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**Columns:** **CASE REPORT**

**Problem of living liver donation in absence of deceased liver transplantation program: Mansoura experience**

Wahab MA *et al*. Problem of excluded living donors

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**Abstract**

We are reporting our experience with potential donors for living donor liver transplant (LDLT) which is the first report to come from an area where there is no legalized deceased donation program. This is a single center retrospective analysis of potential living donors (*n* = 1004) between May 2004 to December 2012. This report focuses on analysis of causes, duration, cost, and various implications of donor exclusion (*n* = 792). Most of transplant candidates (82.3%) had an experience with more than one excluded donor (median=3). Some recipients travelled abroad for deceased donor transplant (*n* = 12) and some died before finding a suitable donor (*n* = 14). Evaluation of excluded donor is a time consuming process (median= 3 days ranging from 1 to 47 days). It is also a costly process with a median expense of about 70 USD ranging from 35 to 885 USD. From these results, living donor exclusion has negative implications on the patients and transplant program with ethical dilemmas and economic impact. Many strategies are adopted by other centers to expand the donor pool; however they are not all applicable in our locality. We concluded that the need for a legalized active deceased donor transplantation program is necessary to overcome the shortage of available liver grafts in our country.

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**Keywords:** Living donor; Liver transplantation; Excluded donors; Deceased donor, Liver disease.

**Core tip:** This is the first case series report to come from a country where deceased donor liver transplantation program is not applied where the echo of the shortage of living liver donors is so high. We report our experience with the problem of excluded donors and possible strategies to overcome this problem. We hope that this experience will be of benefit to the reader of the World Journal of Gastroenterology.

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**INTRODUCTION**

Each center may have its unique criteria for potential donor for living donor liver transplantation (LDLT) regarding the geographical and cultural backgrounds as long as they follow the current global standards of care[1-4]. In Egypt, organization for deceased donor liver transplantation (DDLT) is still awaited and that makes LDLT the only hope for patients with end-stage liver disease or hepatocellular carcinoma on top of cirrhosis[5]. Our experience with short and long term impact of liver transplantation on the living donor has been published in a previous study[5].

Few studies have examined the causes of excluding living liver donors and its impact on the process of transplantation. All of these articles come from countries where DDLT is allowed and the echo of the problem of donation is not so high. Most of available articles are based on small number of potential donors and some of these articles, which are already few, included donors who were excluded for causes related to the recipient[6-9].

In this study, we investigated the impact of excluded living donors on patients, transplant team and medical resources in absence of a DDLT program. Then we discussed different possible strategies to overcome this problem and the expected outcome from adoption of these strategies in our center.

**CASE REPORT**

***Study subjects***

This is a retrospective cohort study of excluded donors (*n* = 792) from potential donors (*n* = 1004) for LDLT using the right lobe graft in the period from May 2004 to December 2012 in Liver Transplant Program, Gastrointestinal Surgical Center, Mansoura University, Egypt. Potential donor was any living donor who comes to our center after the recipient is informed of the criteria of the donor that we accept. Excluded donors were those who were excluded from the process of living liver donation to a certain recipient due to causes related to the donor whether the decision was taken by the transplant team, recipient, or the donor himself.

***Data collection***

Data for this study were retrieved from the internal web-based registry system supplemented by paper-based records of the potential donors included in the medical files of the corresponding recipients. Data were collected and rearranged in a standardized manner including details about donor age, sex, body mass index (BMI), liver function tests, viral serological markers, results of liver biopsy and imaging studies if done, cause and phase of exclusion, duration from the donor first visit till the decision of exclusion was taken and the cost of the investigations and special consultations done in this duration if any.

***Donor evaluation***

Donor candidates were thoroughly evaluated according to a multidisciplinary protocol shown in Table 1. A multistep consent process involving two different surgeons and a hepatologist on separate occasions was used, during which the operative procedure and potential complications were described in details. Donors were informed that the risks of morbidity and mortality were 40% and 0.5%, respectively[5].

Non-related living donation was accepted only when the patient proved to an independent ethical and legal committee that no one of his relatives was suitable to donate his right liver lobe to him. The legal age of consent for donation in Egypt is 18 years when the recipient is one of the parents otherwise it is 21 years old. The upper age limit for living liver donation is 45 years. According to 2006 Census held by the Central Agency for Mobilization and Statistics (CAPMAS), only 6.27% of Egyptians are aged above 60 years[10]. This implies that most of chronic diseases occur at younger age in Egyptians in comparison to other populations. This justifies our choice of upper age limit of 45 years although many centers abroad accept higher age limits even up to more than 60 years.

Routine liver biopsy in the living liver donor evaluation protocol is controversial. Some centers adopted routine liver biopsy after unfortunate experience with the living donors including operation abortion and donor mortality due to undiscovered congenital lipodystrophy[6,15]. Working on the safe side with living liver donor makes liver biopsy necessary. So, liver biopsy was routinely performed by an experienced radiologist.

Liver biopsy is performed prior to imaging studies evaluating the anatomy of the vascular and biliary systems as hepatic angiography, magnetic resonance cholangiopancreatography (MRCP) and liver volumetry. Although the former is an invasive procedure, it is far less expensive (50 USD) than the imaging studies (500 USD). Also, liver biopsy had been performed in our center since 1974 to evaluate patients with portal hypertension for shunt operation and with this cumulative experience the procedure is almost risk-free. The burden of the donor evaluation expenses lies on the recipient with little support from the state. So, we perform liver biopsy prior to imaging studies for economic causes especially when liver biopsy is almost risk free in our center.

Donors with a body mass index (BMI) > 35 were re-evaluated after they committed to a successful weight loss program. Absolute exclusion criteria were ABO incompatibility, pregnancy, mental inadequacy, underlying medical condition that was considered to increase the risk of complications, positive hepatitis B or C serology, underlying liver disease, steatosis > 30%, and abnormal anatomy considered by surgeons to increase the risk of hepatectomy or affect the remaining liver.

***Statistics***

Shapiro-Wilk test is used to assess normality of data. Numerical data are presented as means and standard deviations or as medians with ranges. A P value < 0.05 was considered statistically significant. Statistical analysis was done with the help of IBM SPSS v. 20.

***Causes of exclusion***

Between May 2004 and December 2012, we received a number of 1004 potential donors in Liver Transplant Program, Mansoura Gastrointestinal Surgical Center. 212 donors (21.1%) completed the way to the transplant surgery while 792 candidates (78.8%) were excluded. Most of these donors were excluded during phase I (Table 2) of the evaluation protocol (*n* = 633, 79.9%), while exclusion in other phases was as follows (Table 3): phase II (*n* = 108, 13.6%), phase III (*n* = 48, 6.1) and phase IV (*n* = 3, 0.4%).

The most frequent cause for donor exclusion was exceeding the upper age limit (*n* = 172, 21.7%) while 6.4% of potential donors (*n* = 51) were below the lower age limit. ABO incompatibility represented the 2nd most common cause of exclusion during phase I and the 3rd common cause in the whole evaluation process with a ratio of 12.9% (*n* = 102). 2% of potential donors (n=16) were found pregnant. Candidates excluded due to BMI > 30 were 26 donors (3.3%) while those excluded because of being underweight were 5 donors (0.6%). One donor was excluded because he had algophobia. Two potential donors were excluded because they turned out to be not relatives to the patient during confirmation by the independent ethical and legal committee.

One hundred and forty eight donors (18.7%) withdrew during their evaluation process. Most of them withdrew during the first phase (*n* = 98) while 38 potential donors withdrew during the second phase and 9 withdrew during the third phase. 3 donors withdrew after completion of the evaluation process at the night of surgery. On the other hand, 3 candidate donors expressed much hesitation during first interviews with the transplant team and were excluded. Interestingly, 5 donors were excluded as their families expressed great rejection to donation. Of these 5 cases of family rejection we had a father who refused his daughter donation to himself and a husband who rejected his wife donation to her mother. Of the potential donors, 6 donors were excluded because they had previous nephrectomy and two of them were frankly stated to be done for renal transplant.

In a country where hepatitis C virus (HCV) is endemic, 39 potential donors (4.9%) were excluded because they were serologically positive for HCV infection. 34 (3.4%) were serologically positive for HBV, 6 candidates (0.8%) were positive for both HCV and hepatitis B virus (HBV), 7 candidates (0.9%) were positive for cytomegaoviyns (CMV), one candidate was positive for both HCV and CMV and one candidate was serologically positive for EBV. 10 candidates had abnormal liver function tests in the form of elevated liver transaminase enzymes (*n* = 7), elevated serum bilirubin (*n* = 2) and hypoalbuminaemia with hypoprothrombinaemia (*n* = 1). One donor was excluded because he had fatty liver on ultrasound. One of the excluded donors had splenomegally and 3 candidates were excluded because they had thrombocytopenia.

Anesthesia team excluded 28 candidates (3.5%) because they were smokers who refused to stop smoking before surgery. They excluded other potential donors because they had uncontrolled diabetes mellitus (*n* = 4), uncontrolled hypertension (*n* = 2), ischemic heart disease (*n* = 2), rheumatic heart disease (*n* = 3), valvular heart disease (*n* = 3), atrial ectopic (*n* = 1).

Twenty five candidates (3.2%) were excluded because they had moderate to severe degree of macrovesicular steatosis on liver biopsy. Many donors were also excluded during assessment in phase II by liver biopsy which revealed portal tract fibrosis (*n* = 27, 3.4%), active bilharzial granuloma (*n* = 10, 1.3%), reactive hepatitis changes (*n* = 4, 0.5%), focal portal infilterate and interface hepatitis(*n* = 1, 0.1%), portal lymphocytic infilterate (*n* = 1, 0.1%), mild hemosiderosis (*n* = 1, 0.1%) and hepatic focal necrotic areas (*n* = 1, 0.1%).

During phase III of evaluation, 15 candidates (1.9%) were excluded because liver volumetry revealed decreased right lobe size suspected to cause small for size graft, while 4 donors had small left lobe which would be inadequate reserve in the donor after surgery. Anatomical assessment by angiography and MRCP excluded many candidates because of unsuitable hepatic venous variants (*n* = 9), unsuitable biliary variants (*n* = 6), unsuitable portal venous variant (*n* = 1), unsuitable hepatic and portal venous variant (*n* = 3) and unsuitable hepatic venous and biliary variants (*n* = 1).

***Impact on the recipients***

Of 212 patients who underwent LDLT, 204 patients (96.2%) had an experience with excluded donor with a median number of 3 donors per recipient ranging from 1 to 56 excluded donors. 8 patients (3.7%) didn’t experience donor exclusion and they had underwent liver transplant from the first donor they brought. 14 patients didn’t succeed to bring a suitable living related donor and they died from end stage liver disease. 12 patients travelled abroad and underwent surgery in countries where DLT is legalized especially China (*n* = 7).

***Impact on the transplant team***

The decision of withdrawal was taken by the donor in 148 cases and by pressure from his family in 5 cases. The decision of exclusion was taken by the transplant team in 639 cases. The median duration between the candidate’s first visit to our center and the exclusion or withdrawal date is 3 days ranging from 1 d (*n* = 151) to 47 d (*n* = 1).

***Economic impact***

The average cost of the investigations done for donor’s assessment in phase I is 150 USD, phase II is 200 USD and phase III is 700 USD. We have 1004 candidates entered phase I and 371 of them completed it to phase II. 301 candidates completed phase II and 224 potential donors completed phase III. Of those who completed phase III, 9 candidates withdrew and 215 completed their way to the Phase IV after which 3 patients withdraw and 212 completed to undergo transplant surgery. The median value of the cost of the investigation done for the excluded donor evaluation is 70 USD ranging from 35 USD (*n* = 103) to 885 LE (*n* = 3). 264 donors (33.3%) were excluded without any need for special investigation. The burden of the expenses of donor evaluation lies upon the recipient.

**DISCUSSION**

It is like hitting against strong waves and digging a road into the rocks when you see a worldwide complaint of paucity of liver donors from countries where deceased, living and domino liver transplant are all available while you have to solve the problem of hepatitis C liver cirrhosis in an endemic country with living donors only. Through our experience with 1004 potential living donors, we met a lot of problems that involve the patients and transplant team; some of these problems have social roots with ethical and economic implications. This study proposes the importance of DLT program even after adoption of various strategies to expand the living donor pool, although we believe that it shouldn’t be adopted except after public debate and agreement.

A lot of studies have detailed the evaluation protocol for a living liver donor. Although donor exclusion is discussed in the context of reporting the experience with LDLT[11,12], very few reports, to our knowledge, exclusively discussed the impact of donor exclusion[6-9]. Apart from difference in the evaluation protocols between these reports, some authors include exclusion due to causes related to the recipient in their study. This absence of uniform criteria of the presentation of data makes it difficult to compare our study with previous studies. The authors believe that this is the first study on a large volume of potential donors coming from an area where there is no program for DLT.

Evaluation of living donor for LDLT is a stepwise process consisting of comprehensive medical work-up, refined psychological assessment and accurate anatomical delineation. Donor evaluation is an expensive labor-exhausting and time consuming process. The evaluation process should start by steps which are non-invasive, less expensive and reflective of greater number of unsuitable donors and progress to invasive expensive ones [6]. Based on our abovementioned evaluation protocol, 26.62% of potential donors are excluded before undergoing any investigations.

In our series, 6.9% of potential donors are excluded based on abnormal liver biopsy mainly in the form of steatosis (2.48%) or bilharzial liver insult in the form of active granuloma or portal tract fibsosis (3.67%). This ratio is lower than ratio reported by other studies held by Gamazo *et al*[6] (8%) Marcos (17%) and Pomfret *et al*[13] (22%)[16].

Donor withdrawal during, or even after, his evaluation for LDLT is an inevitable cause of donor exclusion. The ethical dilemma appears when a competent donation candidate gives a voluntary informed consent but his family refuses his donation. Although we adopt the patient centered western bioethics, undue pressure from the candidates’ family makes the team in a hard situation. How can you proceed to surgery when the family brings the police to hospital alleging that the donor is coerced? Shouldn’t you consider a husband who threatens to divorce his wife if she donates her right liver lobe to her mother? These dilemmas are not well discussed in literature although great focus is paid to donors under pressure from the family to donate to a relative not the reverse!

In our experience, 22.21% of potential donors are rejected because their ages lie outside the accepted age range in our center which is between 21 and 45 years. The accepted age for living liver donation is variable between centers. The lower age limit is determined by the law which determines the accepted age of consent[6,15]. In Egypt, the legal age of consent is 18 years when the recipients is one of the parents otherwise it is 21 years. The upper age limits is variable and most centers exceed 50 years of age and even may reach up to 75 years old. Other centers consider old age a risk factor that if associated with another risk factors, as nicotine abuse or hypertension, the donor is excluded otherwise he is accepted[6,11,15,16]. In comparison to these populations, National Census revealed that only about 6% of Egyptians are aged above 60 years and that is why we chose an upper age limit of 45 years[10].

In this series, 10.15% of potential donors are excluded because of ABO incompatibility. Possible solutions include ABO incompatible LDLT and paired donor exchange. The main concern in ABO incompatible transplant is antibody mediated rejection (AMR). Prophylaxis against AMR includes antiCD20 antibody (rituximab), splenectomy, reinforced immunosuppression and local infusion of prostaglandin E1 (PgE1) and/or steroids[17-19]. ABO incompatible transplant remains less favorable than compatible transplant because of inferior long term patient survival[19-21]. Exchange donor transplant was first adopted in Korea in 2003. The two main principles of the procedure are equality and simultaneity meaning that the two pairs are operated upon at the same time. The bad news is that the rate of paired donor exchange after long term application in Korea didn’t exceed 10%[15].

Of 536 candidates who were serological assessed for hepatitis B and C marker in our center, 14.9% of them were accidentally discovered to be serologically positive for HCV and/or HBV. 23 potential donors were excluded because they were hepatitis B core antibody (HBcAb) positive and HBsAg negative. This ratio is lower than those reported in endemic regions where it reaches up to around 50% of the potential donors[22]. There is risk of de novo hepatitis B infection in naïve recipients for HBV who receive grafts from HBcAb positive donors[22,23]. Immunoprophylaxis in naïve recipient using hepatitis B immunoglobulin (HBIG), lamivudine and vaccination is associated with lower incidence of de novo infection[24]. But the low prevalence of HBV infection together with the expensive postoperative prophylactic course (11700 USD) that the recipient cannot afford, make us refuse the use of donors with positive HBcAB.

Precise and accurate knowledge of the anatomy of hepatic vasculature and the biliary system is of paramount importance to plan the best resection and to lessen the risk of morbidity. With refinement of surgical techniques and cumulative experience, exclusion of potential donors due to anatomical variations has decreased over time, however there are still conditions where donor safety necessitates “no go” hepatectomy even after starting the operation[25]. In our experience, 3.38% of potential donors are excluded on anatomical and volumetric base. Examples of cases excluded due to anatomical and volumetric considerations are shown in (Figure 1).

For legislative obstacles supported by social background, deceased donor liver transplantation hasn’t been applied in Egypt yet. Paucity of suitable willing living donor with absence of grafts from deceased donor made many Egyptian patients seek transplant abroad. In nearly all cases, the follow up and management of post-transplant complications is done in Egypt. Thus, this so called “transplant tourism” has a great impact on the progress of LDLT program in Egypt[26]. Great efforts are needed to establish a comprehensive legal system allowing deceased and living donor liver transplantation with airtight safeguards against donor coercion, commercialism and time consuming meaningless obstacles[27].

In conclusion, dependence on LDLT is not enough especially in a country where HCV induced liver cirrhosis is prevalent. Many strategies can be adopted to increase the living liver donor pool. Most, if not all, of these strategies has a risk on the donor (older donors) or on the recipient (ABO incompatible LDLT and HBcAb positive donors). Legalization of DLT is a must to be able to cope with the increasing number of patients in need for liver transplantation.

**COMMENTS**

***Case characteristics***

In this study, the authors investigated the impact of excluded living donors on patients, transplant team and medical resources in absence of a DDLT program.

***Experiences and lessons***

Apart from difference in the evaluation protocols between these reports, some authors include exclusion due to causes related to the recipient in their study. This absence of uniform criteria of the presentation of data makes it difficult to compare our study with previous studies. The authors believe that this is the first study on a large volume of potential donors coming from an area where there is no program for DLT

***Peer review***

Authors reported a retrospective cohort study of excluded donors from potential living-donor for liver transplantation, using the right lobe graft during 8.5 years in Egypt. They suggested that LDLT is not enough especially in a country where HCV induced liver cirrhosis is prevalent, and that strategies to increase the donor pool may involve a risk on the marginal donor or on the recipient with ABO incompatibility and/or with HBcAb(+) donors. They also concluded that legalization of deceased donor for liver transplantation is required. A death concept is so different between countries, and we have respect for if when a deceased-donor will be legislated.

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**Figure 1 Examples of excluded donors due to unsuitable anatomical variations as shown by imaging studies.** (A) Computerized tomographic (CT) portography showing the right portal vein arises from the left portal vein(B)CT volumetry showing that drainage of right lobe is mainly through the middle hepatic vein (C) CT venography showing drainage of the right lobe through multiple hepatic veins (D) CT venography showing small right hepatic vein and inferior right hepatic vein draining into the middle hepatic vein.

**Table 1 Live donor evaluation protocol**

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| --- |
| **Potential donor:** Is any living donor who comes to our center after the recipient is informed of the criteria of the donor that we accept. The criteria that the recipient is told is that we want an apparently healthy relative to the recipient whose age is between 21 and 45 years. Recipient, donor and their families are informed about the risks and benefits of right lobe hepatectomy for LDLT and both the donor and the recipient must sign informed written consent to proceed into the evaluation process |
| **Phase I:** Confirmation of the relation between the living donor and the candidate recipient by independent legal and ethical committee, confirmation of being within the accepted age limits, assessment of BMI, initial anesthetic and surgical evaluation, confirmation of ABO compatibility, complete blood picture (CBC) and biochemistry assays, pregnancy test, abdominal doppler ultrasound, serological tests for hepatitis C and B viruses (Serum HCV RNA qualitative & quantitative assay by PCR method, HBV surface antigen, HB core antibody, HB e antigen, HB e antibody, HB surface antibody), serological assessment for different viruses (human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), Herpes virus I and II, Cytomegalovirus (CMV), Chagas disease and syphilis), electrocardiography (ECG), echocardiography, plain X-ray of the chest, exclusion of specific liver diseases (ferritin, transferrin, and serum iron), Reassessment after previous investigations |
| **Phase II:** Liver biopsy for assessment of degree of steatosis and detection of any pathological conditions. |
| **Phase III:** Hepatic angiography to delineate the anatomy of the portal vein, hepatic artery and hepatic veins. Magnetic resonance cholangiopancreatography (MRCP) is done for assessment of the anatomy of the biliary system. Liver volumetry to assess the right lobe graft size, residual donor liver volume and graft-recipient weight ratio. The donor is accepted if GRWR > 0.8 and the residual donor liver volume ≥ 30%. |
| **Phase IV:** All donors must sign a written informed consent including his frank agreement on participating in LDLT |

LDLT: Living donor liver transplantation.

**Table 2 Number and ratio for each cause of donor exclusion during phase I of live donor evaluation protocol**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Phase** | **Step** | **N** | **Exclusion** | **N** | **% from the step** |
| Phase I | Confirmation of the relation | 1004 | Non related donor | 2 | 0.19 |
|  | Age | 1002 | - Over age limit | 223 | 22.25 |
|  | BMI | 779 | - Overweight  - Underweight | 26  5 | 3.33  0.64 |
|  | Clinical evaluation | 748 | Uncontrolled HTN | 2 | 0.26 |
|  | Initial surgical evaluation | 746 | Upper abdominal surgery | 6 | 0.8 |
|  | Psychological evaluation | 740 | - Algophobia  - Hesitation | 1  3 | 0.13  0.4 |
|  | ABO compatibility | 736 | ABO incompatibility | 102 | 13.85 |
|  |  | 634 | Withdrawal | 23 | 3.62 |
|  | CBC and biochemistry | 611 | - thrombocytopenia  - uncontrolled DM  - elevated liver enzymes  - hyperbilirubinaemia  - hypoalbuminaemia | 3  4  7  2  1 | 0.49  0.65  1.14  0.32  0.16 |
|  |  | 594 | Family rejection | 5 | 0.84 |
|  |  |  | Withdrawal | 6 | 1.01 |
|  | Pregnancy test | 583 | Positive test | 16 | 2.74 |
|  | Abdominal US | 567 | - Splenomegally  - Fatty liver | 1  1 | 0.17  0.17 |
|  |  | 565 | Withdrawal | 29 | 5.13 |
|  | Serological assessment | 536 | - HCV positive  - HBV positive  - CMV positive  - EBV positive  - HCV and HBV positive  - HCV and CMV positive | 39  34  7  1  6  1 | 7.27  6.34  1.3  0.18  1.11  0.18 |
|  |  | 448 | Withdrawal | 9 | 2 |
|  | Anesthetic reassessment | 439 | - Smoker  - IHD  - Rheumatic heart disease  - Valvular heart disease  - Atrial ectopics | 28  2  3  3  1 | 6.37  0.45  0.68  0.68  0.22 |
|  |  | 402 | Withdrawal | 31 | 7.71 |

HCV: Hepatitis C virus; HBV: Hepatitis B virus; CMV: Cytomegaoviyns.

**Table 3 Number and ratio for each cause of donor exclusion during phase II to IV of live donor evaluation protocol**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Phase** | **Step** | **N** | **Exclusion** | **N** | **% from the step** |
| Phase II | Liver biopsy | 371 | - Moderate steatosis  - Severe steatosis  - Portal tract fibrosis  - Bilharzial granuloma  - Reactive hepatitis change  - Focal portal infilterate  - Portal lymphocyte infilterate  - Haemosiderosis  - Focal necrotic areas | 16  9  27  10  4  1  1  1  1 | 4.31  2.42  7.27  2.69  1.07  0.26  0.26  0.26  0.26 |
|  |  | 301 | Withdrawal | 38 | 12.62 |
| Phase III | Volumetry and anatomical  assessment | 263 | - Portal venous variants  - Biliary variants  - hepatic venous variants  - hepatic venous and biliary variants  - hepatic and portal venous variants  - Small for size graft  - Small residual left lobe | 2  6  8  1  3  15  4 | 0.76  2.28  3.04  0.38  1.14  5.7  1.5 |
|  |  | 224 | Withdrawal | 9 | 4.01 |
| Phase IV | Informed consent | 215 | Withdrawal | 3 | 1.39 |
|  | Donors underwent surgery | 212 |  |  |  |