A Catch 22 Situation

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Transplant Hepatologist, QE Birmingham,
BTS Annual Meeting 2018

41 year old male

- First referred for consideration of OLT in mid 2013
- Diagnoses
  - NAFLD cirrhosis
  - Intermittent PR bleeding (OGD showed PHG and grade 1 OV, colonoscopy small caecal polyps and DD)
  - Bipolar disorder
  - Gout
- Medications – allopurinol, fexofenadine, propranolol (160 mg), aripiprazole, omeprazole
- Full time teacher. Lives with his wife. Non-drinker. Never smoked.
- Generally well. No symptoms attributable to his liver disease

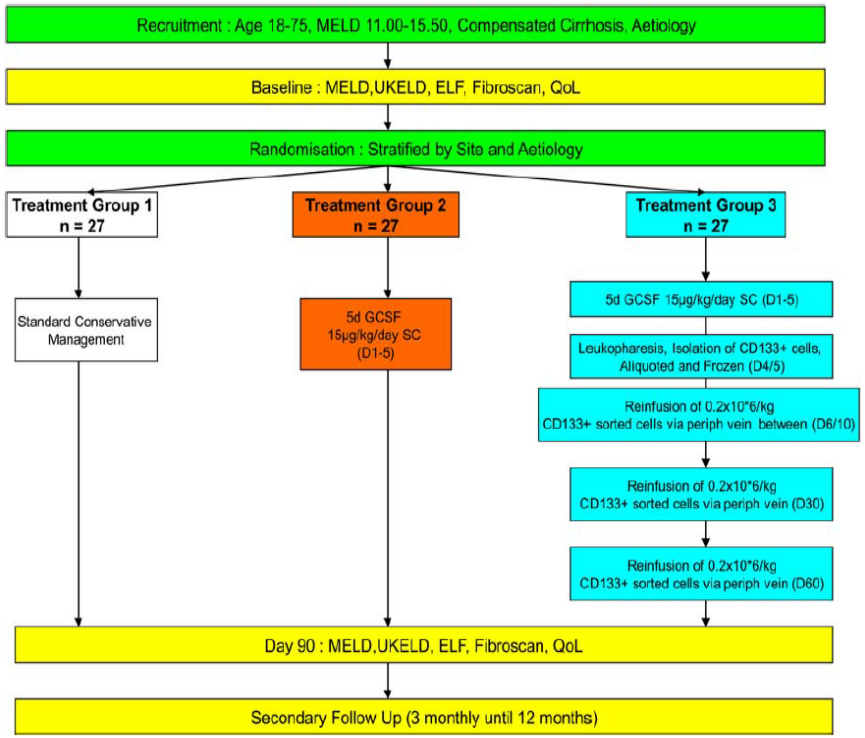
Initial Investigations

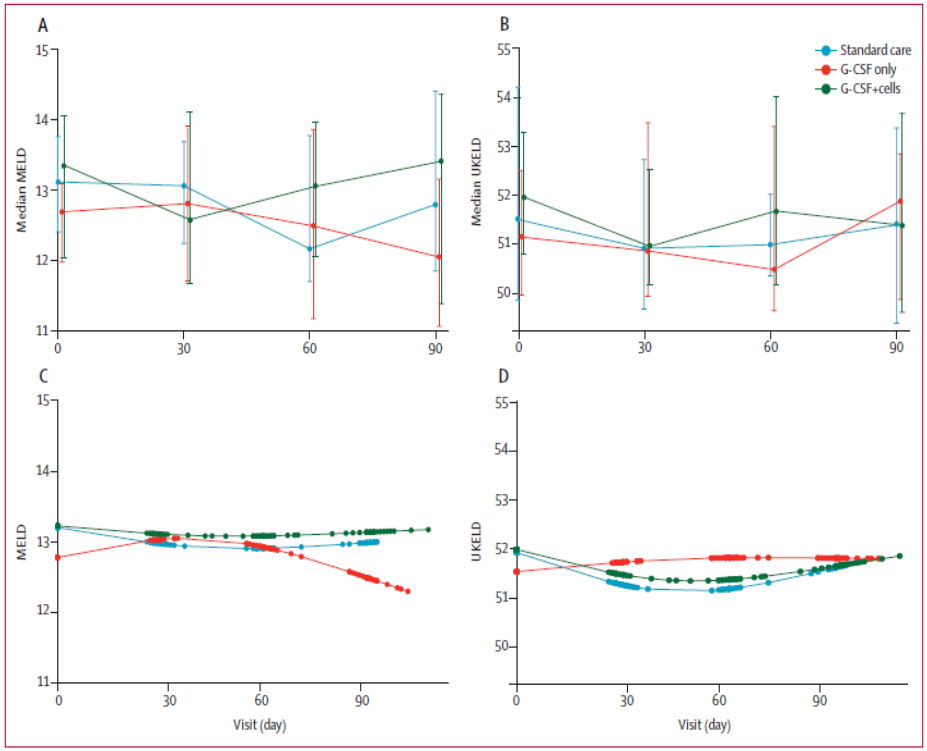
- AST 48, ALT 25, Bili 37, Alb 32, INR 1.6, Plt 75
- UKELD 52
- MELD 15
- Weight 160 Kg
- BMI 49.4
- USS - The liver appears mildly enlarged with an irregular outline and a coarse cirrhotic parenchyma. No focal lesion seen. Patent PV with normal hepato-petal flow demonstrated. Normal gallbladder. No biliary dilatation. Splenomegaly - 16.3cm x 7.5cm x 13.0cm. Ascites -Subhepatic fluid noted. A small amount of fluid in the RIF and LIF.

Q1. Would you consider a transplant assessment?

Progress

- Not felt to have an indication for transplant assessment at that point in time
- Recruited into the REALISTIC (REpeated AutoLogous Infusions of STem cells In Cirrhosis) study – Group 3





King et al BMJ Open 2015 and Newsome et al Lancet Gastro Hep 2018

Seen June 2014

- Starting to complain of dizzy spells and funny turns
- Wife noticed intermittent slurring of his speech
- Had been started on furosemide and spironolactone due to development of moderate ascites in October 2013
- Had to give up work as a teacher
- Lost 30 Kg in weight and BMI 39.6
- USS in March 2014 showed minimal fluid
- UKELD 53, MELD 14.
- Symptoms felt to be possibly related to HE
- CT head organised - Normal

December 2014

- Started on rifaxamin by his local team in July 2014
- Symptoms of dizziness resolved
- Keeping well
- Weight up to 140 Kg (BMI 42)
- UKELD and MELD static – bili 31, albumin 29 and INR 1.6
- No ascites on local scan
- Decision made to continue observing

December 2015

- Remains stable
- No HE or ascites
- UKELD static at 52
- Tried on liraglutide to reduce his weight
- No effect and in fact weight is up to 152.7 Kg with BMI of 46
- Seen by local bariatric surgeon
- Opinion is too high risk – PHG and grade 1 OV on OGD as well as splenomegaly of 16 cm and platelet count of 87
- Decision made to assess him for transplant - ? Right window – aged 43 at this juncture

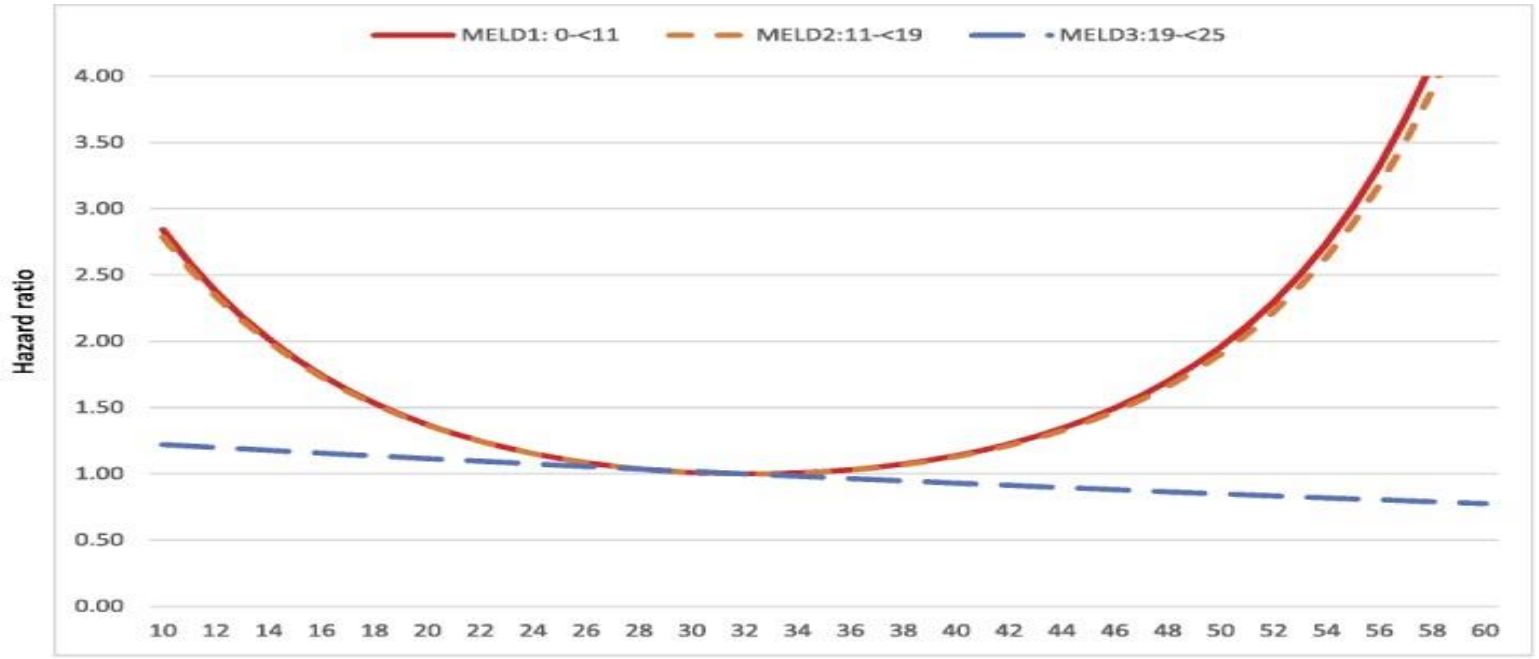
Q2. Is this the right time to consider him for transplant?

Transplant Assessment Outcome

- Cardiovascular and respiratory investigations normal
- MDT agreed that he had a good indication for transplant
- However, deemed too high risk due to BMI
- Recommendation was that he was assessed by our transplant mental health team and that he be referred to weight loss clinic. Also that he is seen regularly by our liver dieticians.

Q3. What is the relationship between BMI and Outcome Post Liver Transplant?

Complex relationship between BMI and OLT Outcome



Hazard ratios were obtained by standardizing hazard rates at various levels of BMI to hazard rates at BMI of 32 (HR=1 at BMI of 32)

Parameter estimates associated with BMI (and the square of BMI, BMI2) from multivariable adjusted survival models

		Quadratic BMI				Linear		
MELD category	n	BMI	BMI2	AIC	BMI*	BMI	HR	AIC
MELD1: 0-<11	7,140	-0.13653**	0.00212**	28687.77	32.2	--	--	--
MELD2: 11-<19	16,230	-0.13312**	0.00206**	71064.58	32.3	--	--	--
MELD3: 19-<25	9,440	-0.04171	0.000542	39681.12	--	-0.00908**	0.991 (0.984-0.998)	39680.53
MELD4: ≥25	15,416	-0.03431	0.000484	68839.72	--	-0.00445	0.996 (0.990-1.001)	68840.54

* BMI associated with the lowest hazard rate for overall mortality

** Statistically significant at 0.05 significance level

Chang et al Transplantation Direct 2017

OLT Complications and BMI

Table 2 Complications of patients who underwent a liver transplant

	No morbid obesity n = 45691		Morbid obesity n = 818		*P*-value
Systemic complications					
Any	20546	44.97%	394	48.20%	0.5253
Post LT infection	13308	29.13%	297	36.26%	0.2103
Cardiovascular complication	781	1.71%	25	3.05%	0.3858
Infections, surgical wound	2035	4.45%	35	4.29%	0.9301
Cardiac complications	1972	4.32%	49	6.00%	0.2737
Peripheral vascular complications	152	0.33%	0	0.00%	--
Respiratory complications	481	1.05%	40	4.87%	0.0433
Digestive system complications	95	0.21%	⩽ 10	1.12%	0.2376
Other postoperative infection	2035	4.45%	35	4.29%	0.9301
Pulmonary insufficiency following surgery	269	0.59%	⩽ 10	0.57%	0.9654
Unspecified intestinal obstruction	145	0.32%	0	0.00%	--
Stroke	149	0.33%	0	0.00%	--
Postoperative shock	69	0.15%	⩽ 10	0.57%	0.4556
Post LT complication	9927	21.73%	142	17.40%	0.1441
Technical complications					
Any	16044	35.11%	263	32.27%	0.4206
Hepatic artery thrombosis	8940	19.57%	113	13.80%	0.0531
History of exploratory laparotomy exploratory laparotomy	221	0.48%	⩽ 10	0.57%	0.8483
Anastomotic leak of biliary tree	1442	3.16%	49	6.00%	0.0837
Perforation of the intestine	148	0.32%	0	0.00%	--
Hemorrhage complicating a procedure	5390	11.80%	58	7.04%	0.0278
Accidental laceration during a procedure	965	2.11%	⩽ 10	0.67%	0.0611
Iatrogenic pulmonary embolism and infarction	169	0.37%	20	2.49%	0.0862
Iatrogenic pneumothorax	691	1.51%	⩽ 10	1.14%	0.6429
Hematoma	3487	7.63%	65	7.94%	0.8931
Seroma complicating a procedure	74	0.16%	⩽ 10	1.15%	0.2145
Disruption of wound	25	0.06%	0	0.00%	--
Disruption of internal operation wound	179	0.39%	0	0.00%	--
Disruption of external operation wound	378	0.83%	20	2.43%	0.1632

Peck et al WJH 2017

More Data

Table 3 Results of multivariate linear/logistic regression for mortality, length of stay and charges for liver transplantation in study cohort

Outcomes	No morbid obesity *n* = 45691 (%)	Morbid obesity *n* = 818 (%)	Adjusted OR/β-coefficient (95%CI)	*P*-value
Mortality	2407 (5.27%)	39 (4.83%)	0.98 (0.50-1.92)	0.95
Length of stay in days, mean (CI)	20.9 (18.7-23.1)	18.7 (15.5-22)	-3.9[1] (-7.94-0.14)	0.06
Total charges, mean (CI)	342324 (305778-378870)	378452 (320453-436452)	612[1] (-54780-56004)	0.98

[1]β-coefficients. Data was adjusted for gender, race, income, modified Elixhauser comorbidity score, weekend admission, and diabetes.

Morbid Obesity defined as BMI >40

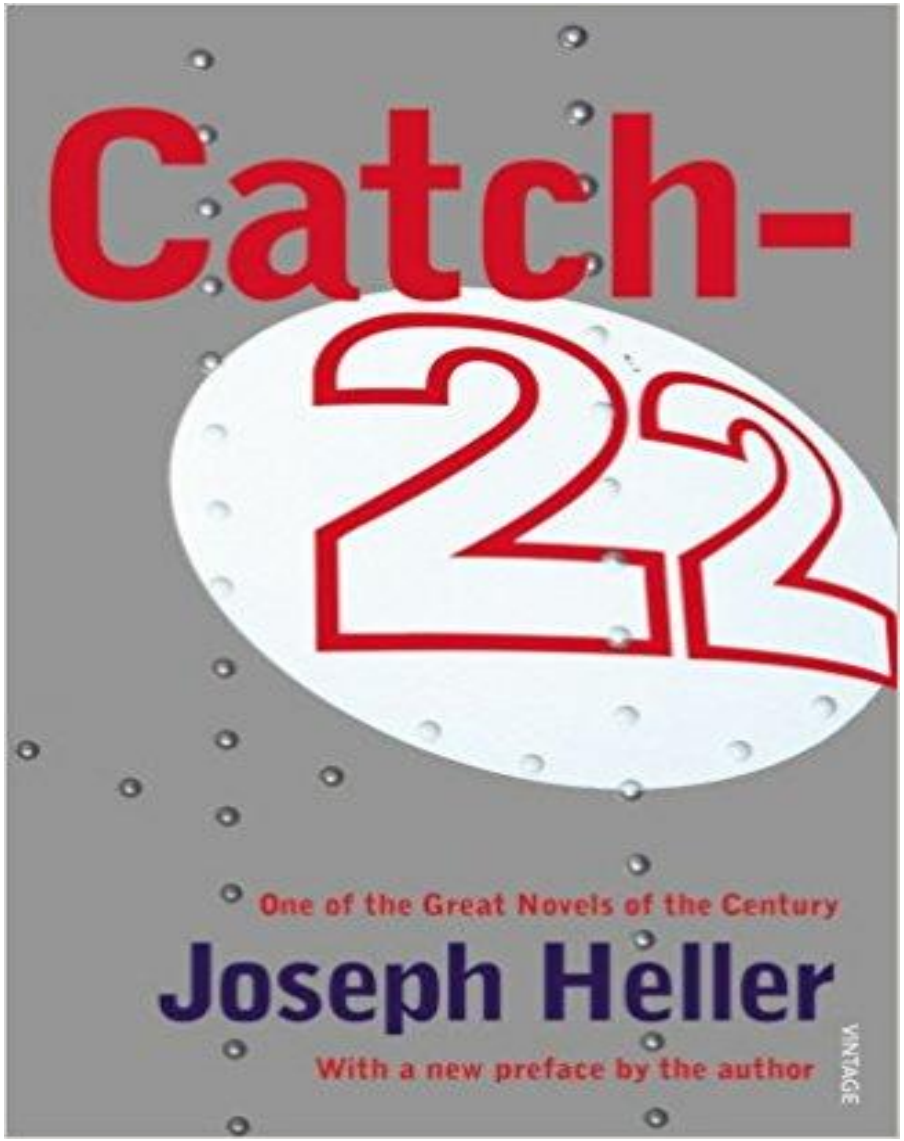
Peck et al WJH 2017

July-December 2016

- Admitted to the ward for 2 days with worsening encephalopathy which started whilst he was swimming (his main form of exercise) – advised against this
- Struggling to control weight – 155 Kg increased to 160 Kg
- BMI up to 50
- UKELD 53 and MELD 14 (static)
- Seen in weight management clinic – nothing to offer him
- On-going mild HE

Catch-22

- Can’t have weight loss therapy due to his advanced liver disease
- Not felt to be suitable for a liver transplant due to BMI



July 2017

- Limping along
- Struggling to control weight
- Re-discussed at weight management and transplant MDTs
- Decision made to arrange a CT of the abdomen to look at the distribution of visceral fat
- Most fat in the subcutaneous tissue on CT with only moderate fat in the abdomen – discussed at MDT and felt to be more favourable for transplantation
- Branch intrahepatic right portal vein thrombosis identified

Q4. What is the evidence that visceral to subcutaneous fat ratio makes a difference?

Visceral to Subcutaneous Fat Ratio and Surgical Risk

TABLE 3.

Univariate and multivariate analyses of prognostic factors for posttransplant survival

	Univariate			Multivariate		
Variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Preoperative SMI						
Normal (n = 197)	1.000	(referent)		1.000	(referent)	
Low (n = 53)	3.086	1.876-4.995	<0.001	2.367	1.399-3.957	0.002
Preoperative IMAC						
Normal (n = 136)	1.000	(referent)		1.000	(referent)	
High (n = 114)	2.566	1.574-4.285	<0.001	2.096	1.271-3.536	0.004
Preoperative VSR						
Normal (n = 172)	1.000	(referent)		1.000	(referent)	
High (n = 78)	3.395	2.106-5.521	<0.001	2.213	1.324-3.726	0.003

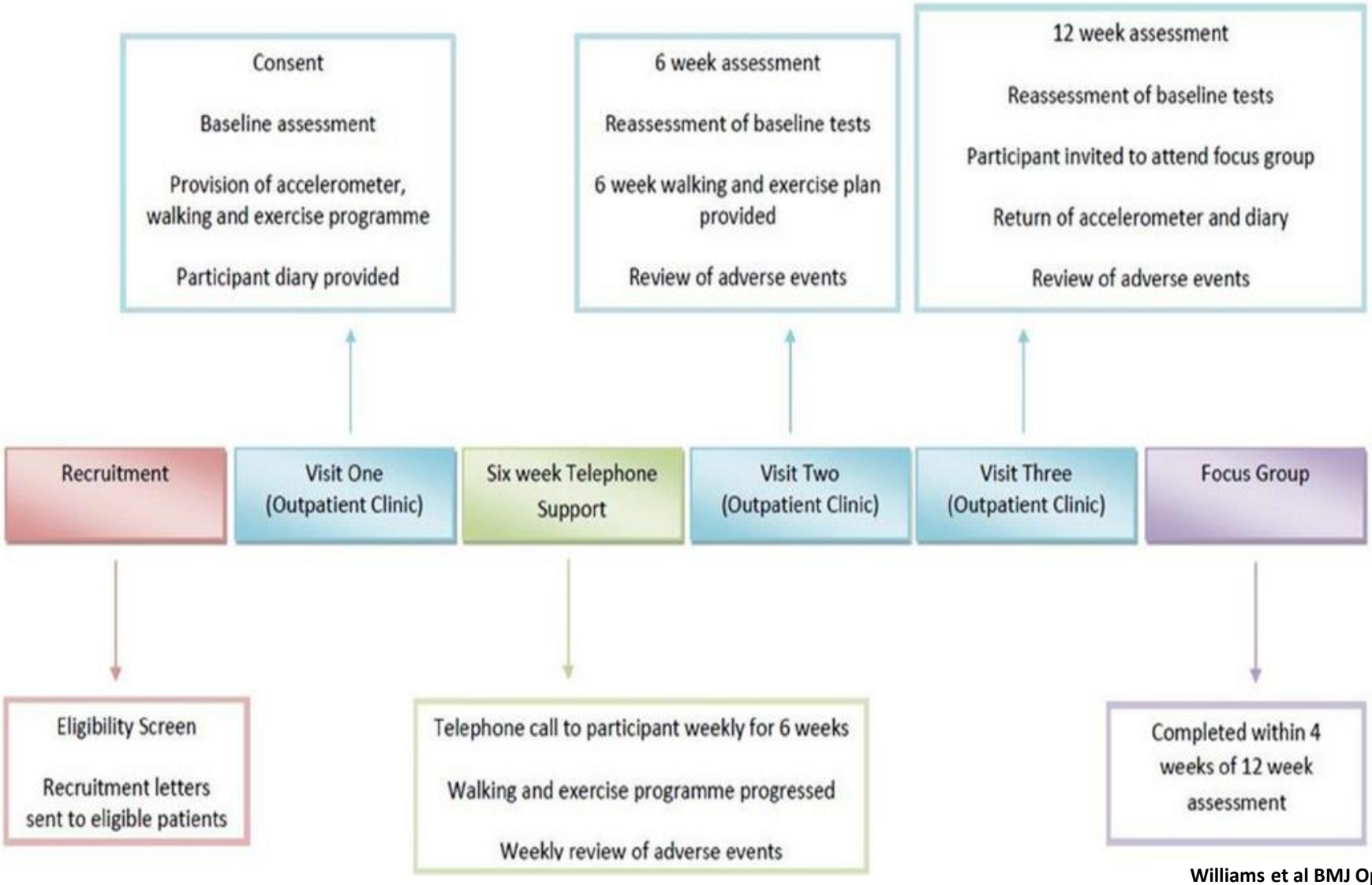
CI, confidence interval.

Hamaguchi et al Transplantation 2017

October 2017

- Re-assessed for transplant
- Still deemed too high risk
- Concerns now about sarcopaenic obesity and also loss of functionality
- But short battery test score of 10/12 although he did fatigue after 250 seconds
- Weight 155 Kg, BMI 48
- Referred for
    1. Prehabilitation exercise programme
    2. Psychological support

Enrolled in a Prehabilitation Clinical Trial



Williams et al BMJ Open 2018

Short Battery Performance Test

SCORING:

A. Side-by-Side stand

Held for 10 sec	❒1 point
Not held for 10 sec	❒0 points
Not attempted	❒0 points

If 0 points, end Balance Tests

Number of seconds held if less than 10 sec:

____.___ Sec

If participant did not attempt test or failed, circle why:

Tried but unable	1
Participant could not hold position unassisted	2
Not attempted, you felt unsafe	3
Not attempted, participant felt unsafe	4
Participant unable to understand instructions	5
Other (specify)	6
Participant refused	7

B. Semi-Tandem Stand

Held for 10 sec	❒1 point
Not held for 10 sec	❒0 points
Not attempted	❒0 points

(circle reason to the right)

If 0 points, end Balance Tests

Number of seconds held if less than 10 sec:

____.___ Sec

If participant did not attempt test or failed, circle why:

Tried but unable	1
Participant could not hold position unassisted	2
Not attempted, you felt unsafe	3
Not attempted, participant felt unsafe	4
Participant unable to understand instructions	5
Other (specify)	6
Participant refused	7

C. Tandem Stand

Held for 10 sec	❒2 point
Held for 3 to 9.99 sec	❒1 points
Held for < than 3 sec	❒0 points
Not attempted	❒0 points

(circle reason above)

Number of seconds held if less than 10 sec:

____.___Sec

If participant did not attempt test or failed, circle why:

Tried but unable	1
Participant could not hold position unassisted	2
Not attempted, you felt unsafe	3
Not attempted, participant felt unsafe	4
Participant unable to understand instructions	5
Other (specify)	6
Participant refused	7

D. Total Balance Tests score _____ (sum points)

Scoring for Complete Short Physical Performance Battery

Test Scores

Total Balance Test score	_____ points
Gait Speed Test score	_____ points
Chair Stand Test score	_____ points
Total Score	_____ **points** (sum of points above)

http://hdcs.fullerton.edu/csa/Research/documents/SPPBInstructions_ScoreSheet.pdf

Q5. What other functional tests are used in Liver Transplant Assessment?

Cardiopulmonary Exercise Testing

Submaximal Cardiopulmonary Exercise Testing Predicts 90-Day Survival After Liver Transplantation

James M. Prentis,[1,4] Derek M. D. Manas,[2,4] Michael I. Trenell,[4,5,6] Mark Hudson,[3,4] David J. Jones,[4] and Chris P. Snowden[1,4]

[1]Department of Perioperative and Critical Care Medicine, [2]Department of Hepatobiliary and Transplant Surgery, and [3]Regional Liver and Transplant Unit, Freeman Hospital, Newcastle upon Tyne, United Kingdom, and [4]Institute of Cellular Medicine, [5]National Institute for Health Research Biomedical Research Centre for Ageing and Age-Related Diseases, and [6]Newcastle Centre for Brain Ageing and Vitality, Newcastle University, Newcastle upon Tyne, United Kingdom

Aerobic Capacity During Cardiopulmonary Exercise Testing and Survival With and Without Liver Transplantation for Patients With Chronic Liver Disease

William Bernal,[1] Rosa Martin-Mateos,[1] Miklós Lipcsey,[1] Caroline Tallis,[1] Kyne Woodsford,[1] Mark J. Mcphail,[1] Christopher Willars,[1] Georg Auzinger,[1] Elizabeth Sizer,[1] Michael Heneghan,[1] Simon Cottam,[2] Nigel Heaton,[3]* and Julia Wendon[1]*

[1]Liver Intensive Therapy Unit, [2]Department of Anaesthetics, and [3]Liver Transplant Surgical Service, Institute of Liver Studies, King's College Hospital, King's College London, London, United Kingdom

Meta-Analysis of CPEX in OLT

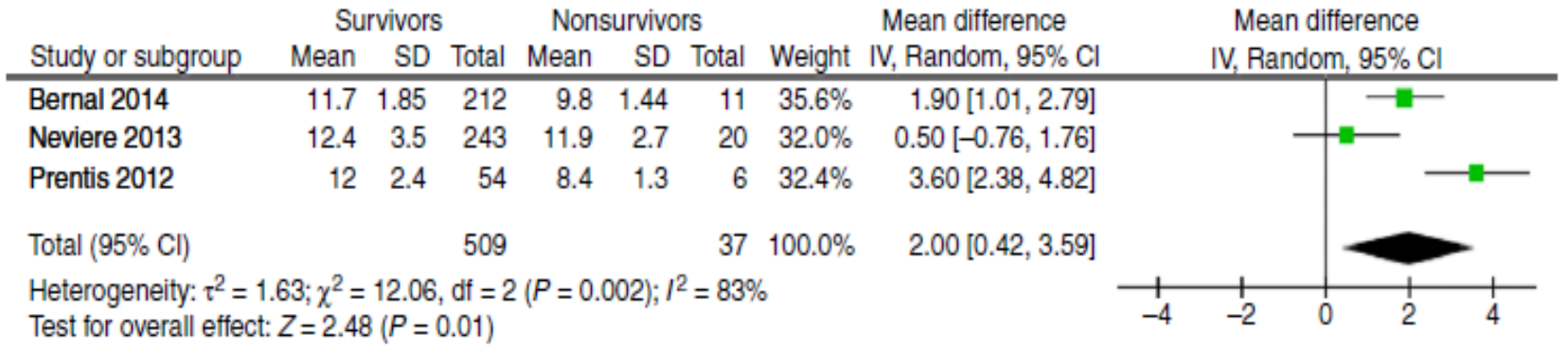


Figure 3 | Mean difference of the AT (ventilator anaerobic threshold) between survivors and nonsurvivors post-transplantation (three studies). The mean difference for AT was significant, with a value of 2.0 (95% CI 0.42–3.59; $Z = 2.48$, $P = 0.01$) and significant heterogeneity ($P = 0.002$).

Aliment Pharmacol Ther 2016; 44: 796-806

December 2017 – Physio reassessment

Baseline Data

- Steps 2,400 per day
- Short Performance Battery Test: 10/12
- Incremental Shuttle Walk Test 1: 180m
- Incremental Shuttle Walk Test 2: 250m

Repeat Data

- Steps 4,000 Average per day
- Short Performance Battery Test 12/12
- Incremental Shuttle Walk Test 310m (this is a significant improvement with regards to FC)

- He has certainly has had several days of achieving over 10,000 steps and has frequently tipped over the 7,000 step mark which is a significant improvement from baseline but is not consistently walking 10,000 steps a day.
- Overall, he has made some good improvements that are significant, and if he continues to hold his own and complete his exercise program into the new year, although still a risk I would support indication.

Re-discussed at Liver Transplant Meeting

- Functional improvement noted
- HG strength increased by 10 Kg
- Engaging with food addiction clinic – had one to one sessions
- Weight actually no different
- BMI 49.7
- Repeat CT had shown no evidence of portal vein thrombosis
- Listed – good DBD only. BG A
- Plan to undertake bariatric surgery post-transplant

February 2018

Incision-
Reverse L

Findings-
Cirhotic liver with marked PH and large umbilical varix and very large varices in the LUQ. No ascites. No tumour. Large man - 156kg

Procedure-
Liver mobilised on the right. CD ligated and cut. CHD divided and cut. Very large replaced RHA found and with 4 branches coming off at the same spot, all tied. LHA tied and cut. PV skeletonised and cleared down to pancreas. Large caudate and not possible to mobilise L to R so R to L. Short hepatics ligated as I went. Large hepatocaval lig stapled. Some bleeding on right and since v large caudate PC shunt - end to side 4.0 prolene. Nice position but flow very poor in PV.
Liver mobilised and taken off cava after stapler to RHV then LHV/MV and both underrun with 4.0.

Lesser sac opened - large varices found and ligated.

This was a DBD 2.2kg with normal anatomy from Walton Neuro retrieved by Newcastle. Donor 62yo Male 108kg BMI 36.5. Died of glioblastoma - recipient aware of risks of tumour transmission and willing to proceed. Parenchymal tears x2.

Side to side cavocavoplasty with 4.0 prolene. then PV trimmed to length after stapler to the shunt. 5.0 prolene end to end. Haemostasis. Reasonable reperfusion - quite high norad requirements but settled quickly.

Large patch made on the recipient rRHA adn then to another large patch on the donor splenic - 7.0 prolene continuous. Lovely anastomosis and flow. Flush via GDA which was ligated.

Haemostasis and 30 minute break - quite 'wet'.

More haemostasis. Cholecystectomy, CD ligated . Both ends of CBD's trimmed back - bleeding. End to end with 5.0 continuous (AC).
Washout. Haemostasis - quite oozy but responding to products. 32 F drain to the RUQ.

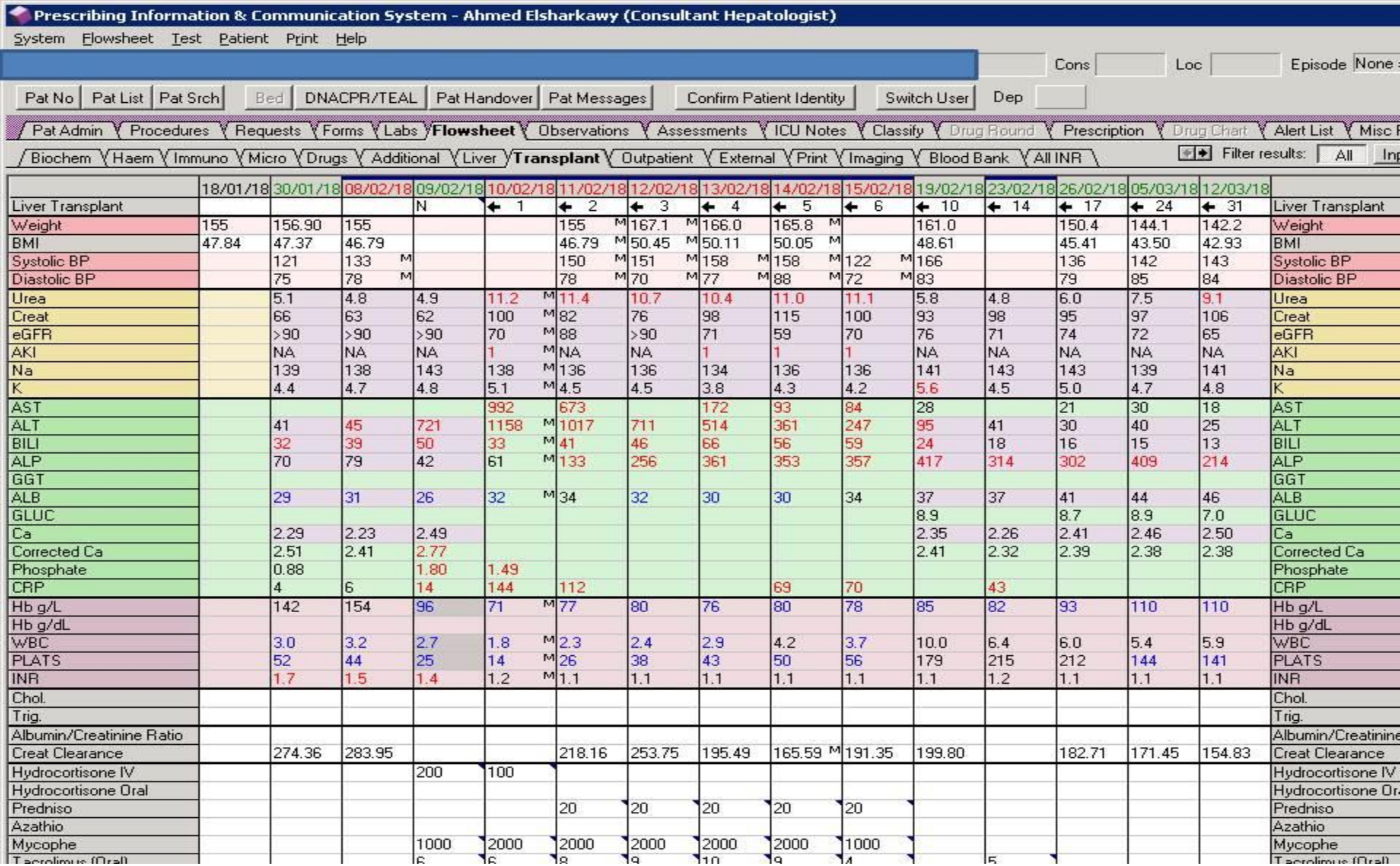
Closure-
Mass closure and staples

Post op instructions
Routine obs and immunosuppression
Liver is reasonable - estimate mildly steatotic but short CIT.

CIT5hr 12
WIT 20 min
Op T 4hr 54

RBC 4
Plet 2
FFP 16
Colloid 2.5l
Crystalloid 4l
Cell saver 1733

Post-Transplant Progress



Prescribing Information & Communication System - Ahmed Elsharkawy (Consultant Hepatologist)

System Flowsheet Test Patient Print Help

Cons Loc Episode None

Pat No | Pat List | Pat Srch | Bed | DNACPR/TEAL | Pat Handover | Pat Messages | Confirm Patient Identity | Switch User | Dep

Pat Admin | Procedures | Requests | Forms | Labs | **Flowsheet** | Observations | Assessments | ICU Notes | Classify | Drug Round | Prescription | Drug Chart | Alert List | Misc

Biochem | Haem | Immuno | Micro | Drugs | Additional | Liver | **Transplant** | Outpatient | External | Print | Imaging | Blood Bank | All INR

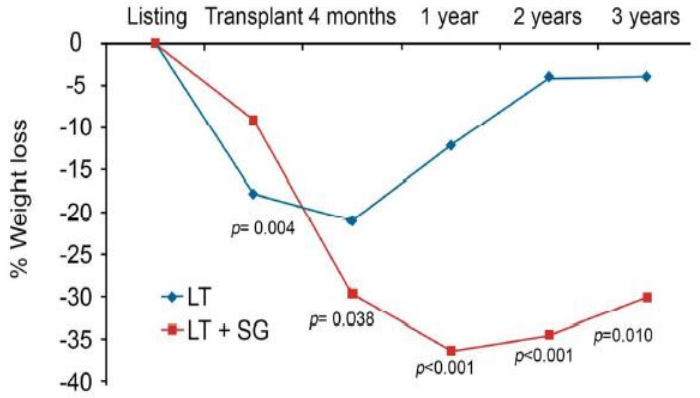
Filter results: All

	18/01/18	30/01/18	08/02/18	09/02/18	10/02/18	11/02/18	12/02/18	13/02/18	14/02/18	15/02/18	19/02/18	23/02/18	26/02/18	05/03/18	12/03/18	
Liver Transplant				N	← 1	← 2	← 3	← 4	← 5	← 6	← 10	← 14	← 17	← 24	← 31	Liver Transplant
Weight	155	156.90	155			155 M	167.1 M	166.0	165.8 M		161.0		150.4	144.1	142.2	Weight
BMI	47.84	47.37	46.79			46.79 M	50.45 M	50.11	50.05 M		48.61		45.41	43.50	42.93	BMI
Systolic BP		121	133 M			150 M	151 M	158 M	158 M	122 M	166		136	142	143	Systolic BP
Diastolic BP		75	78 M			78 M	70 M	77 M	88 M	72 M	83		79	85	84	Diastolic BP
Urea		5.1	4.8	4.9	11.2 M	11.4	10.7	10.4	11.0	11.1	5.8	4.8	6.0	7.5	9.1	Urea
Creat		66	63	62	100 M	82	76	98	115	100	93	98	95	97	106	Creat
eGFR		>90	>90	>90	70 M	88	>90	71	59	70	76	71	74	72	65	eGFR
AKI		NA	NA	NA	1 M	NA	NA	1	1	1	NA	NA	NA	NA	NA	AKI
Na		139	138	143	138 M	136	136	134	136	136	141	143	143	139	141	Na
K		4.4	4.7	4.8	5.1 M	4.5	4.5	3.8	4.3	4.2	5.6	4.5	5.0	4.7	4.8	K
AST					992	673		172	93	84	28		21	30	18	AST
ALT		41	45	721	1158 M	1017	711	514	361	247	95	41	30	40	25	ALT
BILI		32	39	50	33 M	41	46	66	56	59	24	18	16	15	13	BILI
ALP		70	79	42	61 M	133	256	361	353	357	417	314	302	409	214	ALP
GGT																GGT
ALB		29	31	26	32 M	34	32	30	30	34	37	37	41	44	46	ALB
GLUC											8.9		8.7	8.9	7.0	GLUC
Ca		2.29	2.23	2.49							2.35	2.26	2.41	2.46	2.50	Ca
Corrected Ca		2.51	2.41	2.77							2.41	2.32	2.39	2.38	2.38	Corrected Ca
Phosphate		0.88		1.80	1.49											Phosphate
CRP		4	6	14	144	112			69	70		43				CRP
Hb g/L		142	154	96	71 M	77	80	76	80	78	85	82	93	110	110	Hb g/L
Hb g/dL																Hb g/dL
WBC		3.0	3.2	2.7	1.8 M	2.3	2.4	2.9	4.2	3.7	10.0	6.4	6.0	5.4	5.9	WBC
PLATS		52	44	25	14 M	26	38	43	50	56	179	215	212	144	141	PLATS
INR		1.7	1.5	1.4	1.2 M	1.1	1.1	1.1	1.1	1.1	1.1	1.2	1.1	1.1	1.1	INR
Chol.																Chol.
Trig.																Trig.
Albumin/Creatinine Ratio																Albumin/Creatinine
Creat Clearance		274.36	283.95			218.16	253.75	195.49	165.59 M	191.35	199.80		182.71	171.45	154.83	Creat Clearance
Hydrocortisone IV				200	100											Hydrocortisone IV
Hydrocortisone Oral																Hydrocortisone Or
Predniso						20	20	20	20	20						Predniso
Azathio																Azathio
Mycophe				1000	2000	2000	2000	2000	2000	1000						Mycophe
Tacrolimus (Oral)				6	6	8	9	10	9	4		5				Tacrolimus (Oral)

The Future?

Long-term outcomes of patients undergoing simultaneous Liver Transplantation and Sleeve Gastrectomy

Authors: Daniel Zamora-Valdes[1], Kymberly D. Watt[2], Todd A. Kellogg[3], John J. Poterucha[2], Sara R. Di Cecco[2], Nicki M. Francisco-Ziller[2], Timucin Taner[1], Charles B. Rosen[1] Julie K. Heimbach[1]



Variable	LT (n=36)	LT+SG (n=13)	*p* value
Female gender (%)	55.6%	53.8%	1.000
NASH *	44.4%	76.9%	0.057
Cancer **	36.1%	23.1%	0.502
Age at listing (years)	55.4 ± 7.8	50.7 ± 7.4	0.067
Weight at listing (kg)	116.4 ± 15.2	141.6 ± 23.5	0.002
BMI at listing (kg/m^2)	40.0 ± 2.7	47.8 ± 4.5	<0.001
Biological MELD	18.9 ± 8.1	32.0 ± 9.5	<0.001
Waiting time (weeks)	74.1 ± 83.3	76.3 ± 92.6	0.942
Waiting time < 6m	8.3%	23.1%	0.321
Follow-up after transplant (years)	5.25 ± 2.56	4.69 ± 2.35	0.548

Variable	LT cohort	LT + SG cohort	*p* value
Diabetes mellitus	58.3%	30.8%	0.114
# medications	0.5 ± 0.8	0.3 ± 0.9	0.517
Hypertension	63.9%	23.1%	0.021
# medications	1.0 ± 1.0	0.3 ± 0.7	0.023
Dyslipidemia	69.4%	53.8%	0.178
# medications	0.4 ± 0.6	0.1 ± 0.2	0.01
Metabolic syndrome	52.8%	23.1%	0.104
# criteria	2.83 ± 1.0	1.9 ± 0.9	0.008
Hepatic steatosis	66.7%	23.1%	0.01

Hepatology 2018 (In Press)

Take Home Messages

- Absolute BMI cut offs are probably too simplistic
- Prehabilitation may help make some patients list-able but better data is needed
- Head to head comparisons of functional tests in liver transplant are needed
- Innovative combinations of transplant and bariatric surgery should be more widely adopted
- Persistence pays off

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