| Section            | Page | Title                                                                                      | Authors                                      |
|--------------------|------|---------------------------------------------------------------------------------------------|----------------------------------------------|
| REVIEW             | 907  | Chemotherapy for hepatocellular carcinoma: The present and the future                        | Le Grazie M, Biagini MR, Tarocchi M, Polvani S, Galli A |
| MINIREVIEWS        | 921  | Is the 25-year hepatitis C marathon coming to an end to declare victory?                     | Ahmed KT, Almashhravi AA, Ibdah JA, Tahan V   |
| ORIGINAL ARTICLE   | 930  | Small for size syndrome difficult dilemma: Lessons from 10 years single centre experience in living donor liver transplantation | Shoreem H, Gad EH, Soliman H, Hegazy O, Saleh S, Zakaria H, Ayoub E, Kameel Y, Abouehella K, Ibrahim T, Marawan I |
| Observational Study| 945  | Outcomes of pregnancy in patients with known Budd-Chiari syndrome                           | Khan F, Rawe I, Martin B, Knoc E, Johnston T, Ellist C, Lester W, Clon F, Olliff S, Mehrzag H, Zia Z, Tripathi D |
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Small for size syndrome difficult dilemma: Lessons from 10 years single centre experience in living donor liver transplantation

Hany Shoreem, Emad Hamdy Gad, Hosam Soliman, Osama Hegazy, Sherif Saleh, Hazem Zakaria, Eslam Ayoub, Kalid Abouelella, Tarek Ibrahim, Ibrahim Marawan

AIM
To analyze the incidence, risk factors, prevention, treatment and outcome of small for size syndrome (SFSS) after living donor liver transplantation (LDLT).

METHODS
Through-out more than 10 years: During the period from April 2003 to the end of 2013, 174 adult-to-adults LDLT (A-ALDLT) had been performed at National Liver Institute, Menoufiya University, Shbin El-Koum, Egypt. We collected the data of those patients to do this cohort study that is a single-institution retrospective analysis of a prospectively collected database analyzing the incidence, risk factors, prevention, treatment and outcome of SFSS in a period started from the end of 2013 to the end of 2015. The median period of follow-up was 39 months (range 3–106 months). The data were collected from our records in the LT unit and written informed consents were obtained from both donors and recipients regarding operations and researches.

Result
The incidence of SFSS in the period from April 2003 to the end of 2013 was 11.5% (20 patients). The incidence of SFSS in the period from January 2014 to the end of 2015 was 5.8% (9 patients). The median period of follow-up was 39 months (range 3–106 months). The incidence of SFSS was significantly lower in the later period compared to the earlier period (P = 0.03).

Discussion
SFSS is a major cause of early and late graft dysfunction and failure after liver transplantation. The incidence of SFSS varies from 5% to 30% in the literature. The incidence of SFSS in the present study was 11.5% in the first period and 5.8% in the later period. The incidence of SFSS was significantly lower in the later period compared to the earlier period (P = 0.03). The lower incidence of SFSS in the later period might be due to the use of better selection criteria for donors and recipients and better surgical techniques.

Conclusion
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RESULTS
SFSS was diagnosed in 20 (11.5%) of our recipients. While extra-small graft [small for size graft (SFSG)], portal hypertension, steatosis and left lobe graft were significant predictors of SFSS in univariate analysis (P = 0.00, 0.04, 0.03, and 0.00 respectively); graft size was the only independent predictor of SFSS on multivariate analysis (P = 0.03). On the other hand, there was lower incidence of SFSS in patients with SFSG who underwent splenectomy [4/10 (40%) SFSS vs 3/7 (42.9%) no SFSS] but without statistical significance. However, there was none significant lower incidence of the syndrome in patients with right lobe (RL) graft when drainage of the right anterior and/or posterior liver sectors by middle hepatic vein, V5, V8, and/or right inferior vein was done [4/10 (28.6%) SFSS vs 52/152 (34.2%) no SFSS]. The 6-mo, 1-, 3-, 5-, 7- and 10-year survival in patients with SFSS were 30%, 30%, 25%, 25%, 25% and 25% respectively, while, the 6-mo, 1-, 3-, 5-, 7- and 10-year survival in patients without SFSS were 70.1%, 65.6%, 61.7%, 61%, 59.7%, and 59.7% respectively, with statistical significant difference (P = 0.00).

CONCLUSION
SFSG is the independent and main factor for occurrence of SFSS after A-ALDLT leading to poor outcome. However, the management of this catastrophe depends upon its prevention (i.e., selecting graft with proper size, splenectomy to decrease portal venous inflow, and improving hepatic vein outflow by reconstructing large draining veins of the graft).

Key words: Living donor liver transplantation; Outcome after living donor liver transplantation; Small for size syndrome; Small for size graft; Portal inflow; Venous outflow

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Core tip: Small for size syndrome (SFSS) was diagnosed in 20 (11.5%) of our recipients where, small for size dysfunction affected 16 of patients (80%) and small for size non function was present in four patients (20%). Regarding graft size in patients with SFSS; 10, 5 and 5 of patients had extra-small graft [small for size graft (SFSG), graft recipient weight ratio (GRWR) < 0.8], small graft (GRWR ≥ 0.8 and < 1) and medium sized graft (GRWR ≥ 1) respectively. Extra small graft (SFSG), portal hyper-perfusion, severe portal hypertension (PTHN), and venous outflow obstruction were the main direct causes of SFSS in 10 (50%), 3 (15%), 4 (20%), and 3 (15%) of patients respectively. While extra-small graft, PTHN, steatosis and left lobe graft were significant predictors of SFSS in univariate analysis, only graft size was independent predictor of SFSS on multivariate analysis. On the other hand, there was none significant lower incidence of SFSS in patients with SFSG when splenectomy was done, furthermore, there was non-significant lower incidence of the syndrome in patients with right lobe graft when drainage of the right anterior and/or posterior liver sectors by middle hepatic vein, V5, V8, and/or right inferior vein was done. The SFSS related mortalities were recorded in 13/20 of patients (65%). The 6-mo, 1-, 3-, 5-, 7- and 10-year survival in patients with SFSS were 30%, 30%, 25%, 25%, 25% and 25% respectively, while, the 6-mo, 1-, 3-, 5-, 7- and 10-year survival in patients without SFSS were 70.1%, 65.6%, 61.7%, 61%, 59.7%, and 59.7% respectively, with statistical significant difference.

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INTRODUCTION
Living donor liver transplantation (LDLT) is acceptable management option for end-stage liver disease (ESLD) patients to overcome organ shortage and waiting list death. On the other hand, adult-to-adults LDLT (A-ALDLT) is affected by the so-called SFSG[5]. Until now, there is debate about the least volume of the graft required for A-ALDLT[5-8]. The volume of liver graft is determined by either graft recipient weight ratio (GRWR)[5-8], or the ratio of graft volume relative to standard liver volume of the recipient (GV/SLV); SFSG are those with a GRWR < 0.8% and/or those with a GV/SLV < 35%[5-8]. So, if GRWR < 0.8 % or a GV/SLV < 35%, the graft should be regarded as SFSG[5-8]. As SFSS occurrence depends upon the liver graft volume as well as other different negative factors, SFSG and SFSS definitions differ in different institutes and at different times[9,10].

SFSS diagnosis is determined by persistent elevation of bilirubin and large volume of ascites during the early period post liver transplantation (LT) with absence of other possible causes[5,11,12]. Generally, it is characterized by occurrence of the followings at the end of the 1st week post LT: Persistent cholestasis, coagulopathy, ascites, encephalopathy and/or bleeding from gastrointestinal tract and/or renal failure in some severe conditions[4,11-19]. Moreover, SFSS can be defined as Total bilirubin > 10 mg/dL and/or output of ascites > 1 L/d on the 14th day after LT[7].

The loss of balance between the rapid liver regeneration and the increased demand of liver to do his function is the principal pathogenesis of SFSS[2,20], moreover, it has become evident that SFSS is not just caused by SFSG, but by multiple factors. These factors are divided into graft-related factors and recipient
The graft related factors include: (1) high portal inflow [17,20,24], (2) low venous outflow [23,26]; (3) preexisting steatosis in the donor [27,28]; (4) advanced donor age [29]; and (5) both warm and cold ischemia times [16,30,31]. However, recipient-related causes include severe preoperative ESLD and poor health status [7,16,32,33].

As occurrence of SFSS is determined by the balance between the functional mass of the liver; inflow of portal venous (PV), and outflow of hepatic vein (HV), Strategies to prevent it depend upon increasing the volume of liver graft and controlling adequate PV inflow and HV outflow by the surgical and the nonsurgical techniques [22,28]. For increasing graft volume, a larger-sized graft, such as the right lobe (RL) graft, is used as the standard strategy for A-A LDLT to fulfill the required metabolic demands of adult recipients [25-30]. There are different techniques for control of graft inflow (i.e., splenectomy, splenic artery embolization, splenic artery ligation, mesocaval - or portocaval shunts) [39,40]. For outflow modulation; any short HV (especially RIV, V5, V8) larger than 0.5 cm are preserved, to be anastomosed with the recipient inferior vena cava (IVC) [31].

Splanchnic vasoconstrictors, intravenous octreotides, and oral propranolol may improve the persistent hyperbilirubinemia and coagulopathy in SFSS adult recipients [40,41]. The purpose of this work was to analyze the incidence, risk factors, prevention, treatment and outcome of SFSS after LDLT.

MATERIALS AND METHODS

Patients
Two hundred ten LDLT operations were done between April 2003 and December 2013 in our surgical department, National Liver Institute, Menoufiya university, our study included 174 adult patients after exclusion of cases with data loss and pediatrics, after taking the approval of our institutional reviewers (IRB); we did this cohort study which is a single-institution retrospective analysis of a prospectively collected database that analyzed the incidence, risk factors, prevention, treatment and outcome of SFSS in a period started from the end of 2013 to end of 2015, with patients observation from the 1st post-operative day (POD 1) until December 2015 or until patient death. The median period of follow-up reached 40.50 m, range (0-144 m).

The characteristics of recipients and their donors (including operative parameters): Regarding recipient gender, males were 154 (88.5%) while females were 20 (11.5%); furthermore, the mean age of them reached 46.5 ± 8.1 years. As regard donor gender, male donors were 118 (67.8%) and females were 56 (32.2%); the donors mean age reached 27.2 ± 6.7 years. According to Child-Pugh score, child A, B, and C were 9 (5.2%) 53 (30.5%) and 112 (64.4%) respectively, on the other hand, the mean model for end stage liver disease score(MELD) was 16.09 ± 4.3, moreover, MELD < 18, MELD 18-24, and MELD > 24 were 114 (65.5%), 50 (27.8%) and 10 (5.7%) respectively. Pre LT portal hypertension (PHTN) affected 144 (82.8%) of them.

Steatosis affected nine (5.2%) of grafts. The RL graft was given to 166 (95.4%) and the LL was given to 8 (4.6%) of them. The MHV was reconstructed in 17 (9.8%) of patients, furthermore, there were single, double, three and four HV anastomoses in 110 (63.2%), 53 (30.5%), 10 (5.7%) and 1 (0.6%) of them respectively. However, drainage of right anterior and/or posterior sectors by MHV, V5, V6, and/or RIV in RL grafts occurred in 56/166 (33.7%) of patients. The mean actual graft weight and actual GRWR were 820.9 ± 174.2 g and 1.04 ± 0.2 g respectively, moreover, SFSG (GRWR < 0.8) was found in 17 (9.8%) of patients, where splenectomy was done in seven (41.2%) of them to decrease portal hyper-flow. The decision to do intra-operative splenectomy was as follow: 4 cases due to severe pre transplant PHTN and SFSG (GRWR < 0.8) was found in 17 (9.8%) of patients, where splenectomy was done in seven (41.2%) of them to decrease portal hyper-flow. The decision to do intra-operative splenectomy was as follow: 4 cases due to severe pre transplant PHTN and SFSG (GRWR < 0.8) was found in 17 (9.8%) of patients, where splenectomy was done in seven (41.2%) of them to decrease portal hyper-flow.

Regarding cold ischemia and warm ischemia times, their mean reached 74.9 ± 51.2 min and 52.9 ± 15.2 min respectively. On the other hand, the mean intra-operative plasma and blood transfusion reached 8.2 ± 8.9 units and 7.05 ± 7.4 units respectively. Lastly, operative time mean was 13.1 ± 3.2 h while the in-hospital stay mean after LT was 22.4 ± 15.9 d (Table 1).

Methods

We collected our data from the unit of LT of our Institute after obtaining written informed consents for operations and researches from recipients and their donors. Our donor’s age was > 19 years, furthermore, they underwent the followings: Liver function tests, abdominal ultrasound, liver biopsy, CT angiography, CT volumetric study and psychological assessment. We studied the following.

Preoperative data: Age of donors and recipients, their gender, donors body mass index and liver biopsy, recipient Child Pugh, MELD scores and PHTN. For pre-operative prevention of SFSS; the following strategies were done: (1) appropriate donor selection: (2) steatosis < 10%; (3) donor diet program and/or daily exercise for controlling steatosis in donors; (4) younger donors; (5) in the early cases, estimated (by volumetric study) GRWR < 0.8 were refused, and then in late cases we refused estimated GRWR < 1 for obtaining actual GRWR < 0.8; and (6) appropriate recipient selection by refusing MELD scores < 30.

Intra-operative data: RL or LL grafts, graft with or without MHV, No of HV anastomoses, HV drainage of the RT anterior and/or posterior liver sectors, actual graft weight, and GRWR, performing splenectomy or not, cold ischemia and warm ischemia times per
Table 1  Characteristics of patients and their donors

| Character                        | n (%)         | mean ± SD     |
|---------------------------------|---------------|---------------|
| Donor age (yr) (mean ± SD)      | 27.2 ± 6.7    | 46.5 ± 8.1    |
| Recipient age (yr) (mean ± SD)  | 118 (67.8)    | 56 (32.2)     |
| Donor gender                    |               |               |
| Males                           | 53 (30.5)     | 112 (64.4)    |
| Females                         | 9 (5.2)       | 1 (0.6)       |
| Recipient gender                |               |               |
| Males                           | 164 (88.5)    | 20 (11.5)     |
| Females                         | 144 (82.8)    | 56 (32.2)     |
| Child class                     |               |               |
| A                               | 110 (63.2)    | 8 (4.6)       |
| B                               | 53 (30.5)     | 10 (5.7)      |
| C                               | 17 (9.5)      | 1 (0.6)       |
| MELD score (mean ± SD)          | 16.09 ± 4.3   | 10.5 (7.2)    |
| Pre LT PHTN                     | 16.09 ± 4.3   | 10.5 (7.2)    |
| Steatosis                       | 9 (5.2)       | 1 (0.6)       |
| Grafit type                     |               |               |
| Right lobe                      | 166 (95.4)    | 8 (4.6)       |
| Left lobe                       | 8 (4.6)       | 1 (0.6)       |
| MHV with the graft              |               |               |
| RL graft                         | 10 (5.7)      | 7 (4.1)       |
| LL graft                         | 1 (0.6)       | 1 (0.6)       |
| No of HV anastomoses            |               |               |
| 1                               | 110 (63.2)    | 8 (4.6)       |
| 2                               | 53 (30.5)     | 10 (5.7)      |
| 3                               | 17 (9.5)      | 1 (0.6)       |
| 4                               | 1 (0.6)       | 1 (0.6)       |
| Drainage of RT anterior and/or posterior sectors by MHV, V5, V8, and/or RIV in RT lobe grafts (n = 166) | 56/166 (33.7) | 102/144 (66.3) |
| Actual graft weight (g) (mean ± SD) | 820.9 ± 174.2 | 104 ± 17.0 |
| Actual GRWR                     | 57.4 ± 20.2   | 74.9 ± 23.1   |
| SFSG (GRWR < 0.8)               | 17 (9.5)      | 1 (0.6)       |
| Splenectomy in SFSG (n = 17)    | 7/17 (41.2)   | 13.1 ± 3.2    |
| Cold ischemia time (min) (mean ± SD) | 74.9 ± 51.2 | 8.2 ± 8.9    |
| Warm ischemia time (min) (mean ± SD) | 52.9 ± 15.2  | 7.05 ± 7.4   |
| Intraoperative blood transfusion (units) (mean ± SD) | 7.05 ± 7.4 | 13.1 ± 3.2 |
| Intraoperative plasma transfusion (units) (mean ± SD) | 8.2 ± 8.9 | 22.4 ± 15.9 |
| Operative time (h) (mean ± SD)  | 13.1 ± 3.2    | 22.4 ± 15.9   |
| Hospital stay post LT (d) (mean ± SD) | 53 (30.5)    | 10 (5.7)      |

MELD: Model for end stage liver disease; PHTN: Portal hypertension; MHV: Middle hepatic vein; RIV: RT inferior vein; GRWR: Graft recipient weight ratio; SFSG: Small for size graft.

For intra-operative prevention of SFSS, the following strategies were done: (1) in the donor operation, with RL graft without middle hepatic vein (MHV) (our standard technique), any short hepatic vein (specially RIV, V5, V8) > 0.5 cm was preserved for possible anastomosis with recipient veins, while MHV was taken with the graft in some cases (dominant MHV and/or SFSG), on the other hand, MHV was taken with all LL grafts except one of them; (2) during back table preparation, the required interposition vein grafts (patch, pantaloon or jumping grafts) that were obtained mainly from the native PV or PUV were reconstructed with the graft veins and prepared for reconstruction with the recipient veins to maximize the liver graft outflow; (3) in the recipient operation, IVC was preserved during explantation of the native liver, the RL graft HV drainage pathways consisted of the RHV without MHV or with it in some cases, furthermore, the RIV, V5 and/or V8 veins were reconstructed in some cases when indicated (Figures 1-4). The standard technique used in reconstruction of the RHV was an end-to-side anastomosis between RHV of the graft and the RHV of the recipient with causal extension to the IVC. However, the LL graft HV drainage pathways consisted of the MHV with the LHV in one stumpy or separately (N.B the standard technique of HV reconstruction was performing a wide end-to-side anastomosis, between the graft and recipient veins avoiding rotation with extended incision to the vena cava). It was fundamental to perform complete reconstruction of these pathways of HV outflow to avoid HV congestion of the RL or LL grafts.

The portal vein (PV) reconstruction was then performed in an end-to-end fashion using 3 loupe magnification and by using 6/0 prolene continuous stitches with the routine use of about 1 cm growth factor during tying. After PV reconstruction, doppler ultrasonography (US) was done to assess PV flow (PVF).

**Postoperative management:** (1) based on our institutional policy and similar to other schools like Japanese school; immunosuppression protocol was as follow: Triple-drug regimen that included calcineurin Inhibitors (CNIs) as FK-506 or cyclosporin, mycophenolate mofetil (MMF), and steroids. Three months after LT, steroids were withdrawn while we performed withdrawal of MMF 6 mo after operation. In late cases, for minimizing the dose of CNI, we administered an interleukin-2 receptor blocker on the day of LT and on the 4th day postoperative; (2) Doppler ultrasonography (PV and HV patency, flow and velocities) was performed routinely just after vascular reconstruction and after closure of the abdomen and then twice daily until the 7th day after operation (POD7), and once per day until hospital discharge; (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 that was classified into small for size dysfunction of the graft (the presence of persistent hyperbilirubinemia, ascites and coagulopathy) during the early post LT period with absence of other possible causes like Immunological (e.g., graft rejection), technical (e.g., HA or PV obstruction, HV outflow occlusion or biliary leak), infection (e.g., cholangitis). However, SFSS is SFSD or failure of the graft (SFSNF) (loss of graft function leading to patient loss or necessity of retransplantation) during the early post LT period with
absence of those previously mentioned causes; and (4) management of SFSS: Strategies for prevention were mentioned in the pre- and intra-operative data; furthermore, meticulous post-transplant care was taken in cases with SFSG; Treatment: Right now, very little literature paid attention on how to manage the SFSS after its development; however, oral propranolol (2 × 40 mg/d) and a somatostatin infusion (250-μg
bolus followed by perfusion at a rate of 250-500 μg/h for 5 d were given to some of our patients with SFSS to decrease PVF\cite{23,41,45}. Moreover, liver symptomatic support was taken by all patients with the syndrome\cite{15}.

Follow-up and outcome of patients: They were followed-up daily until hospital discharge, then weekly until the end of the 1st month then monthly until the end of the follow-up period to detect SFSS and its outcome regarding survival, mortalities, causes of deaths as well as the outcome of SFSG.

Statistical techniques
We used SPSS software (version 21, Chicago, IL, United States) for data processing. Categorical variables were analyzed with the $\chi^2$ or Fisher exact tests. Continuous variables were compared using the student T or Mann whitney tests. The pre-operative, intra-operative and post-operative variables were descriptively studied. We did comparison between patients with and without SFSS regarding the pre- and intra-operative variables using univariate analysis and then multivariate analysis. Furthermore, their outcome as well as cause of death was compared by univariate analyses. On the other hand, Kaplan-Meier curve was applied and plotted for survival analysis (patient and graft survival) and the log-rank tests were used for comparing patient and graft survival according to SFSS and for comparing patient survival according to SFSG. In the previous tests, if $P$ value was $< 0.05$, it was considered significant.

RESULTS

Some characteristics of patients with SFSS
SFSS was diagnosed in 20 (11.5%) of our recipients where, SFSD affected 16 of patients (80%) and SFSNF was present in four patients (20%). Persistent hyperbilirubinaemia, ascitis, and coagulopathy affected 100%, 90%, and 85% of our SFSS cases respectively, where; all the 16 patients with SFSD had persistent hyperbilirubinemia, ascites and coagulopathy during the early post-LT period; however, all the 4 cases with SFSNF had persistent hyperbilirubinaemia, 2 of them had massive ascites and one of them had coagulopathy; furthermore, they developed graft failure and died from SFSS complications (e.g., Sepsis, MOF, ARDS, DIC) during the 1st week post-transplant. Regarding graft size in patients with SFSS, 10, 5, and 5 of patients had extra-small graft (SFSG, GRWR < 0.8), small graft (GRWR $\geq$ 0.8 and < 1) and medium sized graft (GRWR $\geq$ 1) respectively. Extra small

Figure 3  Venous graft obtained from native PUV, portal venous and hepatic vein to communicate 2 V5, 1V8 and right hepatic vein of liver graft with recipient inferior vena cava.

Figure 4  Small right hepatic vein (encircled) and large right inferior vein harvested and anastomosed with recipient inferior vena cava.

Shoreem H et al. Small for size syndrome after LT
Table 2  Some characteristics of patients with small for size syndrome

| Character                      | n (%) |
|-------------------------------|-------|
| SFSS                          | 20 (100) |
| Type of SFSS                  |       |
| SFSD                          | 16 (80)  |
| SFSNF                        | 4 (20)   |
| Main presentation             |       |
| Hyperbilirubinaemia           | 20 (100) |
| Large volume of ascites       | 18 (90)  |
| Coagulopathy                  | 17 (85)  |
| Graft size                    |       |
| GRWR < 0.8 (SFSG)             | 10 (50)  |
| GRWR ≥ 0.8 and < 1            | 5 (25)   |
| GRWR ≥ 1                      | 5 (25)   |
| Main aetiology of SFSS        |       |
| Extra small graft (SFSG)      | 10 (50)  |
| Portal hyperperfusion         | 3 (15)   |
| Severe PHTN                   | 4 (20)   |
| Outflow obstruction           | 3 (15)   |

SFSS: Small for size syndrome; SFSD: Small for size dysfunction; SFSNF: Small for size non function; PHTN: Portal hypertension.

graft (SFSG), portal hyperperfusion, severe PHTN, and venous outflow obstruction were the main direct causes of SFSS in 10 (50%), 3 (15%), 4 (20%), and 3 (15%) of patients respectively. Moreover; Portal hyperperfusion was assessed by doppler US post operatively, severe PHTN was the persistent pre transplant severe PHTN that was assessed by complete history, clinical examination laboratory and imaging, lastly, venous outflow obstruction was known by post-transplant doppler ultrasonography US (Table 2).

Comparison between patients with and without SFSS

The following variables were statistically significant predictors of SFSS on univariate analysis, Pre LT PHTN, graft steatosis, LL graft, SFSG, mean actual graft weight 640.50 ± 211.049 g, mean actual GRWR 0.862 ± 0.2158 g and mean intra-operative plasma transfusion 11.40 ± 7.816 units. On the other hand, there was lower incidence of SFSS in patients with SFSG who underwent splenectomy [4/10 (40%) SFSS vs 3/7 (42.9%) no SFSS] but without statistical significance. However, there was none significant lower incidence of the syndrome in patients with RL graft when drainage of the RT anterior and/or posterior sectors by MHV, V5, V8, and/or RIV was done [4/10 (28.6%) SFSS vs 52/152 (34.2%) no SFSS], furthermore, there was lower incidence of the syndrome in patients with RL graft without MHV who underwent reconstruction of V5, V8 and/or RIV [3/13 (23.1%) SFSS vs 43/143 (30.1%) no SFSS] but without statistical significance. On the other hand, Child score, MELD score, cold and warm ischemia times had no effect on occurrence of the syndrome (Table 3).

On multivariate analysis, mean actual graft weight 640.50 ± 211.049 g, and mean actual GRWR 0.862 ± 0.2158 g, mean actual graft weight 640.50 ± 211.049 g, mean actual GRWR 0.862 ± 0.2158 g and mean intra-operative plasma transfusion 11.40 ± 7.816 units.

Table 3 Comparison between patients with and without small for size syndrome (Univariate analysis)

| Character                      | SFSS, n (%) | No SFSS, n (%) | P value |
|-------------------------------|-------------|----------------|---------|
| Child class                   |             |                | < 0.05  |
| A                             | 1 (5)       | 8 (5.2)        |         |
| B                             | 7 (35)      | 46 (29.9)      |         |
| C                             | 12 (60)     | 100 (64.9)     |         |
| MELD score                    |             |                | < 0.05  |
| < 18                          | 16 (80)     | 98 (63.6)      |         |
| 18-24                         | 4 (20)      | 46 (29.9)      |         |
| > 24                          | 0 (0)       | 10 (6.5)       |         |
| Pre LT PHTN                   |             |                | 0.046   |
| Yes                           | 20 (100%)   | 128 (83.1%)    |         |
| No                            | 0 (0)       | 26 (16.9%)     |         |
| Steatosis                     |             |                | 0.035   |
| Yes                           | 3 (15)      | 6 (3.9)        |         |
| No                            | 17 (85)     | 148 (96.1)     |         |
| Graft type                    |             |                | 0       |
| RL                            | 14 (70)     | 152 (98.7)     |         |
| LL                            | 6 (30)      | 21 (13)        |         |
| SFSG (GRWR < 0.8)             |             |                | 0       |
| Yes                           | 10 (50)     | 7 (4.5)        |         |
| No                            | 10 (50)     | 147 (95.5)     |         |
| Actual graft weight (g)       |             |                | 0       |
| (mean ± SD)                   | 640.50 ± 211.049 g | 844.39 ± 154.888 g |         |
| Actual GRWR (g)               |             |                | 0.001   |
| (mean ± SD)                   | 0.862 ± 0.2158 g | 1.065 ± 0.1922 g |         |
| Cold ischemia time (min)      |             |                | < 0.05  |
| (mean ± SD)                   | 73.95 ± 55.350 min | 75.13 ± 50.923 min |         |
| Warm ischemia time (min)      |             |                | < 0.05  |
| (mean ± SD)                   | 50.95 ± 14.248 min | 52.08 ± 16.336 min |         |
| Intraoperative plasma         |             |                | 0.021   |
| transfusion (units)           |             |                |         |
| (mean ± SD)                   | 11.40 ± 7.816 units | 7.81 ± 8.943 units |         |
| No. of HV anastomoses         |             |                | < 0.05  |
| 1                             | 11 (55)     | 99 (64.3)      |         |
| 2                             | 8 (40)      | 45 (29.2)      |         |
| 3                             | 1 (5)       | 9 (5.8)        |         |
| 4                             | 0 (0)       | 1 (0.6)        |         |
| Splenectomy in patients with SFSG (n = 17) |             |                | < 0.05  |
| Yes                           | 4 (40)      | 3 (42.9)       |         |
| No                            | 6 (60)      | 4 (57.1)       |         |
| Drainage of RT anterior and/or posterior sectors (MHV, V5, V8, RIV) in RL graft with or without MHV (n = 166) |             |                | < 0.05  |
| Yes                           | 4 (28.6)    | 52 (34.2)      |         |
| No                            | 10 (71.4)   | 100 (65.8)     |         |
| MHV reconstruction in patients with RL graft (n = 166) |             |                | < 0.05  |
| Yes                           | 1 (7.1)     | 9 (5.9)        |         |
| No                            | 13 (92.9)   | 143 (94.1)     |         |
| Drainage of RT anterior and/or posterior sectors (V5, V8, RIV) in RL graft without MHV (n = 156) |             |                | < 0.05  |
| Yes                           | 3 (23.1)    | 43 (30.1)      |         |
| No                            | 10 (76.9)   | 100 (69.9)     |         |

MELD: Model for end stage liver disease; Pre LT PHTN: Pre liver transplant portal hypertension; RL: Right lobe; LL: Left lobe; SFSG: Small for size graft; GRWR: Graft recipient weight ratio; MHV: Middle hepatic vein; RIV: Right inferior vein.
Table 4 Multivariate analysis of predictors of small for size syndrome (Binary logistic regression)

| Predictor                        | P value | Exp(B) | 95%CI for EXP(B) |
|----------------------------------|---------|--------|------------------|
| Pre LT PHTN                      | 0.998   | 0.000  | 0.000            |
| Steatosis                        | 0.06    | 0.145  | 0.020-1.074      |
| Graft type                       | 0.166   | 6.407  | 0.463-88.717     |
| Actual GRWR < 0.8                | 0.050   | 4.503  | 1.024-18.082     |
| Actual graft WT                  | 0.050   | 1.004  | 1.000-1.008      |
| Intraoperative plasma transfusion | 0.235   | 0.963  | 0.905-1.025      |

Pre LT PHTN: Pre liver transplant portal hypertension; GRWR: Graft recipient weight ratio.

± 0.2158 g were the only independent predictors of SFSS, however, graft steatosis had trend towards independence (P = 0.06) (Table 4).

Outcome of patients

Patients with SFSG had statistically significant higher mortality than those without SFSG (76.5% vs 40.8%, P = 0.005), furthermore, mortality was significantly higher in SFSS patients than those without SFSS (75% vs 40.3%, P = 0.003). On the other hand, the most frequent cause of death in patients with the syndrome was the syndrome itself and its complications (i.e., Sepsis, graft failure, DIC, renal failure, ARDS, and MOF), furthermore, the 4 cases with SFSNF died during the 1st week post LT due to the syndrome complications (e.g., sepsis, MOF, ARDS, DIC) and the other 16 cases with SFSD were classified into: Five a live patients, 2 patients died from post LT bleeding, and 9 patients died from the syndrome complications (i.e., Sepsis, graft failure, DIC, renal failure, ARDS, MOF). However, sepsis was the most frequent reason for mortality in non SFSS patients 19 (30.6%); moreover, MOF from causes other than SFSS, post-operating bleeding, intra-operative bleeding, PVT, renal impairment from causes other than SFSS, metastatic cholangiocarcinoma, early graft dysfunction from causes other than SFSS, HCC recurrence, ischemic reperfusion injury, HAT were the other causes of death in 11 (17.7%), 10 (16.1%), 8 (12.9%), 4 (6.4%), 2 (3.2%), 2 (3.2%), 2 (3.2%), 2 (3.2%), 1 (1.6%), and 1 (1.6%) of them respectively. Regarding clavien grading, all the previous causes of death in both groups were grade V. The 6-mo, 1-, 3-, 5-, 7- and 10-year survival in patients with SFSS were 30%, 30%, 25%, 25%, 25% and 25% respectively, while, the 6-mo, 1-, 3-, 5-, 7- and 10-year survival in patients without SFSS were 70.1%, 65.6%, 61.7%, 61%, 59.7%, and 59.7% respectively, with statistical significant difference. Lasty, graft survival in patients with SFSS was 20%, however it was 57.8% in patients without the syndrome with statistical significant difference (P = 0.001) (Table 5 and Figure 5).

DISCUSSION

SFSS limits LT expansion; furthermore, it is the major cause of worse short-term prognosis after LDLT[17]. Therefore, better understanding of its pathogenesis, risk factors, strategies for prevention and treatment may improve outcomes after LDLT.

The incidence of SFSS in LL LDLT is higher than RL LDLT (20% vs 10%)[46]; as the LL graft gives only about 40% of the needed liver mass that affect the metabolic demands of adult recipients leading to SFSG[1,8,47]. Similarly, the syndrome rate was significantly higher in our LL LDLT than RL LDLT (75% vs 8.4%, P = 0.000), and this was due to small NO of our LL LDLT (eight cases), where six of them (75%) had SFSG. On the other hand, LL SFSG was the only independent predictor of graft dysfunction in Yi et al[48] (2008) study. However, SFSS rate was 22.2%, and 19.5% in LL LDLT of Soejima et al[49] (2003), and Soejima et al[50] (2012) studies respectively, and 11.5% in our study that included mainly RL LDLT (166 cases). On the other hand, it was 9.6% and 12.5% in LDLT of Gruttadauria et al[51] (2015) and Ben-Haim et al[52] (2001) studies respectively. In contrast, it was higher (22.7%, 50% and 37.5%) in RL LDLT of Goralczyk et al[53] (2011), LL LDLT of Katsuragawa et al[54] (2009) and LL LDLT of Lauro et al[55] (2007) studies respectively, and obviously lower (6.3%) in Botha et al[56] (2010) study.

SFSS is a disease related to partial liver grafts denoting its inability to perform the functional requirements of the adult recipients resulting in hepatic dysfunction and/or failure and usually manifests as hyperbilirubinemia, ascites, coagulopathy, and encephalopathy[15,19,23,40,46,47]. Furthermore, it is characterized microscopically by cholestasis, hemorrhagic necrosis around the central veins and ballooning of hepatocytes due to microcirculatory disturbances[56]. Similarly, the syndrome was presented by hyperbilirubinemia, ascites, and coagulopathy in 100%, 90%, and 85% of our patients respectively. Moreover, we had 4 (20%) cases with SFSNF and 16 (80%) patients with SFSD.

The principal pathogenesis of SFSS is the unbalance between regeneration of the liver and the increased liver function demand, resulting in graft dysfunction[1]. Furthermore, it is clear that the syndrome is not just caused by SFSG, but also by multiple factors including technical issues, quality of the graft, and recipient factors[13,18,22,32,55,56] (where, the balance between PV inflow, outflow of HV, and functional mass of liver determines its development)[17]. So, for preventing SFSS, it is important to increase the graft volume, and to control adequate PV inflow and HV outflow by the surgical and the none surgical techniques[39]. On the other hand we divided our strategies for preventing the occurrence of the syndrome into pre-operative and intra-operative ones.

The required graft size for successful LT is 30%-40% of the expected liver volume for the recipient (GV/SLV) or 0.8%-1.0% of the body weight (GRWR)[19]; as the insufficient graft size is the primary cause of SFSS due to the relative shortage of hepatic parenchymal cells[23,3,12,16,17,55], furthermore, SFSG suffers from a
transient PHTN early after reperfusion, that is associated with up-regulation of endothelin-1 in the graft and ultra-structural evidence of sinusoidal damage, so, the incidence of SFSS increases when the graft
is SFSS\textsuperscript{11,23,52,57}. In similar, SFSG was independent predictor of SFSS in Lei et al\textsuperscript{58} (2012) study, similarly, SFSG was the most frequent cause of SFSS (50%) in our series, and the only independent predictor of it in our multivariate analysis despite our efforts to decrease SFSS by selecting larger-sized RL graft and by selecting donors with estimated GRWR < 1 (in our late cases) as a pre-operative strategy for preventing SFSS. In contrast, Graft size had no impact on SFSS in Shimazu et al\textsuperscript{59} (2004), and Ikegami et al\textsuperscript{60} (2009) studies.

Although, SFSS is frequently encountered in SFSG (GRWR < 0.8), it may also be found in recipients of larger grafts (GRWR > 0.8)\textsuperscript{9,10,61-64}. Similarly, in our work the incidence of SFSS in normal size graft (GRWR > 0.8) was 6.4% (10/157); and this was due to the effect of other negative factors.

Steatotic liver grafts should not be used if the graft volume is small to avoid SFSS\textsuperscript{16,17}; furthermore, graft steatosis is an exclusion criterion for donation in LDLT\textsuperscript{65}. The mechanisms of poor steatotic graft function after reperfusion include defective anaerobic metabolism of the fatty hepatocytes, decreased lumen of sinusoids by the fat droplets, and higher free radicals caused by lipid peroxidation\textsuperscript{13,27}. In similar, severe steatosis was significantly associated with poor function post LDLT in Hayashi et al\textsuperscript{46} (1999) study. In addition, despite our refusal of grafts with steatosis > 10% to avoid the occurrence of SFSS, steatosis was significant predictor of SFSS in our univariate analysis; moreover it had a trend towards being independent predictor in multivariate analysis. In contrast, graft steatosis had no impact on graft dysfunction in Yi et al\textsuperscript{66} (2008) study. Similarly, Sterneck et al\textsuperscript{67} (1995) reported that grafts with mild to moderate steatosis had good function, and Soejima et al\textsuperscript{56} (2003) found that a graft with 20%-50% macrovesicular steatosis (moderate grade) was accepted for transplantation.

Because LDLT is a scheduled procedure, daily exercise and diet control are required for steatosis control in donors\textsuperscript{1,4}. In similar, donor diet programs and/or daily exercise for controlling steatosis in our donors were parts of our preoperative strategies for avoiding SFSS.

The principal mechanism in SFSS seems to be sinusoidal shear stress secondary to increased PV pressure (PVP) and/or PVF which cause graft perfusion leading to hepatic microcirculatory disturbance, hepatocyte functional insufficiency, over-regeneration of the hepatocytes, hepatocellular damage and death\textsuperscript{3,16,17,19,20,23,46,51,52,68}; furthermore, Portal hyper-perfusion and insufficient venous outflow decrease the arterial perfusion (the so-called hepatic arterial buffer response), with a reduced capacity for regeneration, resulting in impaired liver function\textsuperscript{18,19,23,69}. Similarly, portal inflow volume was independent predictor of SFSS in Lei et al\textsuperscript{58} (2012) study. In similar, in our work, pre LT PHTN was significant predictor of SFSS in univariate analysis; furthermore, severe pre LT PHTN that persisted post LT was the etiology of the syndrome in 4 (20%) of our cases of SFSS, however, portal hyper-perfusion (identified by doppler US) was the cause of it in 3 (15%) of them.
One of the ways to get portal decompression is depriving the splenic part of portal flow by splenectomy [3,17,19,30,46,4,5,62,68,70]. Furthermore, splenectomy increases the HA blood flow leading to increased oxygen supply [18]. Similarly, we did splenectomy in 7/17 of our patients with SFSG to decrease portal overflow that lead to non-significant lower incidence of the syndrome (40% SFSS vs 42.9% no SFSS).

Theoretically, a RL graft including MHV is the best graft for LDLT regarding the recipients; but, this type of graft is not performed in most major transplant centers due to increased donor risk by decreasing the residual volume of the liver [3,23,28]. So, the RL graft without MHV is the standard technique in A-ALDLT [1,16,71]; however deprivation of the anterior segment venous drainage cause graft congestion, leading to graft dysfunction in spite of the increased volume of the graft [1,25,26,30]. Therefore, reconstruction of the anterior segments drainage veins (V5/V8) [15,17,23,72,73] with or without the reconstruction of the RIV is frequently necessary to prevent this [5]. Similarly, in our series, RL graft without MHV was our standard technique of LT, moreover, we did reconstruction of V5, V8 and/or RIV in 46/156 of our patients with RL graft without MHV that lead to non-significant lower rate of the syndrome (23.1% SFSS vs 30.1% no SFSS). Nevertheless, venous outflow obstruction (Known by doppler US) was the reason for the syndrome in 3 (15%) of our SFSS cases. In addition, venous outflow capacity was independent predictor of SFSS in Lei et al [80] (2012) study.

Early graft function is better when the graft is given by a younger donor [74,75]; as, the grafts from older donors have diminished regenerative capacity [79,76], lower blood flow and poor function due to aging [18]. Similarly, Ikegami et al [77] (2000) in their LL LDLT, found that regeneration of grafts from older donors of LDLT were inferior to those of grafts from younger ones and Tanemura et al [80] (2012), in their RL LDLT reported that donor age equal or more than 50 years was independent predictor of impaired regeneration of remnant liver at 6 mo post LT, furthermore, donor age was significant predictor of graft dysfunction and poor graft survival in Yi et al [48] (2008) and Moon et al [79] (2010) studies, and was independent predictor of SFSS in Sanefuji et al [80] (2010) study, while Ikegami et al [79] (2008) found that grafts from younger donors had lower bilirubin levels and ascites production post LDLT. On the other hand, in their RL LDLT, the Kyoto group reported that the functional recovery of recipients from older donors was comparable to that of those from younger ones [80]. Similarly, donor age was not significant predictor of SFSS in our series where our donors had younger age (mean = 27.2 ± 6.7 years).

Both warm [30] and cold ischemia times [31] impair regeneration after LDLT. Conversely, in our series, there was no significant correlation between cold or warm ischemia times and SFSS occurrence. Similarly, ischemia time did not affect graft function in Yi et al [48] (2008) study.

A higher MELD score has negative insult on graft function that may cause its dysfunction or failure especially in SFSG; due to its inability to meet the increased metabolic and synthetic demands of those high-risk recipients with severely damaged liver function [1,16,17]. In similar, MELD score was independent predictor of SFSS in Lei et al [80] (2012) study. However, Yoshizumi et al [75] (2008) reported that a larger liver graft is necessary with older donors (> 50 years) and higher MELD score (> 20), and Emiroglu et al [81] (2007) mentioned that recipients with high MELD scores should be given grafts only when their GRWR is > 1 to improve graft survival also, Ikegami et al [77] (2000) recommended that patients with high-risk should be given a younger and larger grafts to minimize the risk of SFSS. On the other hand, pre-operative MELD score did not affect SFSS rate in our work.

The preoperative Child Pugh score is mostly associated the portal hyper-perfusion state after LT leading to SFSS [1,18]. Similarly, Ben-Haim et al [22] (2001) reported that patients with severe decompensation (Child B, C) require larger grafts to prevent occurrence of SFSS, while, Soejima et al [7] (2003) found that the rate of SFSS after A-A LDLT was higher in cirrhotic patients (43.8%) in comparison with non-cirrhotics (5%). Conversely, there was no significant correlation between Child score and SFSS in our work.

Most literature mentions how to prevent SFSS occurrence. However, very few literatures discuss the treatment of this syndrome after its occurrence. In Goralczyk et al [15] (2011) study, most SFSS cases were treated with successful symptomatic therapy. Furthermore, intravenous octreotide, and oral propranolol were found to decrease the hyperbilirubinemia and coagulopathy seen in patients with SFSS in Ozden et al [83] (2007) study. On the other hand, symptomatic liver support was given to all our patients with SFSS but with poor outcome; moreover, oral propranolol and a somatostatin infusion were given to some of our patients with SFSS to decrease portal flow and improve the syndrome outcome but also with poor outcome.

Approximately 50% of recipients with SFSG die of sepsis 4 to 6 wk after LT [83]; moreover survival rates of patients with SFSG are worse than those with adequate graft size [2,12]. In similar, SFSG was significant predictor of poor survival in our work (P = 0.005), also, it had negative impact on survival in Lo et al [84] (1999), Sugawara et al [55] (2001), and Lee et al [81] (2004) studies. Furthermore, it was independent predictor of graft loss in Katsuragawa et al [85] (2009) study. Conversely, SFSG did not affect survival in Shimazu and Kitajima [59] (2004), Shimada et al [85] (2004), Ikegami et al [80] (2009), Selzner et al [86] (2009), Moon et al [79] (2010), Kaido et al [47] (2011), and Li and Li [87] (2013) studies.

SFSS results in higher incidence of septic compli-
Small for size syndrome (SFSS) is dysfunction of the graft (the presence of persistent hyperbilirubinemia, ascites and coagulopathy) during the early post LT period with absence of other possible causes like Immunological (e.g., graft rejection), technical (e.g., HA or PV obstruction, HV outflow occlusion or biliary leak), infection (e.g., cholangitis)

SFSSF: Failure of the graft (loss of its function leading to patient loss or necessity of retransplantation) during the early post LT period with absence of those previously mentioned causes, SFSS: SFSD and/or SFSNF.

Peer-review
It is an interesting quite large series.

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