

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

ESPS manuscript NO: 31927

Title: Small for size syndrome difficult dilemma: Lessons from 10 years single centre experience in living donor liver transplantation

Reviewer's code: 00505437

Reviewer's country: Australia

Science editor: Jin-Xin Kong

Date sent for review: 2016-12-19 15:28

Date reviewed: 2016-12-27 03:23

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	GoogleSearch:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

COMMENTS TO AUTHORS

Congratulations about the paper. It is an interesting quite large series.

- 1) The result section is very confusing and little detailed. Please try to rewrite it.
- 2) Indication for intra-operative splenectomy are not well described.
- 3) The use of post-operative embolisation should be better comment.
- 4) If possible classify severity of complication using a severity score such Dindo-Clavien score
- 5) Some grammar mistakes

Reply to reviewer comments

- 1- I rewrote the results with more details. See the text.
- 2- There was **seven** cases that underwent intra-operative splenectomy in our study, the decision to do splenectomy was as follow: 4 cases due to severe pre transplant portal hypertension and SFG(intra-operative actual GRWR< 0.8(0.7, 0.73, 0.74, and

0.75))(N.B Severe pre transplant portal hypertension was known by pre operative history, clinical examination, laboratory and imaging investigations). Moreover, the other 3 cases due to very SFSG (0.57, 0.65, and 0.66). See the text.

- 3- If you mean post operative splenic artery embolisation, we did not do any post operative splenic artery embolisation, as I mentioned in the text our management of SGSS was as follow: symptomatic liver support was give to all our patients with SFSS; Moreover, oral propranolol (2×40 mg/day) and a somatostatin infusion (250- μ g bolus followed by perfusion at a rate of 250-50 μ g/h for 5 days were given to some of our patients with SFSS to decrease portal flow and improve the syndrome outcome. See the text
- 4- As I mentioned the complications that lead to patient death either in SFSS group or in the other group, so they were **Dindo-Clavien grade V**. see the text.
- 5- I corrected grammar mistakes. See the text.

N.B. The corrections are underlined and bold in the text

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

ESPS manuscript NO: 31927

Title: Small for size syndrome difficult dilemma: Lessons from 10 years single centre experience in living donor liver transplantation

Reviewer's code: 02844701

Reviewer's country: India

Science editor: Jin-Xin Kong

Date sent for review: 2016-12-19 15:28

Date reviewed: 2017-03-14 12:48

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

COMMENTS TO AUTHORS

- 1- Authors have stated that "3- Diagnosis of SFSS: The patients laboratory and clinical parameters (I.e. Serum bilirubin, INR, volume of ascites, and encephalopathy) were followed up to detect the occurrence of SFSS: As there has been no specific definition and diagnosis of SFSS until now, we diagnosed SFSS according to (12), (46), (47), moreover, we classified SFSS into SFSD and SFSNF, as regard (12)."Please give more clear-cut definition for SFSS and SFSD.
- 2- Authors have stated that "Steroids were withdrawn 3 month after surgery, and MMF was withdrawn 6 months after surgery". What is basis for this strategy.
- 3- There must be uniform evaluation and treatment care including surgical skills in all patients as it may cause unequal outcome in the two groups.
- 4- Comparison between patients with (n=20)and without SFSS (n=154) (Univariate analysis)and in Table (7) Outcome of patients. The numbers in two groups are unequal so it has impact on P value. I will suggest to that in survival analysis Please include death

censored and non-death censored graft survival and patient survival.

Reply to reviewer comments

- 1- **SFSD:** is dysfunction of the graft(the presence of persistent hyperbilirubinemia, massive ascites and coagulopathy during the post-transplant subacute phase without evidence of any other cause like technical, immunological or infection causes.

SFSS: is dysfunction of the graft (the presence of persistent hyperbilirubinemia, massive ascites and coagulopathy during the post-transplant subacute phase without evidence of any other cause like technical, immunological or infection causes, or failure of the graft(loss of its function leading to patient loss or necessity of retransplantation) during the post-transplant subacute phase without evidence of any other cause like technical, immunological or infection causes.(See the text)

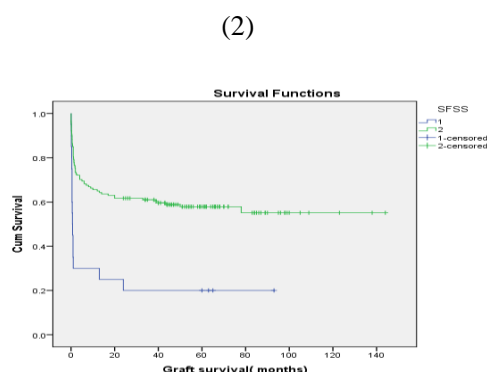
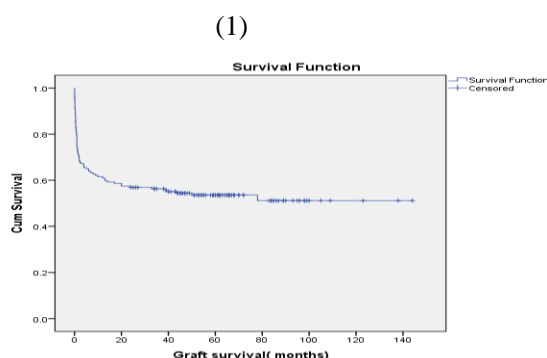
- 2- **Based on our institutional policy and similar to other schools like Japanese school; immunosuppression protocol was as follow:** The standard is combined 3 drugs: Calcineurin Inhibitors (CNIs), steroids and Mycophenolate Mofetil (MMF). Tacrolimus (FK506) was prescribed at an initial dose of 0.05- 0.1 mg/kg/day divided every 12 hours (9 a.m. and 9 p.m.) and adjusted over time to maintain levels of 10-15 ng/mL at 0-14 days, 6-10 ng/mL at 14-28 days, and 5-8 ng/mL thereafter **to be continued for life**. MMF was given at an oral dosage of 250-500 mg twice a day to be stopped 6 months later. The initial methylprednisolone dose is 500 mg intraoperatively with a brief taper of prednisone from 240 to 40 mg/d over 6 days followed by 5-20 mg/d maintenance treatment, with complete withdrawal at the end of 3rd month post LDLT. Cyclosporine (CsA) was used when neurotoxicity or nephrotoxicity developed with Tacrolimus. It was given at an oral dosage of 8-10mg/kg/day, where blood trough levels were maintained between 150 and 250 ng/ml in the 1st 6 months and between 100 and 150 ng/ml thereafter. **So, the protocol starts with 3 drugs(Steroids+MMF+CNI) to minimize doses and side effects of CNIs and then stop steroids to avoid their side effects then stop MMF to avoid their side effects then continue with (CNIs) after adjusting and minimizing their blood level so minimizing their toxicity** (EASL Clinical Practice Guidelines: Liver transplantation. European Association for the Study of the Liver. Journal of Hepatology 2016 vol. 64 j 433–485) (Chuan L, Wen TF, Yan LN, Li B, Yang JY, et al. (2011) Predictors of patient survival following living donor liver transplantation. Hepatobiliary Pancreat Dis Int 10: 248-253). (Goldstein MJ, Salame E, Kapur S, Kinkhabwala M, LaPointe-Rudow D et al.(2003) Analysis of Failure in Living Donor Liver Transplantation: Differential Outcomes in Children and Adults. World J. Surg 27: 356-364). (Ikegami T, Shirabe K, Yoshiya S, Yoshizumi T, Ninomiya M, et al. (2012) Bacterial sepsis after living donor liver transplantation: the impact of early enteral nutrition. J Am Coll Surg 214: 288-295).(Kim BS, Lee SG, Hwang S, Ahn CS, Kim KH, et al. (2009)

Influence of Pre-transplantation Bacterial and Fungal Culture Positivity on Outcome after Living Donor Liver Transplantation. Transplant Proc 41: 250-252).(See the text)

- 3- Our evaluation and treatment care including our surgical skills were uniform in all patients as the pre operative, intra-operative and post operative strategies for prevention of SFSS including surgical skills were the same in all patients and they are the standard strategies used in many transplant centers to avoid occurrence of the syndrome and the surgical skills were uniform and standard like other centers and differed according to the type of graft (RT or LT and according to dominance of the RT or middle HV and the size of the veins and the liver graft(going in line with the standard techniques), so there was no effect on outcome in the two groups .(see the text)
- 4- No effect of NO on P value as the multivariate analysis by Binary logistic regression was true and gave independent predictor result.(see the text)

1-KM graft survival curve

2-SFSS and graft survival (Log rank=0.00)



Total number	SFSS		No SFSS		P value
	No	%	No	%	
	20	(100%)	154	(100%)	
<u>Graft survival</u>	<u>4</u>	<u>(20%)</u>	<u>89</u>	<u>(57.8%)</u>	<u>.001</u>
<u>Graft survival per months (Mean±SD)</u>	<u>16.2±28.9</u>		<u>39.7±34.3</u>		<u>.003</u>

N.B. The corrections are underlined and bold in the text