

Acute Liver Failure And Liver Transplantation : Indian Scenario

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The Beginning...December 2004



In air ambulance

21 years young lady air lifted from Kashmir Valley

- Had taken Flutamide (antiandrogen) for Acne & facial hair
- Jaundice 8 days, Altered Sensorium 3 days
- Bilirubin 24mg%, AST/ALT 1800/2250, INR 7
- Acute Liver Failure
- On Ventilator, grade 4 HE

The Beginning...



In air ambulance



3 weeks post op

21 years young lady air lifted from Kashmir Valley

**Donor- Mother
Right Lobe Graft**



3 months post surgery !

Issues in LT for ALF

- No DDLT
- Live donor
- Few centers
- Prognostic Scores - which one?
- Recipient selection
- Donor selection
- Indian Experience



Issues in LDLT for ALF

Prognostic scores: Limitations

Controversial issue: Whom to transplant / When to transplant ?

Impact of the experience of a program on selection for liver transplantation in ALF

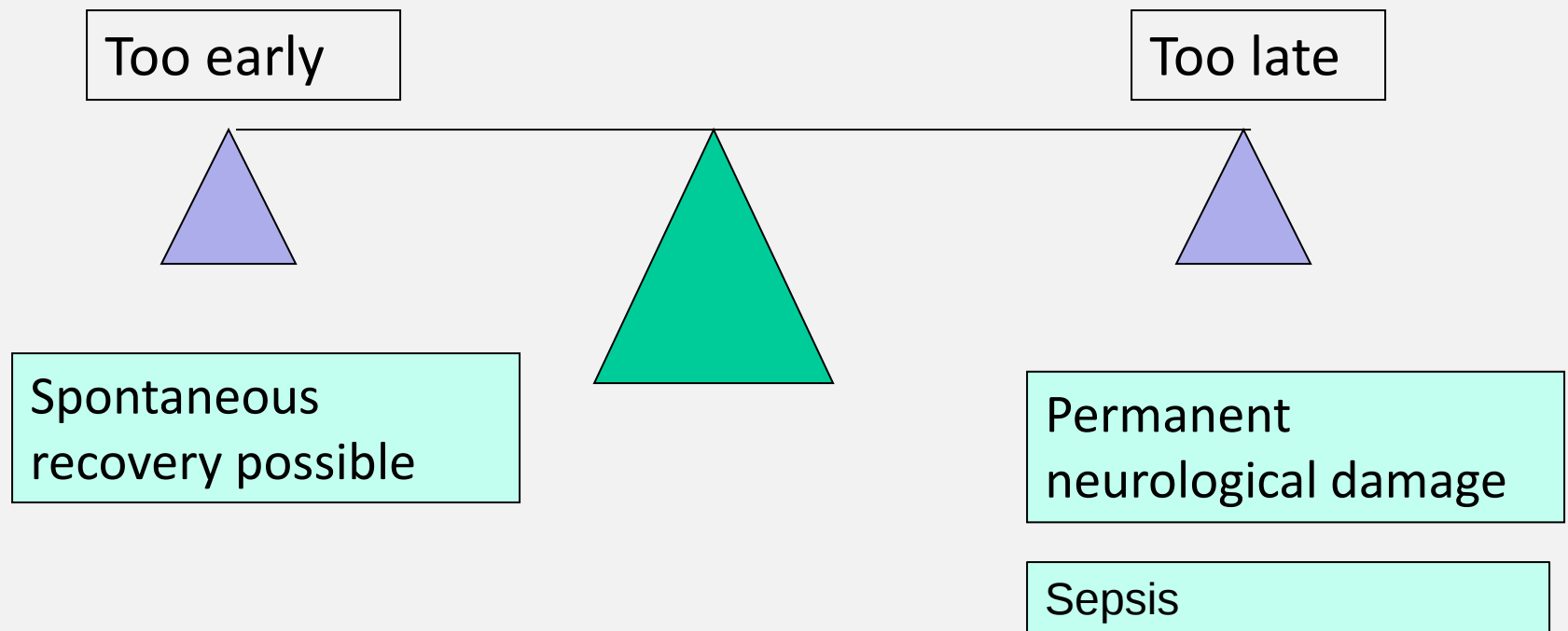
Impact of LDLT vs DDLT in selection for liver transplant in ALF

Our experience

Indian Data: LT for ALF

Author, year	n	Center	Survival
Bavikatte, IJG 2017	7, ATT DILI	Kochi	72%
Choudhary NS, Clin Tx 2018	18, DILI Adults	Medanta	88%
Mehrotra, IJG 2018	36	SGRH	86%
Pamecha, Liver Tx 2019	61	ILBS	65.5% actuarial
Mallick, JCEH 2020	70	Kochi	65% at 90 days

Living Donor Liver Transplantation in ALF



Prognostic Scores : which one to use ?

- King's College Hospital (KCH) Criteria
- CLICHY (French)
- ALFED Model (India)

KCH Criteria – Predictive Value

Authors	N°	PPV	NPV	Accuracy
O'Grady et al	42	97%	75%	90%
Pauwels et al	81	96%	50%	80%
Donaldson et al	46	94%	75%	89%
Izumi et al	17	93%	67%	88%
Annand et al	25	79%	50%	68%
Shakil et al	144	91%	42%	74%
Chung et al	11	100%	30%	36%
Yantorno et al	64	80%	77%	78%

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The fulfillment of the KCH criteria is generally useful in predicting death, but a lack of criteria does not predict survival

Early Dynamic Model for Predicting Mortality in ALF: ALFED score

Persistent or increasing on day 3

▪ HE grade >2	2
▪ INR >5	1
▪ Art Ammonia >123	2
▪ Bilirubin> 15	1

▪ Low	0-1
▪ Moderate	2-3
▪ High	4-6

Prospective derivation and validation of early dynamic model for predicting outcome in patients with acute liver failure

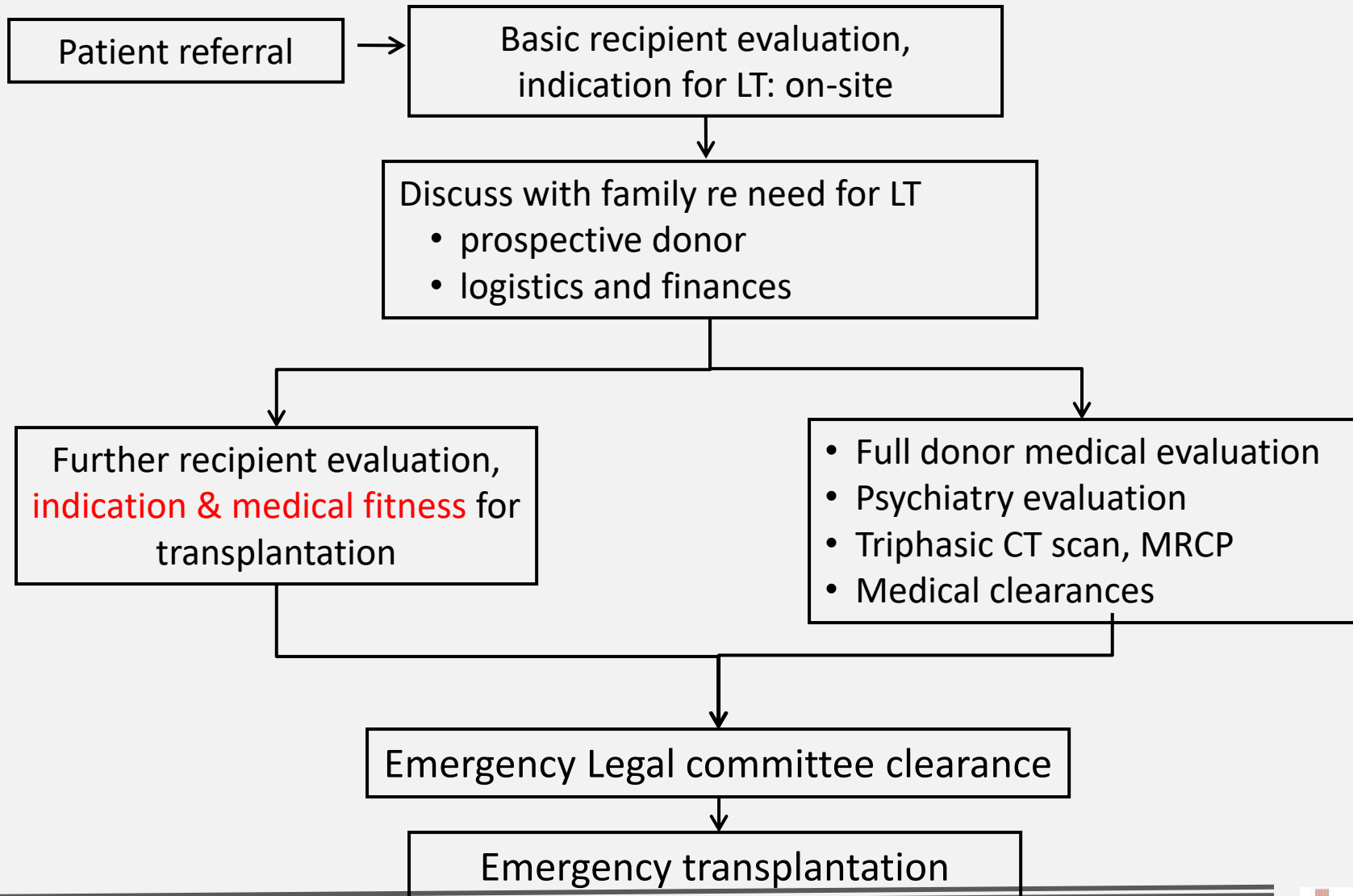
AIIMS study, India, Gut 2012;61:1068-1075.

LDLT for Acute Liver Failure

Study & year	N	Dominant etiology	Selection criteria	Grade of 3-4 HE at presentation	Median TB(mg/dl)	Median INR	MEDIAN J TO E (DAYS)	1YEAR SURVIVAL
Miwa et al (1999)	14	Indeterminate	KCH	10/14(71%)	25(12-29)	21%(7-40%)	12(8-16)	90%
Uemoto et al (2000) (Kyoto)	34	Non A Non B	NA	NA			NA	59%
Matsui et al(2008) (Tokyo)	36	Indeterminate	Six set of Criteria	21/36(58%)	15.7(2.4-43.1)	17.2(11.9-28.6)-PT	NA	87%
Park et al(2009) (Seoul)	40	HBV	AASLD with Progression of HE	6/40	22.0(11.0-30.8)	3.1(2.7-4.2)	5(1-13)	85%
Yamashiki et al(2012) (Japanese registry data)	209	Indeterminate	Mochida	NA	16.7(9.1-23.6)	3.2(2.2-4.1)	9(3-19)	79%
Jin et al(2012)	36ddl 124ldlt	Viral	Progression to grade 3,4 HE	NA	28.6(17.0-37.2)	3.0(2.3-4)	NA	79%
Pamecha et al(2018)	61	Viral	KCH	40/61(70%)	24(18.5-29.5)S	4.3(3.4-6.2)	15(9-29)	65.6%

Pamecha V, Living Donor Liver Transplantation for Acute Liver Failure: Donor Safety and Recipient Outcome. Liver Transpl. 2019

Planning LDLT for ALF in India



Challenges in Donor Selection in LDLT

Family related

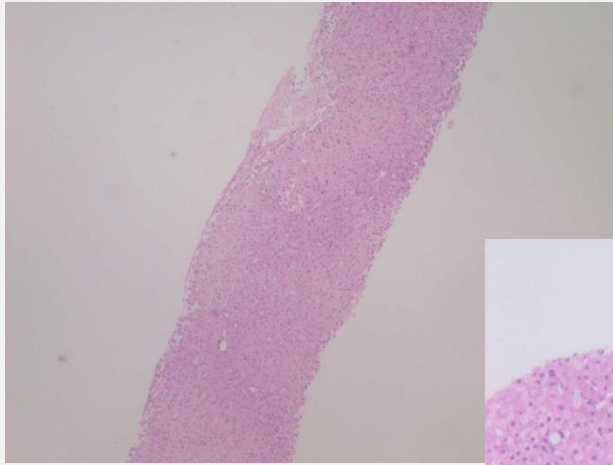
Rapid workup

Legal/ Ethical clearance

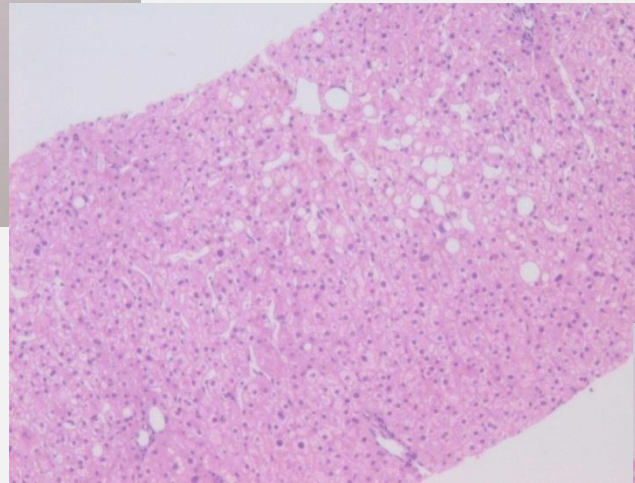
Age	18-55 yrs
BMI	18-33
Transaminases	<40
Steatosis	<20%
GRWR	>0.8
Remnant	>30%
Inflammation	Nil
Fibrosis	Nil

CT Liver Volumetry & angiography
MRCP for biliary anatomy

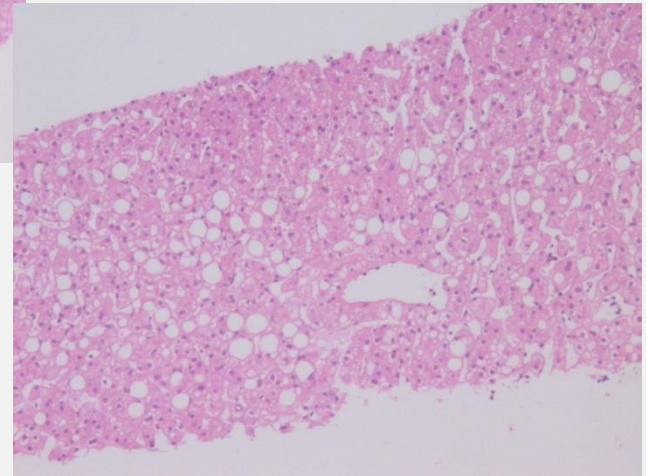
Donor Histologic assessment : Rapid Biopsy



Steatosis- <5%

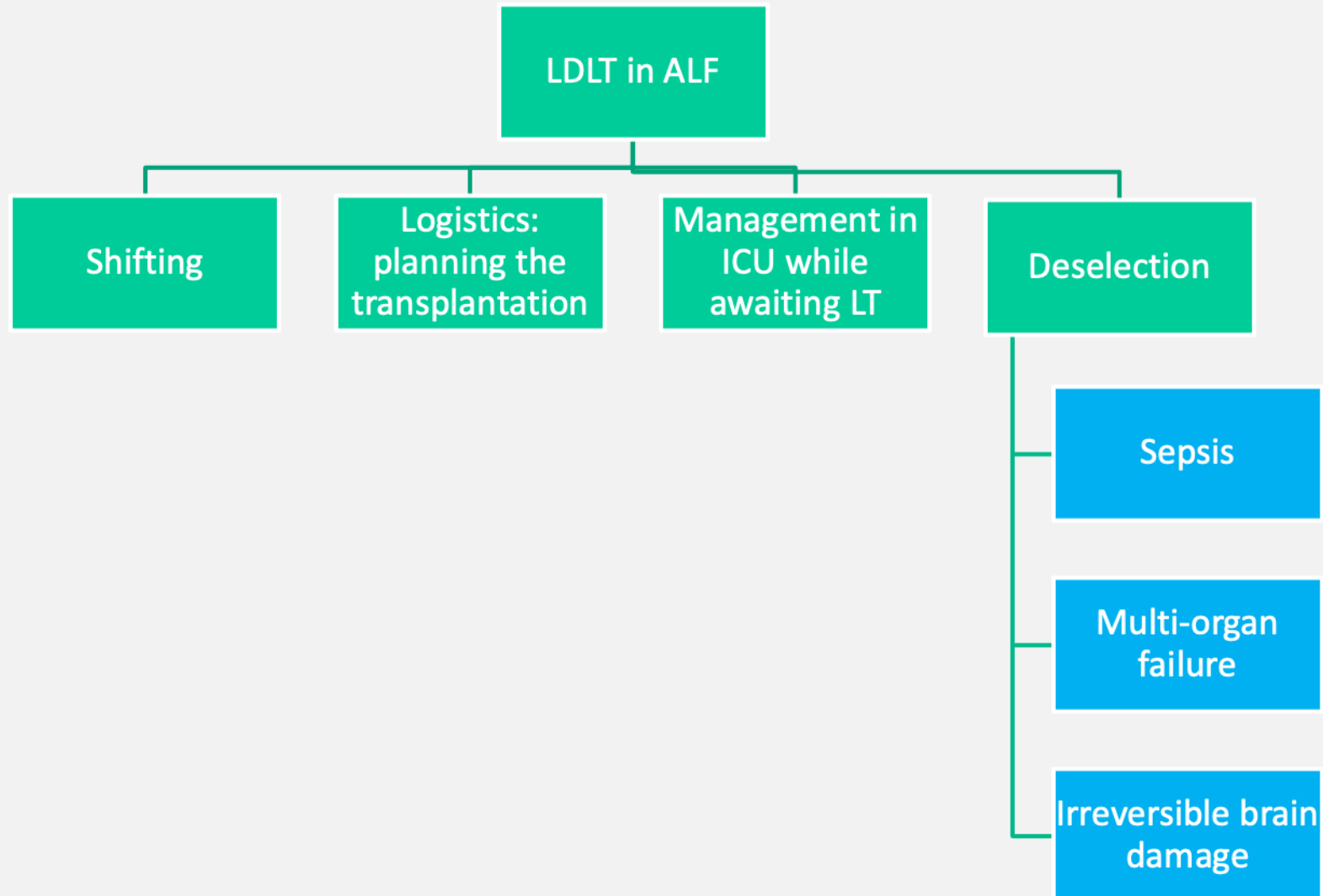


Steatosis- 10%

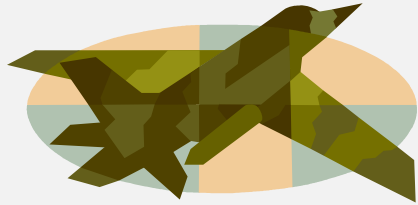


Steatosis- 25%

Decisive factors for LDLT in ALF



Shifting of ALF patient: Crucial Component



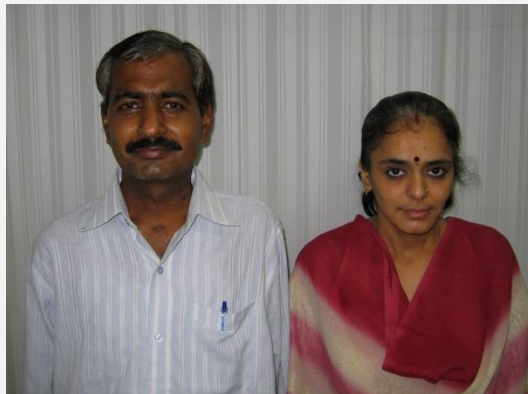
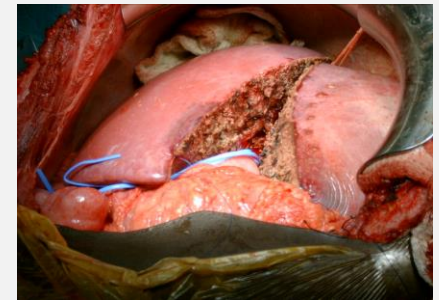
Raipur



In ambulance



Delhi



Emergency LT
Donor: Wife

6 weeks post LT with wife (donor)

Management of ALF patient awaiting LT

For exclusion: NCCT Head, EEG

To preserve

- Na > 140
- PCO₂: 30-35 (RR 18-20)
- Head-end elevated, CVP around 3-5
- Avoid fever (hypothermia practiced routinely)
- Ventilated and sedated once >grade III HE
- Non-invasive neuro monitoring: **ONSD**
- Fluids, electrolytes, antibiotics
- FFP only for procedures

Deselection of patients

Patient is improving

Uncontrolled sepsis

Advanced multi-organ failure

Advanced cardiopulmonary disease

Advanced neurological damage

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Living Donor Liver Transplantation for Acute Liver Failure: Donor Safety and Recipient Outcome

Viniyendra Pamecha,¹ Ankur Vagadiya,¹ Piyush Kumar Sinha,¹ Rommel Sandhyav,¹ Kumaraswamy Parthasarathy,¹ Shridhar Sasturkar,¹ Nihar Mohapatra,¹ Ashok Choudhury,² Rakhi Maiwal,² Rajeev Khanna,³ Seema Alam,³ Chandra Kant Pandey,⁴ and Shiv Kumar Sarin²

¹Department of Liver Transplant and Hepato-Pancreato-Biliary Surgery; ²Department of Hepatology; ³Department of Pediatric Hepatology; and ⁴Department of Anaesthesiology and Critical Care, Institute of Liver and Biliary Sciences, New Delhi, India

- Mar 2011 & Feb 2018, a total of 188 patients met the KCC for ALF.
- 61 (14.9%) of total 410 LDLT
- For the remaining 127 (68%) patients, the reasons for not undergoing LT were
 - Development of irreversible complications of ALF (n = 30, 24%),
 - No suitable available donor in the family (n = 46, 36%),
 - Financial constraints (n = 35, 28%), and
 - Collective decision by the family not willing to proceed with surgery (n = 16, 13%).



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- Median admission to transplant time was 48 hours (range, 24-80.5 hours),
- Median living donor evaluation time was 18 hours (14-20 hours)
- Median MELD 37 (32-40) with > 2/3rd grade 3 or 4 HE and 70% being on MV
- The most common etiology was viral (37%).
- Median jaundice-to-encephalopathy time was 15 (9-29) days.
- Preoperative culture was positive in 47.5%.



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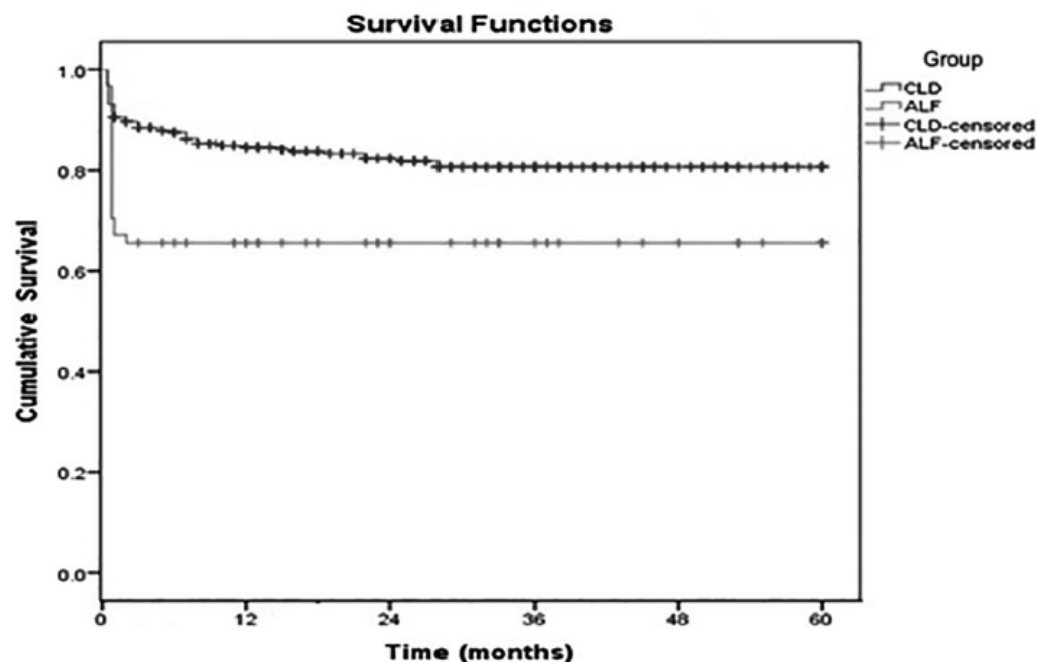
- There was no difference in the complication rate among emergency and elective living liver donors (13.1% versus 21.2%; $P = 0.19$).
- There was no donor mortality.
- For patients who met the KCC but did not undergo LT, survival was 22.8% (29/127).
- The 5-year post-LT actuarial survival was 65.57% with a median follow-up of 35 months.
- On multivariate analysis, predictors of poor outcomes:
 - Postoperative worsening of cerebral edema (CE; [HR], 2.53; 95% [CI], 1.01-6.31),
 - Systemic inflammatory response syndrome (SIRS; HR, 16.7; 95% CI, 2.05-136.7),
 - Preoperative culture positivity (HR, 6.54; 95% CI, 2.24-19.07), and
 - A longer anhepatic phase duration (HR, 1.01; 95% CI, 1.00-1.02)



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CLD, Event (Number at risk)	0 (308)	52 (227)	57 (160)	60 (91)	60 (49)	60 (16)
ALF, Event (Number at risk)	0 (61)	12 (49)	21 (37)	21 (25)	21 (13)	21 (1)

Live donor liver transplantation for acute liver failure: A single center experience

Siddharth Mehrotra¹  • Naimish Mehta¹ • Prashantha S. Rao¹ • Shailendra Lalwani¹ • Vivek Mangla¹ • Samiran Nundy¹

Received: 8 May 2017 / Accepted: 22 December 2017 / Published online: 17 February 2018
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- 479 patients underwent LT between Jan 2009 & Dec 2015
- 36(7.5%) of 479 underwent emergency LT for ALF
- Mean age 27.5 years (range 4– 59 years) M:F ration of 2:3
- Preoperative intubation required in 15 of 25 patients who had encephalopathy.
- Wilson's disease was the most common cause of ALF in children
- In adults, it was acute viral hepatitis
- The time interval between listing and transplantation was mean of 36 ± 12.4 h
- Mean GRWR was 1.06 ± 0.3

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- Postoperative infection was the most common complication and required upgradation of antifungal and antibiotic treatments.
- Neurological complications occurred in five patients. Thirty-one of 36 (86.1%) patients survived, and progressive cerebral edema and sepsis were the most common causes of mortality.
- Patients who died had
 - Higher MELD,
 - Longer cold ischemia time (CIT), and
 - Higher grades of encephalopathy (though 80% patients with encephalopathy survived).
- There was no donor mortality.
- At long-term follow up of a median of 56 months, 29 (80.5%) of 36 patients were still alive.

Univariate analysis of factors affecting mortality

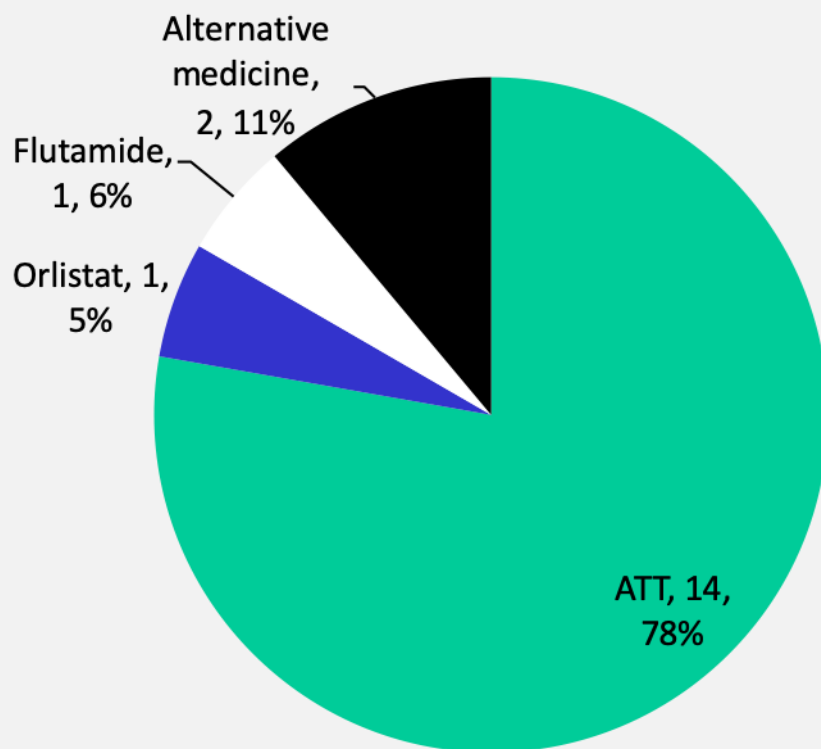
S no.	Variable	Group A (survival)	Group B (mortality)	<i>p</i> -value
1	Mean age (years)±SD	26.2±16.7	36±14.2	.001
2	Male:female	1:2	4:1	.04
3	Jaundice to encephalopathy (days)±SD	16.8±17.8	9±4.3	.36
4	Time from listing to surgery (days)±SD	2.4±2.3	1.6±0.8	.58
5	MELD score±SD	34.6± 9.3	38.4±10.1	.02
6	Preoperative ventilator±SD	0.33 ± 0.4	1	.006
7	Mean WIT (min)±SD	50.8 ± 20.5	76±34.6	0.01
8	Mean CIT(min)±SD	74.3 ± 28.8	126.4 ± 20.6	0.002
9	Mean transfusion±SD	3.2 ± 2.7	5.8 ± 3.7	0.12
10	Mean GRWR±SD	1.1 ± 0.3	0.91 ± 0.15	0.08
11	Graft R:L	4:1	21:8	0.2

Good outcome of living donor liver transplantation in drug-induced acute liver failure: A single-center experience

Narendra Singh Choudhary¹  | Sanjiv Saigal¹ | Neeraj Saraf¹ | Amit Rastogi¹ |
Sanjay Goja¹ | Prashant Bhangui¹ | Vijay Vohra² | Deepak Govil³ | Arvinder S. Soin¹

Total LDLT = 1396, ALF = 64 (4.5%)

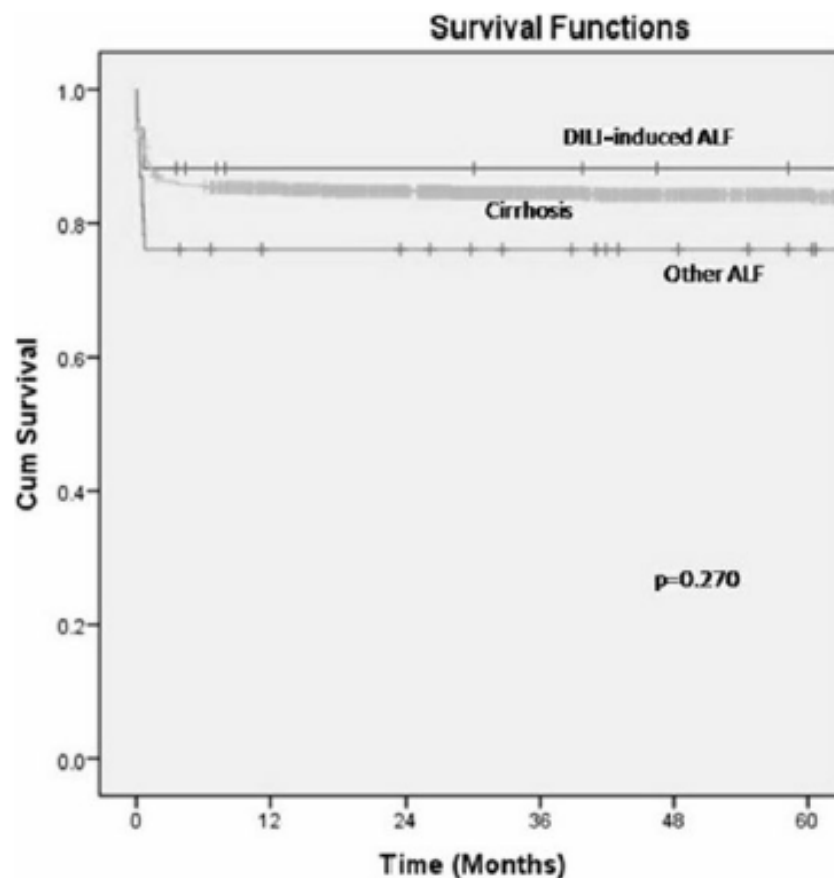
LDLT for DILI-ALF = 18 (28.1%)



Parameter	Number (median)
Age (years)	34 (25-45)
Sex	15 females, 3 males
Bilirubin mg/dL	17.7(16.3-23.8)
INR	3.3 (2.5-4.0)
Arterial Ammonia	109 (73-215)
HE grade	3(2-4)
Waiting time (days)	1(1-3)

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Living donor liver transplantation (LDLT) for acute liver failure (ALF): Experience from a large volume center

Saigal S, Choudhary NS, Saraf N, Rastogi A, Bhangui P, Thiagrajan S, Yadav
S.K, Vohra V, Soin AS

*Medanta The Medicity, Institute of Liver Transplantation and regenerative medicine,
Gururgam, India*

Oral presentation, ILTS 2019, Toronto

Methods

LDLT for ALF

N=70

17 males and 53 females

Age: 33.9 ± 11.5 years

Donor

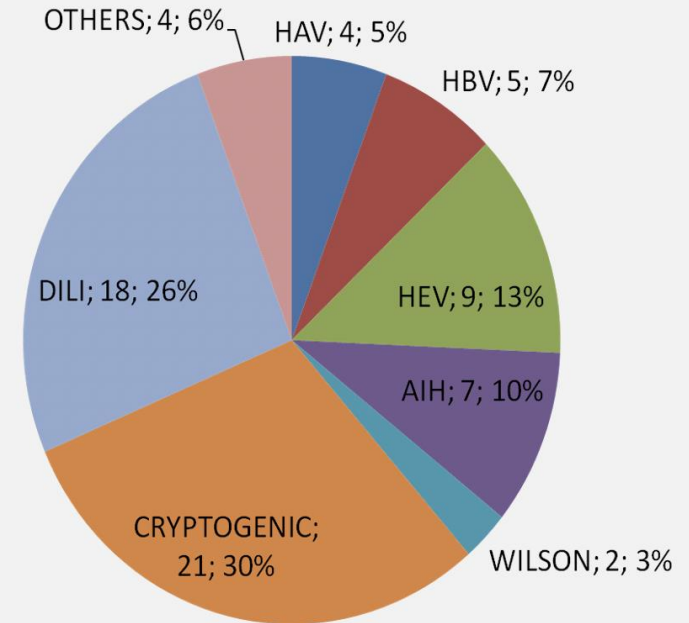
Age: 36 ± 10 years

Immunosuppression

Tacrolimus

MMF

Steroids- tapered at 3 months



All donors were family related (siblings being the commonest)

Oral presentation, ILTS 2019, Toronto

Results

Parameter	Results
Admission to surgery interval	2(1-3) days
ICU stay	5(5-7.5) days
Hospital stay	16(13-22) days
CIT	83 $\pm$ 30 minutes
WIT	47 $\pm$ 9 minutes
PRBC	5(3-7)
Follow up (median)	63 (IQR 3-93) months
Mortality	15 patients died in first month and none died thereafter

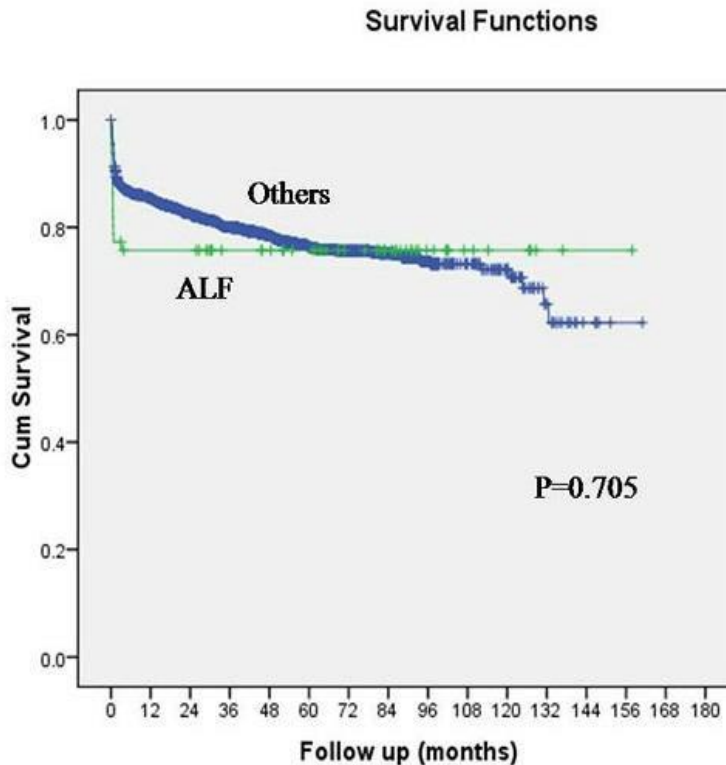
Oral presentation, ILTS 2019, Toronto

Post op complications

Parameter	Results
Bile leak & biliary strictures	3 & 6 (12.8%)
HAT	1 (1.4%)
ACR	17 (24.2%)
CMV	6 (8.5%)
Infections	13 (18.5%)

Oral presentation, ILTS 2019, Toronto

Survival



1-yr survival 78.5%

Mortality due to sepsis

No mortality after first year

GRWR - AUROC 0.84, $p=0.000$, 95% CI 0.680 to 0.949 to predict mortality

GRWR <0.905 , Sensitivity 78.6% and Specificity 86% for mortality

Oral presentation, ILTS 2019, Toronto

Decision making triggers in patients with acute liver failure

PROCEED

Persistence of accepted criteria associated with a poor prognosis

Absence of co-morbidity independent of ALF that would impact on survival

Absence of complications of ALF associated with reduced survival

Absence of psychosocial profile suggestive of poor adaptation of rigour of post-transplant survival

Adapted from John O'Grady. Timing and benefit of liver transplantation in acute liver failure. Journal of Hepatology 2014 vol. 60 j 663–670

Decision making triggers in patients with acute liver failure

WAIT

Patients showing sustained evidence of improvement of prognostic criteria in the absence of clinical deterioration

Paracetamol induced ALF patients who do not have grade 3 or 4 encephalopathy irrespective of severity of coagulopathy

Most patients when the liver allocated is marginal, especially steatotic, non-ABO identical or split, ABO incompatible or the donor is aged over 60 years

Adapted from John O'Grady. Timing and benefit of liver transplantation in acute liver failure. Journal of Hepatology 2014 vol. 60 j 663–670

Decision making triggers in patients with acute liver failure

STOP

Evidence of compromised brainstem function, especially fixed and dilated pupils

Invasive fungal infection

Rapidly escalating inotrope requirements

Severe pancreatitis [usually in paracetamol-related ALF]

Adapted from John O'Grady. Timing and benefit of liver transplantation in acute liver failure. Journal of Hepatology 2014 vol. 60 j 663–670

Living donor liver transplant in ALF: Conclusions

LDLT in ALF is a formidable challenge

LDLT can be offered in ALF setting with good outcome

Most challenging task is to prognosticate the patients and to select out those who will recover on medical measures alone

Experience & maturity of a program is crucial in deciding when not to transplant

Summary

- Unique challenges in LT for ALF in India
- Most of transplants are LDLT
- Rapid donor evaluation in LDLT – a challenge !
- Prognostic scores should be validated for Indian patients
- Cost implications
- Need for greater awareness and early referral of ALF patients



sanjivsaigal@hotmail.com

Medanta Adult LDLT (n=2416), June 2019

