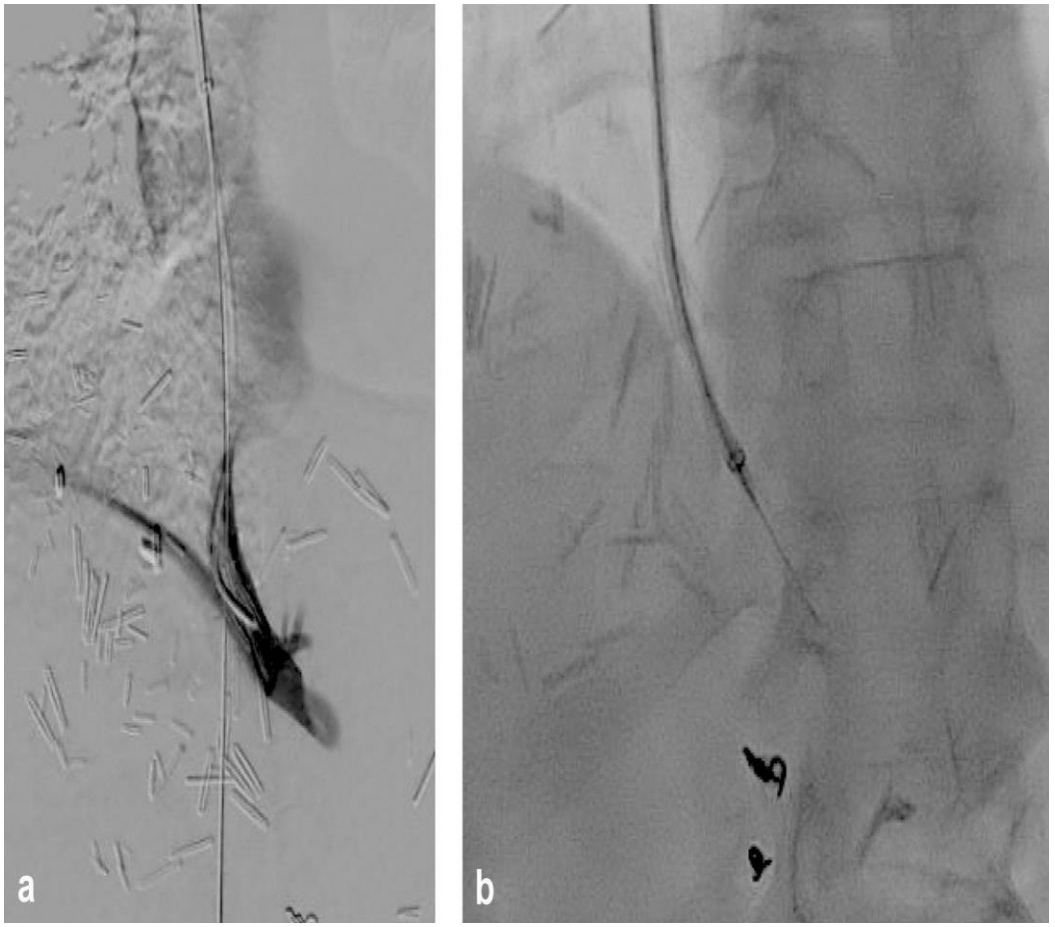
- Can be done as an out patient
- Most complications occur in the first 3 hours
- Sepsis
- Risk factors
  - Cirrhosis
  - Older Age
  - Liver tumours



Transjugular Liver Biopsy

- Poorer sampling
- Greater Cost

- Obesity
- Coagulopathy
- Ascites
- Additional procedures



Protocol vs Event Driven

Pros	Cons
Biochemistry doesn't equal Histological changes	Risk of Morbidity and Mortality
Protocol Biopsies detect early change and allow for an earlier intervention	Non Invasive mechanisms of acquiring information
Knowledge of the disease processes allow for treatment adaptation	Histological change doesn't always impact management
	Costs
	Sampling Error
	Inter observer variability

Non Invasive markers

SYSTEMATIC REVIEW ARTICLE

Front. Immunol., 11 April 2019 | https://doi.org/10.3389/fimmu.2019.00758

Diagnostic Biomarkers to Diagnose Acute Allograft Rejection After Liver Transplantation: Systematic Review and Meta-Analysis of Diagnostic Accuracy Studies

Non Invasive markers

Author	Center	Design	Index test	Sample size	Acute rejection (*n*)	Follow-up
Devlin et al. (17)	Institute of Liver Studies, Kings College School of Medicine, London, UK	Prospective cohort trial (consecutive)	NOx (acid labile nitroso compounds)	50/50 patients included Test samples = 55	33	28 days
Feussner et al. (18)	Universität Heidelberg, Abteilung Innere Medizin, Endokrinologieund Stoffwechsel, Germany	Prospective cohort trial (consecutive)	Serum Amyloid A protein	12/12 patients included Test samples = 42	14	70 days
Kuse et al. (19)	Medizinische Hochschule Hannover, Viszeral und Transplantationschirurgie, Hannover, Germany	Open prospective cohort trial (consecutive)	Procalcitonin	20/40 patients included; Test samples = 40	10	2 weeks
Okubo et al. (20)	Graduate School of Medicine and Immunology Frontier Research Center, Osaka University, Suita, Osaka, Japan	Exploratory study	CHMP2B KCTD14 KCNAB3 TPI1	80/80 patients included Test samples = 80	20	1 year
Hughes et al. (21)	Department of Clinical Biochemistry, Addenbrooke's Hospital, Cambridge, England	Prospective cohort trial (consecutive)	EOS (eosinophil count), ECP (eosinophil cationic protein)	51/51 patients included Test samples = 71	36	100 days
Lun et al. (22)	Insitut für Laboratoriumsmedizin und Pathobiochemie, Campus Virchow Klinikum,Berlin, Germany	Prospective cohort trial (consecutive)	Peripheral blood T-Cell activation and IL-2 Receptor	119/119 patients included Tests samples = 119	69	20 days
Barnes et al. (23)	Liver Transplant Unit, Royal Free Hospital, Pond Street, London, UK	Consecutive cohort study	Blood eosinophilia	101/101 patients included Test samples = 275	166	2 weeks
Kobayashi et al. (5)	Department of Surgery, Osaka University, Suita, Osaka 565-0571, Japan	Prospective cohort trial	Guanylate-binding protein 2 mRNA	46/46 patients included Test samples = 46	19	Unclear
Massoud et al. (24)	Division of Gastroenterology and Hepatology, University of Alabama at Birmingham, Birmingham, AL, USA	Exploratory study	Proteomics and ELISA (C4)	62/62 patients included Test samples = 62	33	7 days
Rodriguez-Peralvares et al. (25)	The Royal Free Sheila Sherlock Liver Centre and University Department of Surgery, Royal Free Hospital London, UK	Prospective cohort trial	Blood eosinophil count	615/690 patients included Test samples = 690	532	14 days
Wang et al. (26)	Liver Transplantation Center, the Third Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China	Retrospective cohort trial	Blood eosinophil counts	37/37 patients included Test samples = 40	24	6 months
Schütz et al. (27)	Clinical University Hospital, "Virgen Arrixaca"-IMIB, Murcia, Spain.	Prospective observational multicenter cohort trial	Graft-derived cell-free DNA	115/115 patients included Test samples = 107	107	1 year
Dickson et al. (28)	Section of Hepatobiliary Diseases, University of Florida, Gainesville, USA.	Prospective cohort trial	Alpha-GST and Pi-GST	44/52 patients included Test samples = 44	14	7 days
Nagral et al. (29)	Hepatobiliary Medicine and Liver Transplantation, Royal Free Hospital School of Medicine, London, United Kingdom	Prospective cohort trial (consecutive)	Plasma alpha-glutathione S transferase	23/23 patients included Test samples = 56	38	46 days
Renna Molajoni et al. (30)	Divisione Tranpianti Dórgano,Catedra di Patologia, Chirurgica II, La Sapienza University, Rome, Italy	Prospective cohort trial (consecutive)	Serum HLA class I antigen	14/14 patients included Test samples = 16	8	30 days

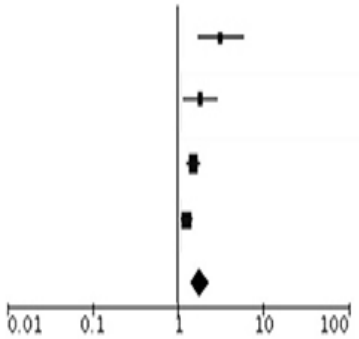
Systematic literature searches (Medline, Cochrane Library, and Embase) were conducted to identify studies that evaluated biomarkers to diagnose allograft rejection in patients following liver transplantation. Studies were included when the non-invasive index test(s) and reference test (liver biopsy) were performed at the same time and the sensitivity and specificity were given (n = 15).

Non Invasive Markers - IL2 Receptor

- Soluble IL2R concentration up regulated in rejection
- >3850IU/ml 56%specificity and 100% sensitivity
- best Diagnostic efficacy achieved: Day -3 to day of rejection
    - >631IU/ml 81% Sensitivity and 89% Specificity

NonInvasive Markers - Peripheral Eosinophilia

	Index test +		Index test –			
Study	TP	Total	FN	Total	Weight	Risk ratio (95% CI)
Hughes et al. (21)	27	37	9	36	0.13	2.92 (1.60–5.31)
Wang et al. (26)	11	13	13	27	0.18	1.76 (1.12–2.77)
Barnes et al. (23)	53	65	113	210	0.34	1.52 (1.28–1.80)
Rodriguez-Peralvarez et al. (25)	104	147	134	231	0.36	1.22 (1.05–1.42)
Total (95% CI)		262		504	1	1.56 (1.21–2.02)

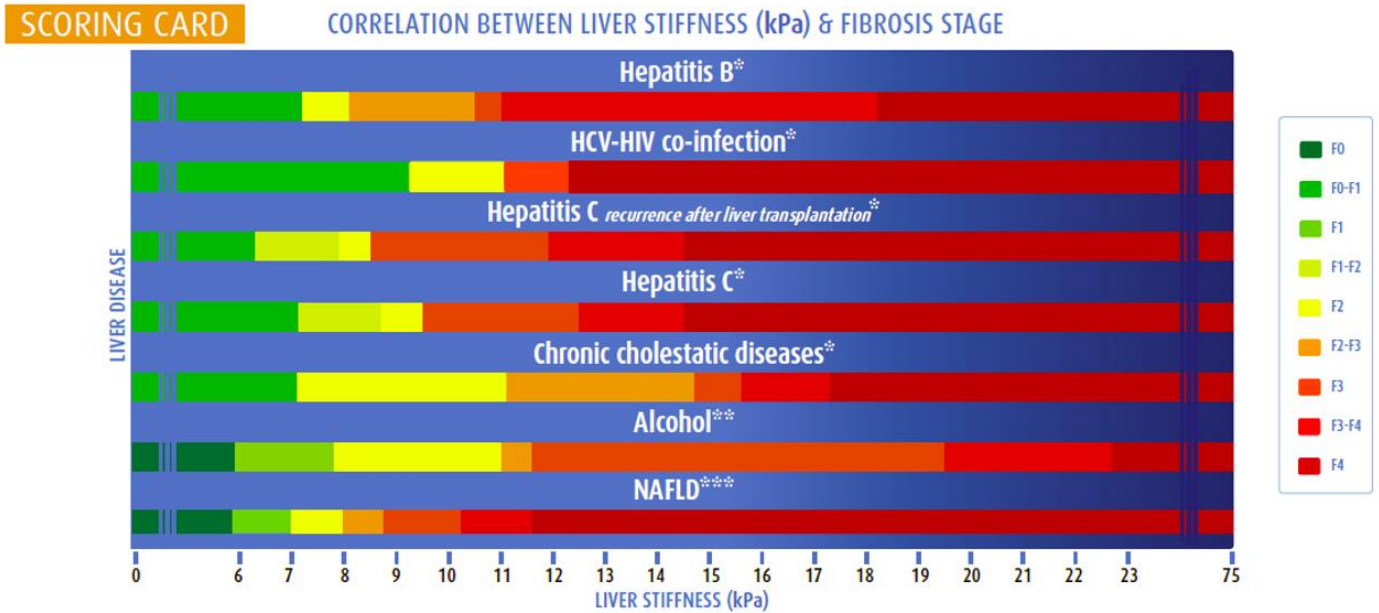


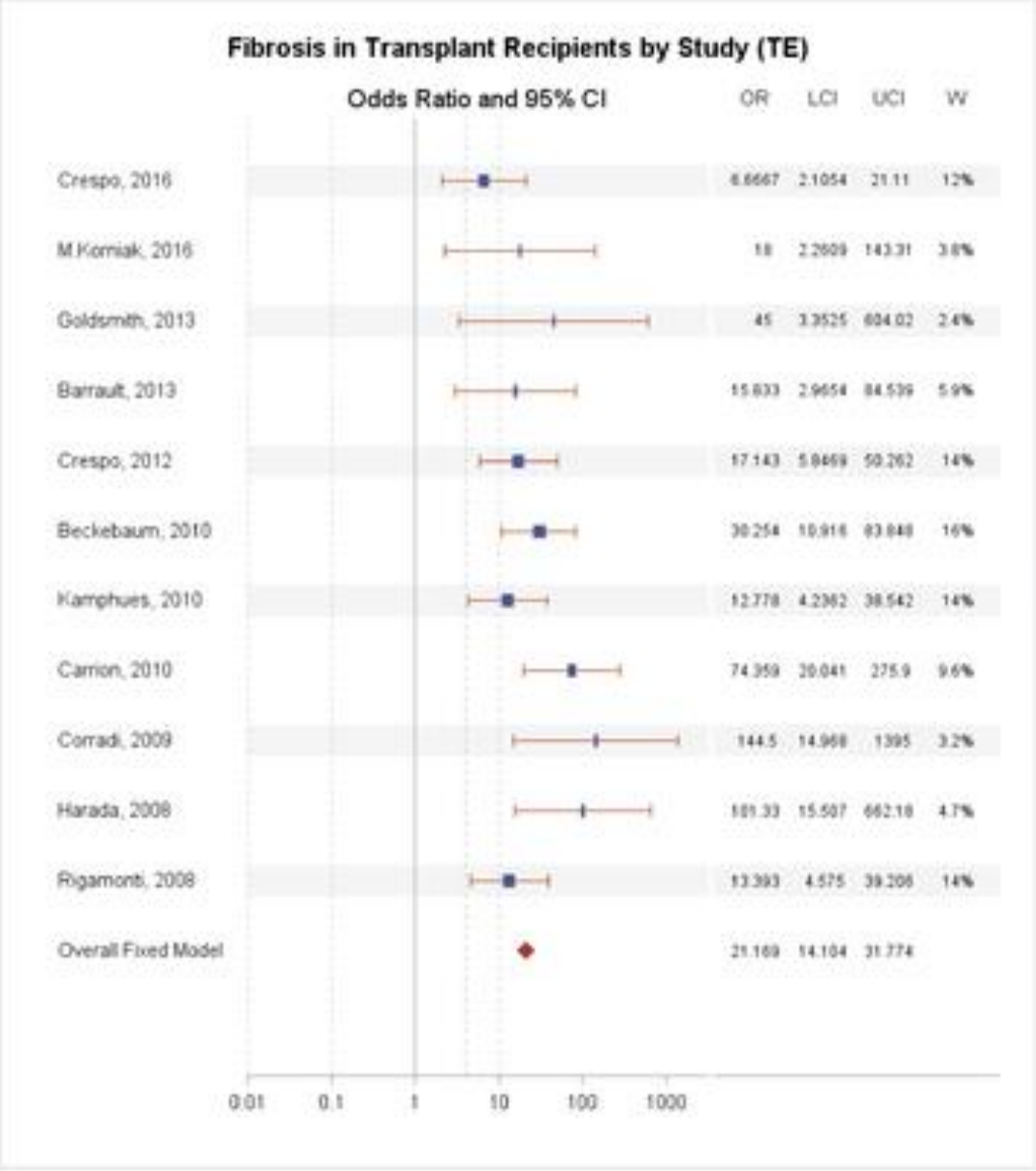
Each study is shown by the point estimate of the risk ratio (RR) and the respective 95% confidence interval (CI), represented by the lines. The RR was calculated using the true positive (TP) value for blood eosinophilia and total number of eosinophilia-positive patients for the index test-positive group (TP/Total+) and the false positive (FP) value for blood eosinophilia and total number of eosinophilia-negative patients for the index test-negative group (FP/Total–). The combined RRs and CIs are represented by the diamond. The DerSimonian and Laird random effect model was used. I^2 statistics was used as a measure of heterogeneity. A statistically significant overall effect was obtained (P = 0.0006). Heterogeneity: Tau^2 = 0.04; Chi^2 = 10.89; df = 3 (P = 0.01); I^2 = 72%. Test for overall effect: Z = 3.44 (P = 0.0006).

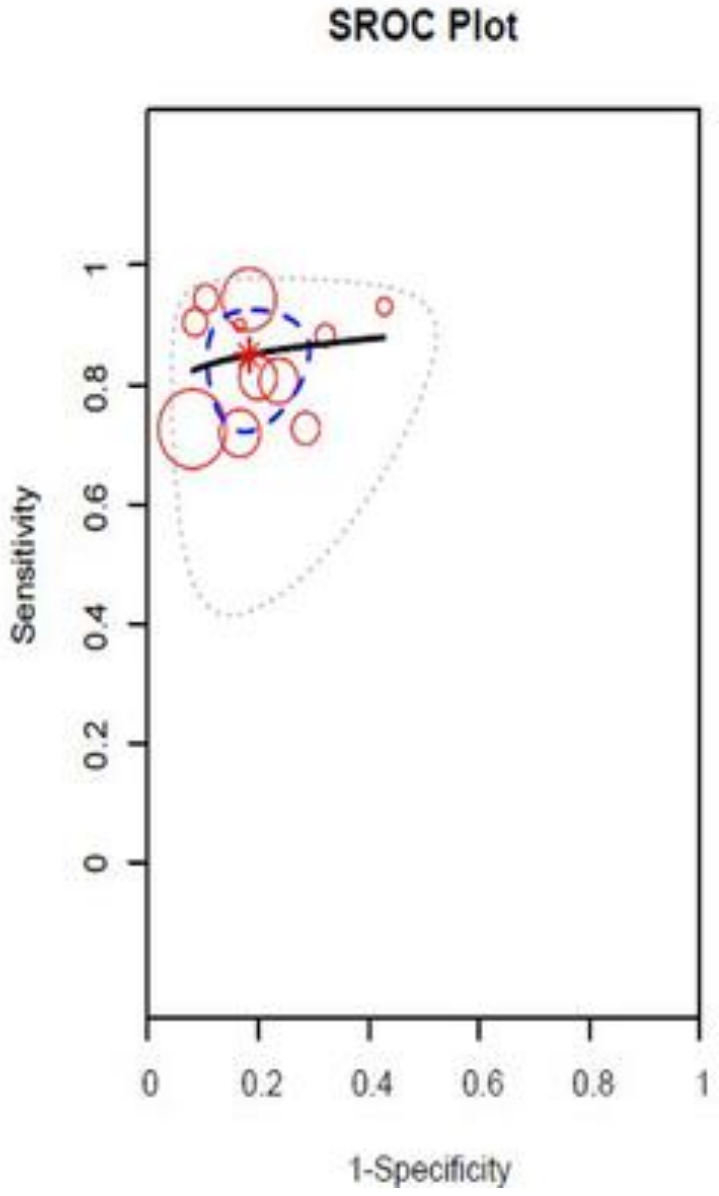
Non Invasive markers

- Unable to Grade severity
- Most markers up in inflammation
- Lack Specificity

Non Invasive markers







Bhat M, Tazari M, Sebastiani G (2017) Performance of transient elastography and serum fibrosis biomarkers for non-invasive evaluation of recurrent fibrosis after liver transplantation: A meta-analysis. PLOS ONE 12(9): e0185192. https://doi.org/10.1371/journal.pone.0185192
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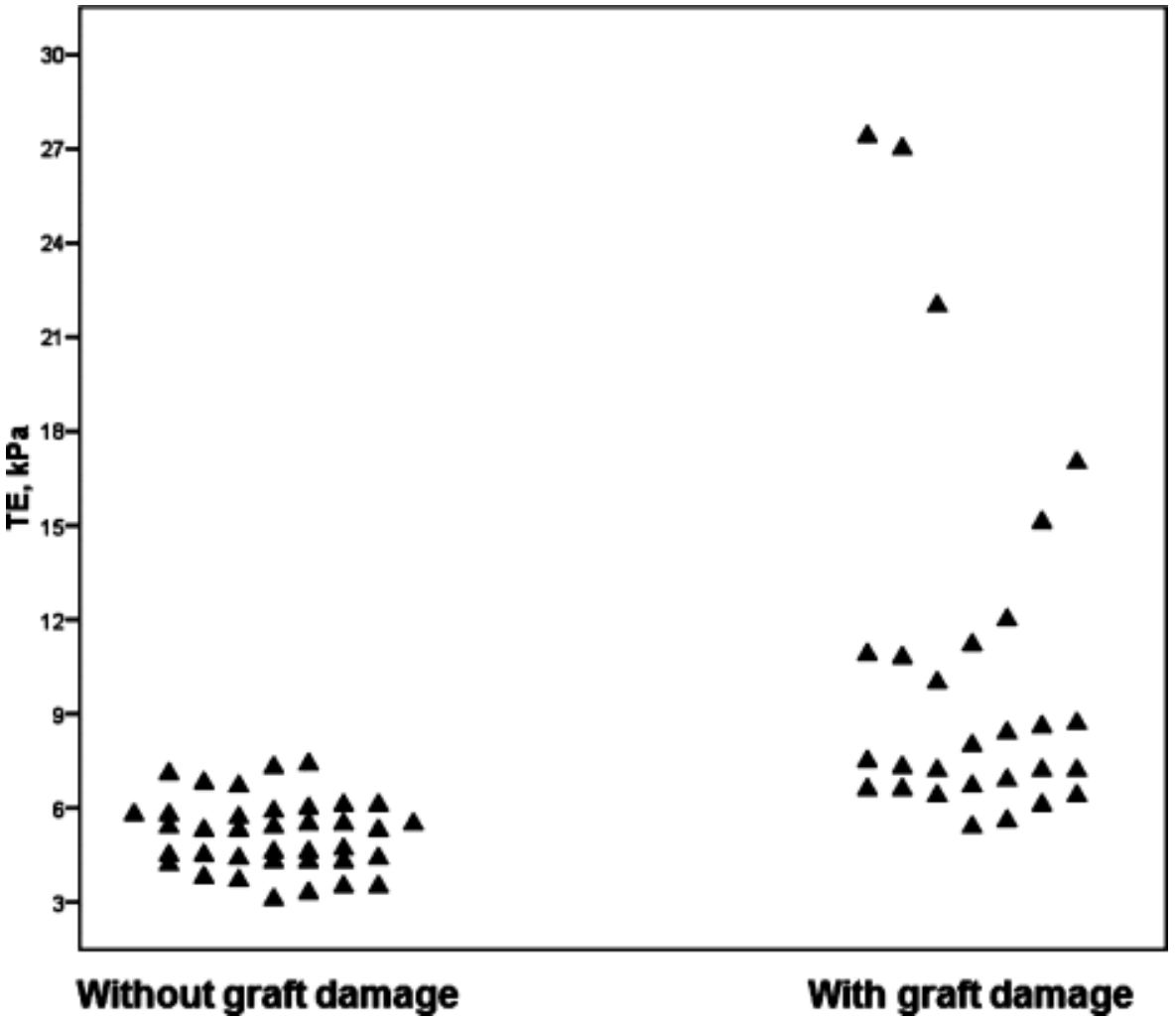
Transient elastography identifies liver recipients with nonviral graft disease after transplantation: A guide for liver biopsy



Liver Transplantation, Volume: 18, Issue: 5, Pages: 566-576, First published: 23 January 2012, DOI: (10.1002/lt.23391)

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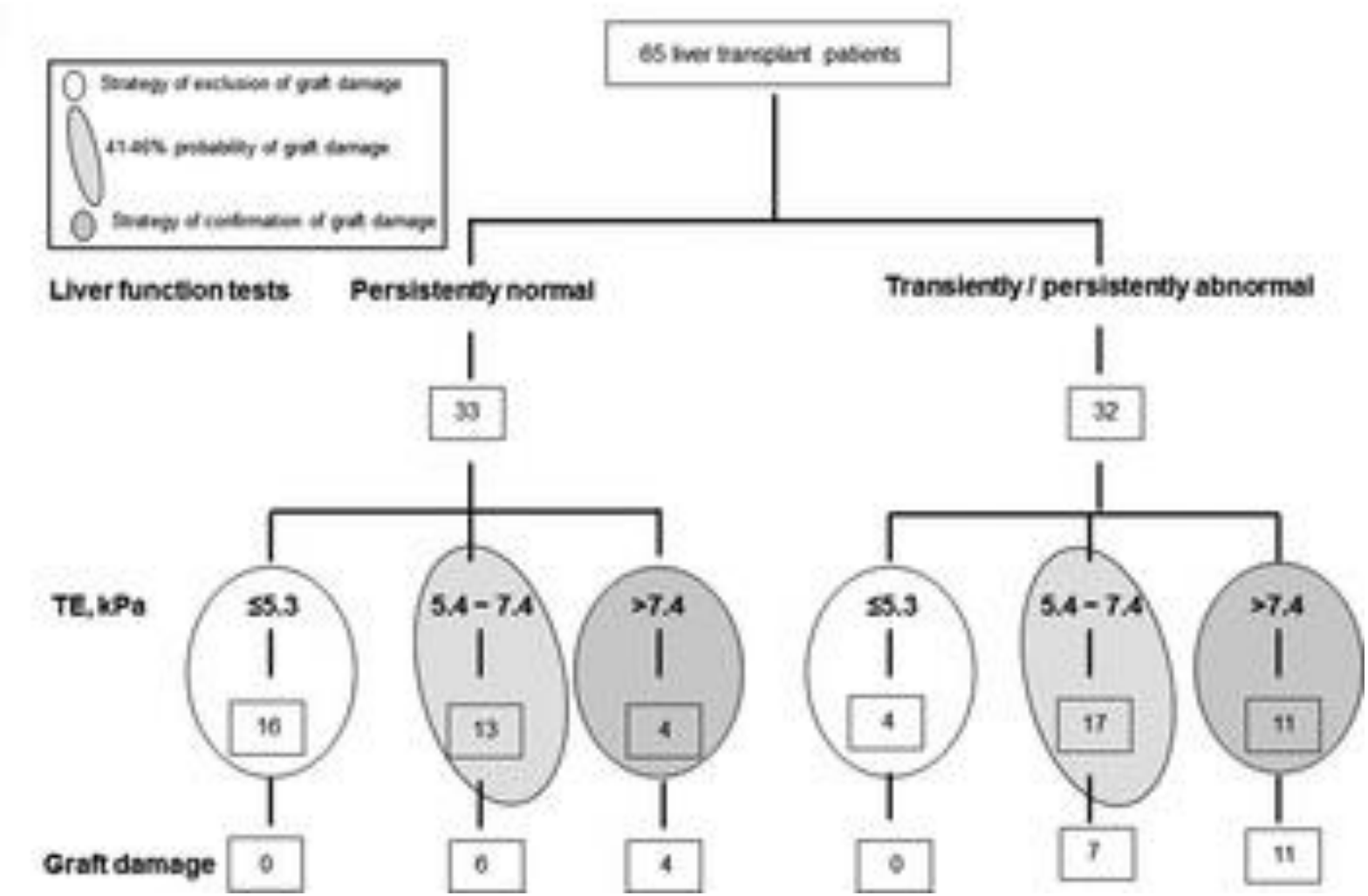

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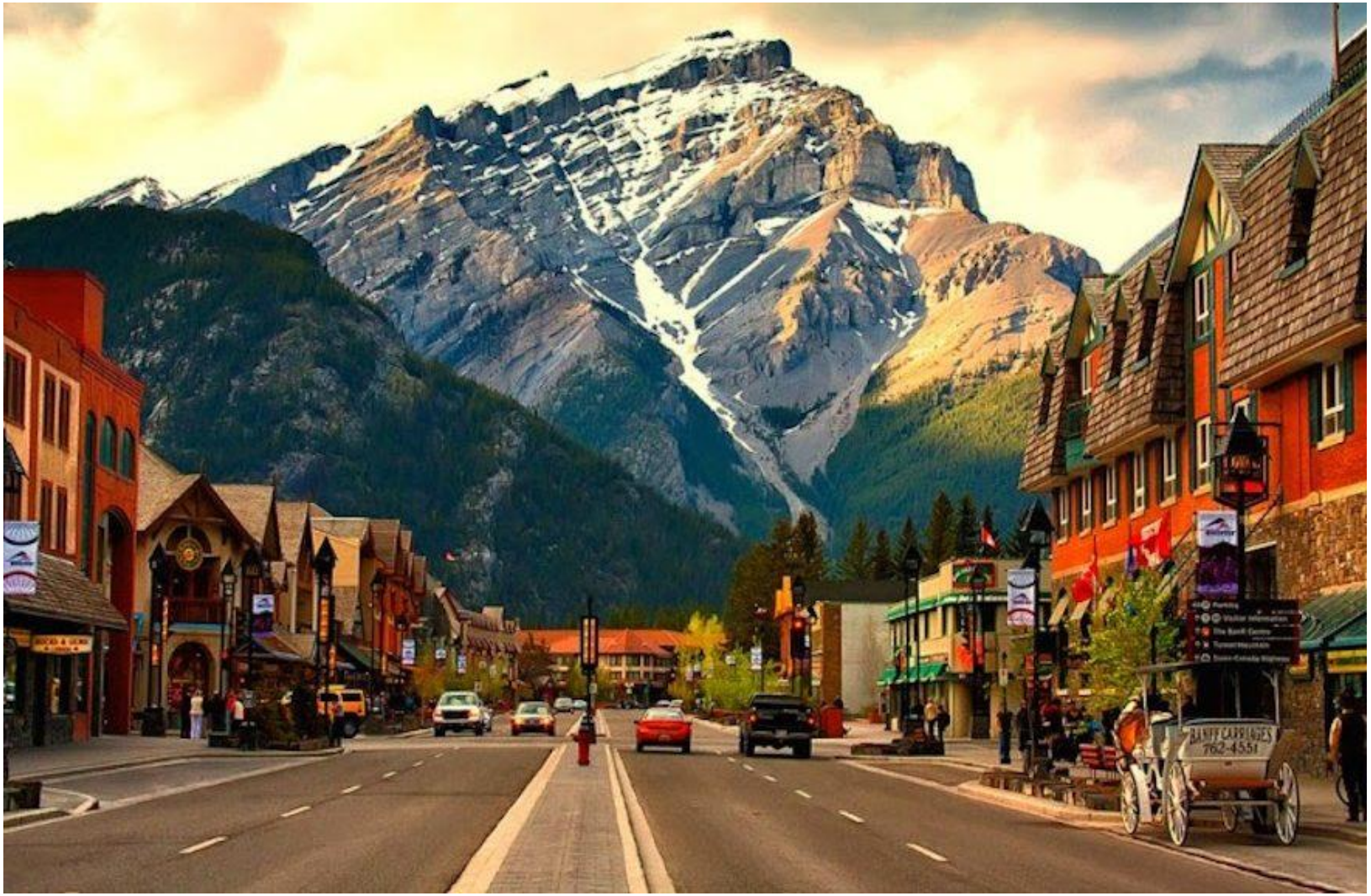
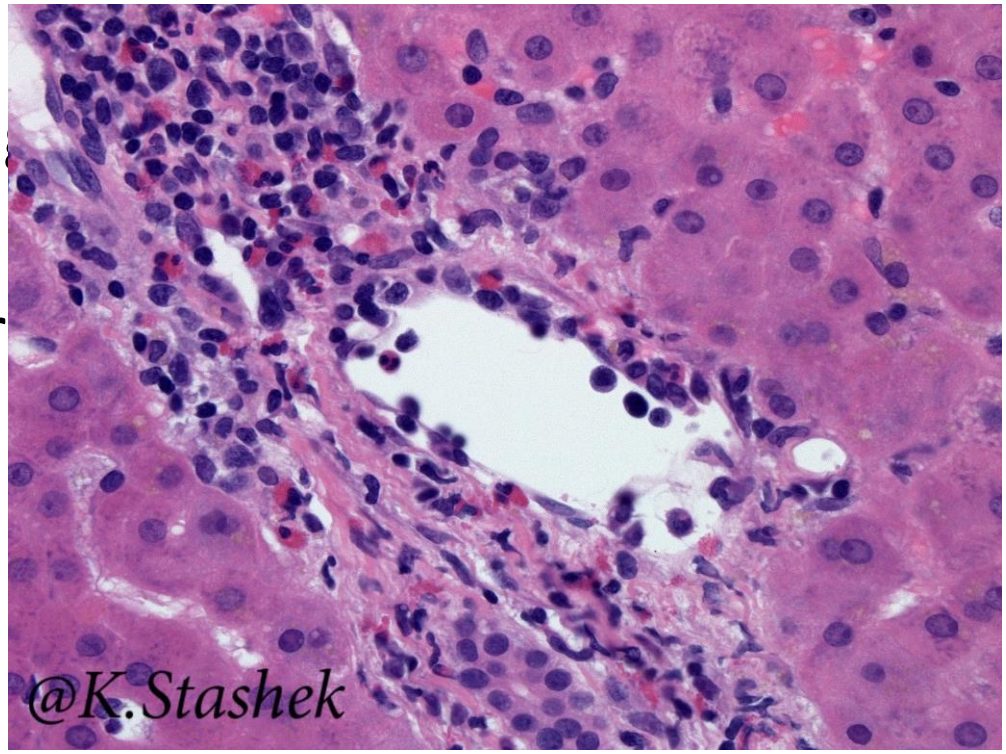
In conclusion



In Conclusion

- Liver biopsy is here to stay
- Mechanisms at reducing risk to patients
- Decreasing the number of biopsies required



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Thank You

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