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III Consensus Meeting of the Spanish Society of Liver Transplantation. Hepatitis C, Living-donor Liver Transplantation, Quality of Liver Grafts and of Liver Transplantation Programs☆,☆☆

Sociedad Española de Trasplante Hepático[a,b]

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ABSTRACT

The constant updating in the field of liver transplant led to the holding of the III Consensus Meeting of the Spanish Liver Transplant Association. Three current topics of great clinical interest were debated during this meeting; transplant in patients with liver cirrhosis due to hepatitis C, live donor liver transplant and the evaluation of the quality of liver grafts. A subject of great interest to Liver Transplant Units was also discussed: the assessment of their quality.

III Reunión de consenso de la Sociedad Española de Trasplante Hepático (SETH). Hepatitis C, trasplante hepático de donante vivo, calidad de los injertos hepáticos y calidad de los programas de trasplante hepático

RESUMEN

La constante actualización en el campo del trasplante hepático llevó a la celebración de la III Reunión de consenso de la Sociedad Española de Trasplante Hepático. En ella se debatió acerca de 3 temas actuales y de gran interés clínico: el trasplante en pacientes con cirrosis hepática por virus C, trasplante hepático de donante vivo y la evaluación de la calidad de los injertos hepáticos. También se abordó un tema de gran interés para las unidades de trasplante hepático: la evaluación de su calidad.

Introduction

This document is a summary of the III Consensus Meeting of the Spanish Society of Liver Transplantation (SETH) that took place in November 2010. In previous meetings, indications for and access to waiting lists, prioritisation, paediatric transplants, and quality indicators were discussed.[1–4] On this occasion, the meeting was structured into 4 working groups that focused on the following subjects: (a) transplant in

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[a] iherrero@unav.es

[b] Appendix A shows all the participants in the Consensus Meeting.

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Table 1 – Grading System Used for Assigning Class and Level of Evidence.

Class	Description
I	Conditions under which there is evidence and/or general agreement that a diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective
II	Conditions under which there is conflictive evidence and/or divergent opinions regarding the usefulness/efficacy of a diagnostic evaluation, procedure, or treatment
IIa	Evidence/opinion in favour of usefulness/efficacy
IIb	Usefulness/efficacy not well established by evidence/opinion
III	Conditions under which there is evidence and/or general agreement that a diagnostic evaluation/procedure/treatment is not useful/effective and in some cases may be harmful
Level of Evidence	**Description**
A	Data derived from multiple randomised clinical studies or meta-analyses
B	Data derived from a simple randomised study or non-randomised studies
C	Only consensus opinions from experts, case studies, or standards of treatment

patients with liver cirrhosis due to hepatitis C virus (HCV); (b) living-donor liver transplant; (c) the quality of liver donors; and (d) the quality of liver transplant programmes.

Liver Transplant and Cirrhosis Due to Hepatitis C Virus[5–40]

This working group presented their recommendations according the evidence summarised in Table 1.

Factors Associated With Greater Severity and Lower Survival Rates From Infection With Hepatitis C Virus Post-liver Transplant

1. Indications for liver transplant in patients infected with hepatitis C virus and pre-transplant factors in potential recipients
   - Given the worse diagnosis in these patients, strict selection criteria should be followed for liver transplant recipients with hepatocarcinoma associated with HCV (Class I-Level B) (Table 1).
   - Age, diabetes, metabolic syndrome, and response to combined antiviral treatment should all be taken into account before indicating liver transplant in patient with HCV infections (Class I-Level B).
2. Donor/surgical and transplant factors
   2.1 Donor age (Tables 2 and 3)
   - Although there is sufficient scientific evidence to show that the age of the liver donor is the most important independent factor that negatively affects the severity of HCV recurrence, as well as the survival of the graft and the patient, we cannot identify a clear cut-off point for donor age after which they would not be suitable for HCV cirrhotic recipients.
   - The preferential assignment of young liver donors to patients infected with HCV could be a detriment to other patients without HCV infections, and taking into account that a large proportion of the donor population is aging, this could result in increased mortality rates for HCV patients on the waiting list.
   - The recommendation was made that transplant groups study the impact of the age of the donor on recipient survival in patients with and without HCV.

Table 2 – Survival of the First Graft Based on Donor Age in Adult Patients With HCV Cirrhosis (Excluding Hepatocarcinomas). Elective Transplants (1984–2009).

Survival of the 1st Graft (%)	1 Month	1 Year	3 Years	5 Years	10 Years	15 Years
Donor age						
16–19 years (266)	92.8	83.7	78.6	70.3	60.1	48
20–24 years (283)	87.9	75.4	69	65.2	56	43.5
25–29 years (201)	90	79	73.1	65.4	56	45.8
30–34 years (231)	93.9	82.5	77.2	70.1	58.4	52.1
35–39 years (235)	91.5	83.2	73.1	69.2	57.3	43.2
40–44 years (236)	92.3	76.5	63.2	58.8	44	29.9
45–49 years (336)	90.1	77.6	65.7	53.7	38.1	34.2
50–54 years (307)	93.1	76.7	65	58.2	41.2	27.3
55–59 years (315)	93.3	75.3	62.5	57	43.5	33.8
60–64 years (319)	90.6	75.2	61.7	50.5	27.4	–
65–69 years (261)	90.4	71.5	55	45.9	25.1	–
70–74 years (206)	87.3	70.7	57.3	43.7	33.4	–
75–79 years (126)	90.5	69.3	48	42.8	29.3	–
>.80 years (40)	75	58.7	34.3	34.3	25.7	–

Report by Gloria de la Rosa. Date: January 2011. Source: RETH.

Table 3 – Survival of the First Graft Based on Donor Age in Adult HCV (–) Patients (Excluding Hepatocarcinomas) in Adults. Elective Transplants (1984–2009).

Survival of the 1st Graft	1 Month	1 Year	3 Years	5 Years	10 Years	15 Years
Donor age						
16–19 years (546)	92.3	82.4	76	72.6	62.3	55
20–24 years (618)	92.4	82.2	77	72.4	62	49.5
25–29 years (485)	89.5	79	72.7	69	59.8	52.3
30–34 years (390)	90.2	79.2	71.7	66.2	54	50.2
35–39 years (421)	90.5	79	74.3	69.2	57.2	47
40–44 years (481)	89	78.4	71.5	68.8	57.9	46.8
45–49 years (567)	90.6	78.4	72	67.8	56.1	44
50–54 years (594)	90.6	79.9	71.5	67.7	57	44.5
55–59 years (581)	90.7	80.8	74.9	68.5	55.5	40.3
60–64 years (536)	91.8	83	75.6	69.8	54.8	43.9
65–69 years (497)	92.5	82.6	75.2	71.8	57	44.9
70–74 years (437)	94.9	79.2	71.7	66.2	54	50.2
75–79 years (289)	95.5	81.3	72.2	65.7	50.6	–
>.80 years (72)	89	83.2	74.3	69.5	69.5	–

Report by Gloria de la Rosa. Date: January 2011. Source: RETH.

2.2 Ischaemia time
- Prolonged duration of ischaemia negatively impacts the severity of HCV recurrence, as well as the survival of the graft and patient.
- Cold ischaemia should be limited to less than 8 h, and/or hot ischaemia should be limited to less than 90 min.

2.3 Anti-HCV donors (+)
- Donors with HCV infections can be used for cirrhotic patients with HCV infections under the following conditions: donor age <56 years, normal hepatic biochemistry tests, ultrasound results, and visual inspection of the liver, and the recipient must have a genotype 1b HCV infection.
- The duration of ischaemia should be minimised as much as possible.
- Although liver biopsies are recommended, we should not wait for the results if ischaemia was to exceed the 8 h mark.

2.4 Other factors
- We have no recommendations to make regarding other variables such as stenosis, donor–recipient HLA-DR compatibility, the use of non-heart beating donors, or partial grafts from in vivo or split donors.

3. Viral factors
Infection from cytomegalovirus should be closely monitored in order to detect and treat it early (Class IIa-Level B).

4. Recipient factors: metabolic syndrome/diabetes/insulin resistance (post-transplant)
Effective treatment should be given for diabetes and other components of metabolic syndrome in an attempt to improve the evolution of post-transplant recurrent hepatitis C (Class I-Level B).

5. Biochemical and histological patterns of recurrence and early histological findings (first 12 months post-transplant)
- The higher risk of evolution towards cirrhosis can be predicted using the biochemical and histological pattern of recurrence (Class I-Level B).
- Biochemical cholestasis and/or jaundice at the moment of recurrence are associated with a higher risk of developing cirrhosis (Class I-Level B).
- Histological findings from a biopsy taken within 12 months of the transplant are very useful for predicting the risk of developing cirrhosis (Class I-Level B).
- Moderate/severe inflammation and/or fibrosis pose a high risk of developing cirrhosis and the need for starting anti-viral treatment (Class I-Level B).

6. Biliary complications
Although there is some controversy regarding the possible influence of biliary complications on the more severe progression of histological lesions from HCV, we recommend an active attitude towards the detection and early treatment of biliary stenosis in order to minimise the negative effects this may have on the development of recurrent HCV hepatitis (Class IIb-Level B).

The Role of Immunosuppression in the Evolution of Recurrent Post-liver Transplant Hepatitis From HCV and in Response to Anti-viral Treatment

1. Role of immunosuppression in the natural history of recurrent hepatitis C

1.1 Calcineurin inhibitors
Based on the data currently available, we cannot recommend the use of specific calcineurin inhibitors (CNI), since no differences have been found in graft or patient survival, or in the evolution of recurrent hepatitis C (Class I-Level A).

1.2 Corticosteroids
- We recommend avoiding the use of steroid boluses in mild-moderate rejection cases (Class IIa-Level B).
- Non-steroid treatment plans are safe in patients infected with HCV (Class IIa-Level B).
- If corticosteroids are used, we recommend progressive withdrawal of the treatment after sixth months (Class IIa-Level B).

1.3 Role of other immunosuppressive drugs (IS): mycophenolate, azathioprine, mammalian target of rapamycin inhibitors, and interleukin-2 receptor antibodies
- The use of treatment protocols that include mycophenolate mofetil, non-steroid treatments, or interleukin-2 receptor antibodies does not influence mid-term recurrence severity (Class IIa-Level B).
- There is no optimal protocol for immunosuppression in patients with HCV infections. The only concrete recommendation is to avoid a state of over-immunosuppression. To this end, we recommend avoiding corticosteroids in boluses and triple or quadruple treatments at full doses (Class I-Level B).

2. The role of immunosuppression in the response to anti-viral treatment
The modification of IS treatment has not shown any impact on sustained virological response (SVR), and should be modified according to the toxicity profile in each IS (Class IIa-Level B).

Pre-transplant Anti-viral Treatment

- We recommend anti-viral treatment in all patients on the transplant waiting list that are in a compensated state and class A on the Child-Pugh scale, regardless of the patient's genotype and viral load, as long as contraindications are not present and the patient has responded to previous combined anti-viral treatment (Class I-Level B).
- We also recommend treating patients with functional class A–B on the Child-Pugh scale and a ''model for end-stage liver disease'' (MELD) score <18, with a good virological response profile (naïve, genotypes 2–3, or genotypes 1–4 with low viral load) (Class I-Level B).
- Treatment is contraindicated in all patients with a functional class C on the Child-Pugh scale or MELD$\geq$18 (Class I-Level B).
- The treatment of choice is a combination of pegylated interferon-alpha and ribavirin at standard doses (Class I-Level C).
- We also recommend the use of growth factors (erythropoietin and granulocyte colony-stimulating factor) if necessary (Class IIa-Level C).

Post-transplant Anti-viral Treatment

- Anti-viral treatment in liver transplants must be carried out by doctors dedicated to the transplant, or doctors with close contact with the transplant centre (Class I-Level C).
- Post-liver transplant anti-viral treatment is based on the same drugs as those used in immunocompetent patients. However, in order to optimise results, the treatment may not involve the same duration, dosage, rules for early interruption, or the use of growth factors (Class I-Level A).
- In genotypes 2–3, there are no data that indicate that treatment should be shortened (Class I-Level C).
- The absence of an early virological response (EVR) predicts the absence of a response to 12-month-therapies (Class I-Level B).
- Prolonging treatment may be beneficial in some situations. As such:
  - o In patients with mild histological lesion and no EVR, anti-viral treatment should be suspended (Class I-Level C).
  - o Prolongation/maintenance of treatment may be justified in patients with advanced histological lesions and/or poor prognostic factors, clinical improvement and/or biochemical response, and who tolerate the treatment (Class II-Level C).
- The modification of IS treatment has not been shown to impact SVR, and should be modified according to the toxicity profile of each IS (Class II-Level A).
- Immunosuppression levels should be strictly monitored (Class I-Level C).
- Anti-viral treatment does not imply any modifications to the therapeutic range of IS (Class I-Level C).
- A liver biopsy must be taken before commencing anti-viral treatment (Class I-Level B).
- Treatment is recommended in severe acute cases of hepatitis and in cholestatic hepatitis (Class I-Level B).

Follow-up and Monitoring in Post-liver Transplant HCV Hepatitis

- The severity of the hepatitis C infection must be serially evaluated (Class I-Level B).
- Liver biopsy is the gold standard for evaluating the severity of post-transplant recurrent hepatitis C (Class I-Level B).
- A liver biopsy should also be taken 12 months after transplant (Class I-Level B).
- Elastography has been shown to be the non-invasive method with the greatest capacity to identify significant fibrosis and portal hypertension in this context, and can serve as an adequate alternative to biopsy for following the evolution of post-transplant hepatitis C (Class I-Level A).

Liver Retransplantation

- Liver retransplantation is not contraindicated in patients infected with HCV.
- We recommend using the ''Rosen Score'' for determining the indications for retransplantation in these patients.
- In patients with a Rosen score $\geq$20.5, retransplantation is contraindicated since expected survival after one year is less than 50%.

Living-donor Liver Transplant

Tendencies in Living-donor Transplants

Liver transplants have spread throughout the world in the last 25 years, with current survival rates close to 95% at one year and above 80% after 5 years. In Spain, in spite of the high rate of cadaveric donation, the number of donors does not meet the needs of recipients. Living-donor liver transplant (LDLT), which was developed especially in Eastern countries due to a lack of cadaveric donors, was quickly extended to Western countries. In Spain, approximately 300 living-donor transplants have been performed, half of these being paediatric cases, with no changes in recent years. This type of transplant represents little over 2% of transplants. In Spain as in other

countries, the tendency for this type of transplant is decreasing, contrary to the trend in live kidney transplants.

The results from LDLT are better than those obtained with cadaveric donors, mortality rates on the waiting list appear to remain stable, and in 2010, the possibility of receiving a transplant within one year of entering the waiting list was below 50% in Spain. Additionally, satisfaction surveys filled out by donors revealed that less than 4% feel pressured to donate, and the vast majority are content to have donated.[41] The question, then, why is LDLT is on the decrease? Firstly, the almost universal implementation of severity-based prioritisation (model for end-stage liver disease [MELD]) has considerably reduced the urgency of donations, since the patients at the highest risk of death are placed higher on the waiting list.[42] Even so, using living donors reduces waiting list mortality rates still more.[43] On the other hand, donor morbidity and mortality rates act against LDLT, and for every case of donor death (even though this does not even reach a rate of 0.3%), the interest in live donation decreases, and some programmes even abandon the practice.[44–48] In the evaluation process, a large number of donors are ruled out, the majority due to insufficient residual volume or incompatible blood group, which lowers the applicability of this technique, falling below 20%.[49–51]

LDLT is a good option for patients with hepatocarcinoma (HCC) and conserved liver function, since these patients are not always placed high on the waiting list, even though they receive additional points on the MELD scale. Additionally, there is a tendency to expand the Milan criteria, and LDLT could avoid reducing the quantity of cadaveric organs available for other indications if the criteria are expanded. On the contrary to this advantage, the shorter time spent on the waiting list would avoid the typical progressive worsening of biologically aggressive tumours and results would be worse. However, this same effect is produced if patients with HCC are prioritised giving them additional points. The option of LDLT should be taken into account in HCC patients.[52–56]

Living-donor Liver Transplant in Paediatric Patients

LDLT is considered a good option in children, with lower rates of mortality and morbidity for donors (usually their parents) as a consequence of implanting left lateral segments. This also tends to be an option demanded by the parents.

LDLT in children has shown the same or better survival than in cadaveric transplants, especially in children younger than 2 years, and does not imply a greater risk of graft loss, which does occur in the case of split and reduced liver transplants.[57,58]

One ethical dilemma presented by this option is the possibility of offering LDLT in emergency situations, when decisions are made by the patient's parents in an emotionally charged context.

Causes for Living Donation

In order to promote living donations, the physical, psychological, and economic consequences for the donors must be minimised.The process of donor evaluation must be exhaustive in order to understand any problems that could affect the risk of morbidity/mortality from the procedure. The impact of scarring, which is generally categorised by the donor as seriously inconvenient, could be greatly reduced by performing part of the procedure, or even all in the case of left lateral segment donation, laparoscopically.[59–61]

The large majority of donors affirm that they suffer economic losses, most of which are due to lost wages. They also communicate difficulties in obtaining life insurance and having to pay increased premiums.[62,63] Living liver donors should have a similar protection system to that provided to post-partum mothers (maternal leave and job preservation). This type of donor could be given the status of ''social benefactor,'' including this type of protection and perhaps even fiscal incentives, since living donors benefit society as a whole, facilitating access to transplants for patients who do not have access to living donors.

The idea of establishing direct economic incentives for living donors is still a controversial issue, but it may be the state that makes this decision, as occurred in other countries to promote living kidney transplants.[64,65]

On the other hand, it is necessary and should be obligatory to inform recipients on the waiting list in all transplant units as to the option of live donations and all its advantages and inconveniences, even if LDLT is not performed at the hospital where the patient is being treated. Public organisations should assume the costs derived from transferring patients and their possible donors to centres with the capacity for live donations.

Evaluation of Donor Risk

Donor evaluation must be an exhaustive process in order to minimise the risks inherent to donation. In all cases, morbidity ranges around 25% and mortality around 0.3%.[66,67] These values should be even lower, since the appeal of live donation depends largely upon them.

The evaluation must include an estimate of the general risks of a hepatectomy and a detailed anatomical analysis, which reduces post-operative risk for the donor as well as the recipient.

In the first phase of the analysis, after obtaining informed consent, the clinical history is completed along with a physical examination, laboratory analysis (with serology), Doppler ultrasound, and psychological evaluation, which checks the mental stability of the donor along, that he/she is informed of the whole process, and establishes the altruistic nature of the voluntary donation.

The second phase of the analysis involves laboratory analytical evaluation (complete biochemistry test, immunoglobulins, tumour markers, lipid profile, iron, ferritin, transferrin, alpha-1-antitrypsin, thyroid function, coagulation factors, etc.) This is followed by a cardiopulmonary evaluation (chest X-ray, electrocardiogram, echocardiogram, and spirometry if needed) and a radiological examination of the liver (cholangio-MRI, angio-CT, and other optional methods such as MeVis), with the goal of assessing liver anatomy with the greatest possible level of accuracy, and to avoid the technical difficulties inherent to anatomical variations.

The third phase of the analysis involves a liver biopsy to evaluate the level of steatosis and the presence of portal fibrosis, non-alcoholic steatohepatitis, and inflammatory

changes. The need for a biopsy is controversial, and the Vancouver Forum concluded that it should be taken only when there are changes in liver test results or radiological results, or if the patient's body mass index (BMI) is >30, and when the donor is a family member of a recipient with primary biliary cirrhosis or auto-immune hepatitis.[68] Some groups perform the biopsy systematically.

During the entire process, blood reserves are also taken for later transfusions.

Before the case can be passed on to the ethics committee, informed consent must be obtained. After the ethics committee has given its approval, the law requires judicial authorisation from the civil registry.[69]

The ideal donor is between 18 and 55 years, with a BMI<30, no cardiopulmonary, renal, or metabolic diseases, with a liver remnant greater than 30% and an estimated graft weight >0.8% of the recipient's weight, with steatosis lower than 20% and favourable vascular and biliary anatomy.

The donor must also be adequately informed as to the physical, psychological, and work-related consequences of the procedure (scarring, hospitalisation, possible complications, estimated duration of sick leave, risk of recipient death, possibility of late complications, etc.)

Transplant Candidate Selection

The indications for LDLT are the same as for cadaveric transplants. With the current severity-based prioritisation system, which is fundamentally built off the MELD score, patients with a greater risk of death on the waiting list are placed higher on the waiting list. These patients should not be considered for LDLT, since they will receive a cadaveric organ relatively quickly. However, there are other patients who are under-prioritised using the MELD, such as cirrhotic patients with encephalopathy, ascites, and bacterial peritonitis, and are at a high risk of dying while on the waiting list. They would benefit greatly from LDLT. Patients with HCC are excellent candidates for LDLT, since in spite of receiving extra points on the MELD, these patients are always at a high risk of disease progression while on the waiting list. LDLT is a good option for patients who comply with or surpass the Milan criteria and that would fall within the expanded criteria. These patients, in which good survival rates have been demonstrated following cadaveric transplants, are excluded from transplantation by many groups for the sake of avoiding large waiting lists. Even so, LDLT should be developed as an indication for patients with ''expanded'' criteria in the context of controlled studies.

Procedure in Adult Donors

The incision for extracting the right liver may be subcostal bilateral, or more frequently, vertical supraumbilical, with right transverse prolongation. Other incisions more prone to eventration should be avoided.

Cholangiography is a mandatory step in the correct identification of the patient's biliary anatomy and abnormalities, which are not always entirely revealed by imaging tests, and for estimating the point at which the right hepatic duct(s) will be severed.

The pedicle should be dissected to the right of the bile duct in order to avoid damaging its vascularisation and the left pedicle.

The right liver is released using the piggy-back manoeuvre, respecting the major retro-hepatic veins >5 mm, which will provide important drainage to the graft and so must be anastomosed to the recipient.

Ultrasound is used to identify the plane of dissection and the cut-off points for the possible drainage veins in segments V and VIII towards the middle hepatic vein. This vein remains in the donor, although some authors defend its inclusion in the graft, which appears to us to be an unacceptable risk for the donor. The parenchyma is normally dissected using an ultrasonic dissector or similar tool. The bile duct is dissected in the last third of the section, taking special caution not to damage any remnant biliary radicals.

Upon finishing the transection, some surgeons wait 30–45 min in order to allow the venous collaterals to open towards the right vein, thus facilitating the future drainage of middle sections of the graft.

Bench Surgery

The graft is portally perfused in a bench procedure. Normally, the drainage veins of the middle segments must be reconstructed and joined to the right suprahepatic vein using plasty or cryopreserved grafts, with the goal of obtaining venous drainage. In the case of a double artery, the reconstruction is also best performed using a bench procedure so that only one anastomosis is needed. In the case of a double bile duct, plasty can be used if the distance between the two is less than 3 mm.

Procedure for Donors to Paediatric Patients

Liver transplants in children involve the left lateral segments, and have a much higher anatomical variability. In fact, the vast majority have only one bile duct. Some experienced groups perform this procedure successfully using a laparoscopic approach.

Procedure in Adult Recipients

The venous drainage of the graft is vital for proper immediate functioning, and so retrohepatic veins greater than 5 mm in diameter or that drain for more than 5% of the graft in the volume analysis (MeVis) must be anastomosed.

The portal anastomosis is similar to that of the cadaveric donor procedure. The majority of authors describe a temporal portacaval anastomosis in the recipient. It is important to evaluate portal flow rates before the transplant and measure again after revascularising the graft, since a flow rate greater than 2000 ml/min could damage the graft and may require other steps to reduce it (ligation of the splenic artery, shunts, etc.)

Biliary anastomosis is the greatest problem in living-donor recipients. The vascularisation of the bile duct can be poor, and may lead to leaks or stenosis. In general, the best anastomoses are duct-to-duct, with or without a Kehr drain, but occasionally a hepaticojejunostomy is necessary. A double anastomosis is not uncommon, and can be performed

between the left and the right hepatic ducts of the recipient or using the cystic duct. The rate of biliary complications is greater than 30% in the majority of cases, and requires significant interventional radiological support and an endoscopy.

Procedure in Infant Recipients

Infant recipients frequently have undergone previous operations (the majority for biliary atresia) and have severe portal hypertension and hypoplasia. This affects the procedure, since good portal flow is difficult to achieve, which is absolutely necessary for graft survival. Arterial anastomoses, performed using meticulous technique, do not usually give problems, and the rate of thrombosis is very low. Biliary reconstruction always involves a hepaticojejunostomy, and stenosis is not rare, requiring interventional radiological treatment.

Results

In the 2000 Bethesda Conference, held by the National Institute of Health (NIH), the objectives for LDLT were established: increasing the number of donors, reducing recipient morbidity and mortality rates, and increasing long-term survival.[70] The results from American, European, and Spanish registries have allowed us to evaluate these objectives. In the USA, the number of LDLT has decreased since 2001, when the peak number of 524 was reached, with only 219 performed in 2009. In 2010, the number increased again to 282, and we predict this upwards curve to continue. There is a 90.1% survival rate after one year, with only an 86.3% survival rate in cadaveric transplants. The 5-year survival rate for live donations is 77.7%, and 71% for cadaveric donations. Graft survival at 1 and 5 years is the same for both types.[71]

In the European Registry (ELTR), LDLT has increased in recent years, although the global rates are below those from the USA. Survival at 1 and 5 years is better for LDLT than in cadaveric transplants, both for the patient and the graft.[72] According to the data from the Spanish Register of Liver Transplants, more than 250 LDLT have been performed in Spain, with similar graft and patient survival rates to those from cadaveric transplants.[73] There have been no cases of donor deaths in Spain, although the complication rate is 20%. In infant LDLT, both overall and Spanish results are better than in the case of adults, with 1 and 5 year survival rates around 90%.[71–73]

Final Considerations

LDLT is currently a valid transplant option, allowing quick access to transplants for many recipients, with patient and graft survival rates above those from cadaveric donors, once the learning curve has been passed by the surgical team.

Decreased donor mortality and morbidity rates are crucial for the expanded development of this procedure.

This type of transplant should be offered to all recipients on the waiting list, regardless of the centre in which it can be performed.

Living donors should be considered as ''social benefactors'' and receive protection from public administrations in medical, economic, and work-related fields, such that they are not put at a disadvantage in any way.

A debate must be opened in order to evaluate the possibility of expanding the indications for LDLT, accepting the fact that recipient survival rates will be somewhat lower than for normal cadaveric donations.

Liver Donor Quality

The quality of liver donors determines the results of the transplant in terms of recipient survival, graft survival, and early and/or late graft dysfunction. These encompass several different concepts: primary graft dysfunction, delayed graft function, and poor initial graft function.[74] The work from this study group focused on 3 sections: to analyse the existing biological limits for donation and the scoring systems used, along with their applicability in Spain; strategies for using donors with expanded criteria; and the current magnitude of the problem and an analysis of its evolution in recent years.

Analysis of the Existence of Biological Limits for Donation and Scoring Systems Used and Their Applicability in Spain

The use of expanded criteria donors (ECD) determines increased risk due to more ischaemia/reperfusion damage.[75] This risk must be considered as a continuum of risk that can be measured.[76] An analysis of recent studies indicates that there are no donor variables that, alone, constitute a contraindication for donation. This is especially true in the case of donor age.[77] In the case of macrovesicular steatosis, which is the main cause of liver graft rejection in Spain, the influence of other variables, such as cold ischaemia, must also be evaluated so that the limit of 30% macrosteatosis can be expanded.[78]

The scarcity of donors to be able to satisfy current demand has created the need for liver donors with greater risk, as well as the use of donors with whom multiple risk factors are present. This implies higher scores in the scales that evaluate risk, as well as a greater probability of developing ischaemia/reperfusion damage, and in turn, graft dysfunction. Of special interest is the combination of prolonged ischaemia with all other donor variables, which requires intense efforts to minimise it as much as possible whenever another risk factor is present.[79,80]

Changes in the epidemiological profiles of patients registered in our country have led to a continuously more common scenario: an elderly donor who is brain dead due to a stroke, with added metabolic disorders, inotropic support drugs at high doses, and prolonged hospitalisation in the intensive care unit (ICU). Although the study group was conscious of the excess effort being placed on this subject, they insist that both the personnel in charge of coordinating the transplants in each hospital and those in charge of maintaining the donors must prioritise patient care and optimise their management. Given the pro-inflammatory state that leads to brain death and damage to the liver graft prior to extraction, it is easy to understand that using expanded criteria donors involves and additional burden.[81]

The need to clarify donor risk has led to the elaboration of multi-factorial scoring systems that use donor variables alone or in association with recipient variables. In this sense, the Donor Risk Index (DRI),[82] the SOFT scale (Survival Outcomes Following Liver Transplantation),[83] and the D-MELD (Donor-MELD)[84] stand out. Although the recent modifications of the data in the Spanish Register of Liver Transplants (RETH) will facilitate the calculation of D-MELD, we must point out that the other scoring systems are not appropriately applicable for donors in Spain, since some of the variables used in these risk scoring systems do not adjust to Spanish donors (for example: African-American racial type, or split-type transplant). The working group therefore recommends the intensification of the collaboration between the Spanish National Transplant Organisation (ONT), and RETH for the expert-coordinated elaboration of a Spanish liver donor risk index, one that is better adjusted to the characteristics inherent to our donors.

The working group does not recommend a systematic usage of liver biopsies from donors, although consensus has not been reached in the case of expanded criteria donors. The possibility of obtaining a biopsy with adequate parameters should be guaranteed in authorised donation centres, or in their absence, hospitals where the transplant will take place, in cases in which the surgical team finds this information pertinent to making the correct decision. The parameters to be measured using the liver biopsy should not be limited to graft steatosis, and the pathologist responsible should be instructed to look for the following[85]: size of the biopsy and number of portal spaces included, semi-quantitative estimation of micro- and macrovesicular steatosis, level of portal inflammation and periportal necrosis, presence of patchy lobular necrosis, presence of polymorphonuclear infiltrates, presence of bridging lobular necrosis, expansion of fibrosis expressed as the number of fibrous tracts, portal/porto-portal fibrous expansion, level of cholestasis, presence of pigments, ballooning and Mallory bodies in hepatocytes, and an evaluation of intimal narrowing of the arterioles in portal spaces in terms of original arteriole diameter.

The systematic use of expanded criteria for liver function evaluation systems (dyes such as indocyanine green, bioelectric impedance) must still be listed in the category of experimental models, since they have yet to accumulate sufficient scientific evidence in their support.[86]

Strategies for the Use of Expanded Criteria Donors

The assignment of a given donor to a certain recipient (donor matching) is the subject of much controversy. There are 3 different criteria that can be used to assess this issue: the principle of efficacy, the principle of justice, and the benefit to survival. According to the principle of efficacy, the donor must be assigned to the candidate who would theoretically have the best postoperative results, based on the quality of the donor. Recent studies in this field have shown that the combination of an expanded criteria donor with a recipient with a high MELD score is the combination that offers the worst results. However, this same type of donor paired with recipients with a lower MELD score offers high survival rates after one year. The principle of justice considers that the donor should be assigned to the candidate with the greatest need, this being the patient with the most severe clinical situation and the highest risk of death on the waiting list. According to this principle, there would be no selection process or matching, but rather a strict order of recipients based on the severity of their conditions. The prioritisation scheme for the waiting list in this second case is based on the MELD score, such that patients with higher scores should be the first to receive a transplant.[87] The third principle, the benefit of survival, is based on a function that relates the severity of the recipient's condition, and so survival on the waiting list, with post-liver transplant survival, theoretically, based on the quality of the donor. The primary advantage of this principle is that it defines those candidates in which a transplant would be futile, since the survival rate after the liver transplant would not surpass the survival on the waiting list. Applying this line of reasoning, the most severe recipients would receive a greater benefit in terms of survival from a transplant, even when assigned to expanded criteria donors (combined risks) whereas the assignment of this type of donor in patients with lower risk would notably decrease the survival value of the transplant.[88,89]

The working group did not come to a consensus regarding whether the global series results should prevail over the benefit to recipient survival, and have found advantages and disadvantages in both viewpoints, with more information needed from the practical application of the principle of benefit of survival. Even so, in those groups that currently use the MELD system in Spain, and as such do not have the possibility of matching donor and recipient, the benefit of survival criteria supports that the combination of donor–recipient risks is ethically justifiable.

In light of the recent evidence that the combination of certain donor characteristics with specific diseases in the recipient leads to worse results, we recommend not to designate these donors to other recipients. This is especially relevant in recipients with HCV, elderly donors,[6] and in some cases, grafts with severe or moderate steatosis,[90] which lead to worse results when compared to other aetiologies. In this sense, sufficient scientific evidence exists to recommend not allocating elderly donors to recipients with HCV-derived cirrhosis.

Given the evolution of cadaveric donation rates and the waiting list for liver transplants, the working group recommends: to stimulate the development of living-donor programmes and to optimise those already in effect, to promote asystolic donation, and to implement the use of normothermic perfusion machines[91,92] in donors at a high risk of damage from ischaemia/reperfusion (over the practice of ischaemic preconditioning).

However, a consensus was not reached regarding the implementation of a telephone check-list to determine donor criteria (or combination) that would lead to telephone denial of the donor, thus avoiding useless travel.

Current Magnitude of the Problem and an Analysis of its Evolution in Recent Years

An analysis of the data provided by the ONT highlighted that, although Spanish liver transplant teams have been able to adapt in recent years to the epidemiological changes that have

occurred in donors, the magnitude of the time spent on the waiting list and its associated mortality, along with the stabilisation and possible reduction of donation rates in Spain, makes the search for alternatives to conventional liver transplants an imperative task. These alternatives include living-donor liver transplant, asystolic donor transplant, and split-type transplant. The need for more development in this field is even more apparent when considering that in 2010 these alternative donors were only 6% of the total number of liver transplants performed in Spain.

The initiatives, conclusions, and recommendations from other working groups, as well as the creation of the national programme for the development of asystolic donation by the ONT, all stand out.

Quality of Liver Transplant Programmes[93,94]

Introduction

Following the SETH consensus meetings in 2005 and 2008, a series of liver transplant quality indicators were developed, which formed part of the previously published consensus documents.[1–4] In the consensus meeting held in Madrid on 18 November 2010, a working group was dedicated to the Quality and Accreditation of Liver Transplant Programmes. On this occasion, the previously proposed quality indicators were reviewed and updated, and specific quality and reference criteria to be required of a clinical unit or health professional that participates or collaborates in the process of a liver transplant.

Quality Indicators in Liver Transplants

1. Postoperative mortality in liver transplants

Definition

Percentage of transplanted patients who die within the first month or first hospitalisation following transplant.

Justification

Performance indicator that determines early post-transplant mortality and allows for focusing the aetiological study on the candidate evaluation process, the characteristics of the donor, the procedure, and recent postoperative care.

Formula/Format

Number of transplanted patients who die within the first month post-transplant/number of transplanted patients in a given period×100.

Explanation of Terms

Includes patients who die from the start of the liver transplant procedure (operating room, ICU, and hospital rooms).

Population

All patients who undergo a liver transplant.

Type

Result based on percentages.

Source of Data

Clinical documentation from the Minimum Basic Data Set (MBDS).
Computer analysis from the admissions department.
Mortality and clinical history commission for the qualitative analysis.

Standard

Less than 10%.

Comments

The periodicity of the measurement should be bi-annual.

2. Perioperative mortality

Definition

Percentage of transplanted patients who die between the start of surgery and the first 24 h following surgery.

Justification

To evaluate transplant mortality rates within the first 24 h. Aetiological study. Correlation with recipient complications (portal thrombosis, severe cardiovascular complications unknown before the transplant) in relation to all transplanted patients.

Formula/Format

Number of deaths during the first 24 h of the transplant/total number of transplants×100 during a given period.

Explanation of Terms

Includes transplanted patients who die in the operating room, reanimation, and/or ICU.

Population

All liver transplant patients.

Type

Performance indicator based on percentages

Data Source

Registries from the transplant unit at each institution.

Standard
Less than 1%
Comments

The objective is to analyse whether deaths are produced in correlation with the clinical situation of the recipient, as a consequence of unknown conditions that were not detected in the pre-transplant evaluation, or due to intra-operative complications. The periodicity will be bi-annual.

3. Early liver retransplantation rate
Definition

Percentage of liver retransplants that are indicated within the first 7 days, taken as an overall value from each transplant cohort (from cadaveric donors).
Justification

To evaluate the frequency and causes of early retransplantation. To detect the inadequate selection of recipients and donors (cadaveric) and the technical problems that lead to severe graft dysfunction.

Formula/Format

Number of liver retransplants indicated within the first week post-transplant/total number of transplants in the study × 100 in a given period of time.

Explanation of Terms

Patients who received a second liver transplant during the first week post-transplant.

Population

The entire transplanted patient cohort, excluding non-cadaveric donor transplants.

Type

Results based on percentages.

Data Source

Clinical histories, the data from each individual cohort.

Standard
Less than 5%
Comments

This could be a quality indicator for the immediate post-transplant period.
Periodicity should be bi-annual.

4. Rate of late liver retransplantation

Definition

Percentage of liver retransplants, excluding those indicated within the first week following transplant (over overall population from each transplant cohort).

Justification

To evaluate the frequency and causes of late retransplantation. To detect the long-term consequences of technical problems and medical error (inadequate protocols for immunosuppression or prophylaxis against viral recurrence).

Formula/Format

Number of liver retransplants indicated after the first week post-transplant/number of transplants in the study × 100 for a given period.

Explanation of terms

Patients who receive a second liver transplant.

Population

The entire liver transplant cohort.

Type

Results based on percentages.

Data source

Clinical histories, the data from each individual cohort.

Standard
Less than 8%
Comments

This is a post-transplant quality indicator and long-term function indicator.
Periodicity should be bi-annual.

5. Rate of early reintervention

Definition

Percentage of transplanted patients who require a second intervention during the first hospitalisation, due to complications from the first intervention.

Justification

Evaluation of the frequency of technical transplant problems and derived surgical complications. The complications and reinterventions may occur in spite of correct surgical technique.

Formula/Format

Number of transplanted patients who undergo a second intervention during the first hospitalisation/total number of transplanted patients × 100 in a given period.

Explanation of Terms

Any surgical procedure (excluding percutaneous and endoscopic techniques and all deaths that occur before the evaluated period) performed under general anaesthesia due to a complication derived from the liver transplant that appears during the first hospitalisation.

Population

All liver transplant patients.

Type

Results based on percentages.
Data source
MBDS.
Standard
Less than 10%
Comments
Bi-annual periodicity.

6. Transplant patient survival

Definition

Survival rate of transplanted patients within the study after 1, 3, 5, and 10 years following transplantation.

Justification

To evaluate whether survival results at 1, 3, 5, and 10 years post-transplant fall within published standards in order to identify problems and implement solutions in the case of deficient values.

Formula/Format

Actuarial survival curves at 1, 3, 5 and 10 years.

Explanation of Terms

Transplanted patients who are still alive after 1, 3, 5, and 10 years following the intervention. Include all deaths not related to the process.

Population

All patients who receive a liver transplant.

Type

Index-based performance indicator.

Data Source

Clinical histories of transplanted patients. Yearly databases from transplant centres. Spanish National transplant registry.

Standard

Global survival rates of 80% at one year, 75% at 3, 70% at 5 years, and 60% at 10[2].

7. Patients studied within 30 days of being referred to the Functional Liver Transplant Unit (UFTH)

Definition

Percentage of patients who have been evaluated (included or not in the waiting list after evaluation) by the liver transplant unit within 30 days from their first visit.

Justification

To evaluate the efficacy of the process of inclusion in the waiting list. The delays caused in the evaluation process of a patient are frequently due to organisational causes at the health institution or department. A reduction in delays reduces patient anxiety and facilitates better decision making.

Formula/Format

Number of patients evaluated within 30 days following the request for an appointment for transplant evaluation/number of patients sent for transplant evaluation × 100 for a given period.

Explanation of terms

Patients sent to the transplant unit in a first visit for evaluation as possible liver transplant candidates.
Time elapsed between the request for evaluation and the decision made by the transplant committee.
Number of patients who completed the decision making analysis within 30 days over the total number of patients evaluated.

Population

All patients sent to the transplant unit for evaluation and inclusion on the waiting list.

Type

Process indicator.

Data source

Clinical history analysis from patients studied by the UFTH and a review of time spans between the first visit and inclusion or not in the liver transplant waiting list.

Standard

Proportion of patients analysed within a time span equal to or less than 30 days: at least 75%.

8. Percentage of primary functional failure

Definition

Percentage of transplanted patients who develop primary graft dysfunction.

Justification

To assess the rate of primary graft dysfunction as an indicator for the level of communication, coordination, ability, and experience of surgical teams, in relation to duration of cold and hot ischaemia, quality of the liver graft, technical factors, logistics, equipment coordination, etc.

Formula/Format

Transplanted patients who develop primary graft dysfunction that causes retransplant or death/total number of transplanted patients ×100 in a given period.

Population

Transplanted patients.

Type

Performance indicator.

Data source

Transplant unit registries, clinical histories.

Standard
Less than 2%.
Comments
Measurements should be tri-annual.

9. Rate of non-transplanted livers with no justifiable objective cause

Definition

Percentage of non-implanted livers, following their acceptance, with no justifiable objective cause (ideally, there would be histological proof demonstrating why the liver cannot be used –objective cause–. We can name as a justifiable cause the presence of disorders in the organ, whether observed histologically or by the surgeon that removed the piece). Graft histology is always recommendable.

Justification

Evaluation of the adequacy of rejection rates for livers offered for transplantation based on the donor acceptance criteria in force. The objective is to detect unjustifiable rejections and to maximise the transplant options for patients on the waiting list.

Formula/Format

Number of non-implanted livers/number of implantable livers×100 in a given period.

Population

All total or partial livers with inclusion criteria for implantation.

Type

Process indicator.

Data source

Transplant unit and ONT registries.
Donor protocol. Pathological anatomy at the moment of transplantation. Analysis of causes for rejection. Evolution of rejected livers that have then been transplanted by another surgical team.

Standard
0%–1%.

10. Satisfaction of the transplanted patient

Definition

Satisfaction survey in the group of transplanted patients.

Global satisfaction level in liver transplant recipients.

Justification

To evaluate the quality perceived by transplanted patients regarding integrated care received during the liver transplant process.

Formula/Format

Overall measurement of user satisfaction after responding to each item on the survey.

Population

All transplanted patients.

Type

Performance indicator.

Data source

Analysis of surveys filled out by patients and family members.

Standard

Filling out the survey.
% Satisfied or very satisfied >80%.

Comments
Should be annual. Validate a common questionnaire and compose a survey form.

11. Mortality on the waiting list

Definition

Percentage of patients excluded from the liver transplant list due to death or disease progression.

Justification

To evaluate the quality of the management of liver transplant candidates on the waiting list.

Formula/Format

Number of patients excluded from the ONT liver transplant waiting list (due to death or disease progression)/total number of patients included on the transplant waiting list.

Population

All patients included in the waiting list.

Type

Performance indicator.

Data source

ONT liver transplant waiting list.

Standard
<15%.

Comments

Measurements should be taken annually.

12. Early post-transplant mortality with a functioning liver

Definition

Percentage of transplanted patients with adequate liver functioning who die during the post-transplant hospitalisation.

Justification

A performance indicator that monitors patient selection and allows for focusing the analysis of causes on the candidate evaluation process.

Formula/Format

Number of transplanted patients with normal liver function who die during the post-transplant hospitalisation period/number of transplanted patients × 100 in a given period.

Explanation of Terms

Includes all patients who die from the start of the liver transplant procedure (operating room, ICU, and hospital rooms).

Population

All patients receive a liver transplant.

Type

Performance indicator. Results based on percentages.

Data source
Clinical documentation from the minimum basic data set (MBDS).
Computer analysis from the admissions department.
Mortality and clinical history commission for the qualitative analysis.

Standard
<1%

Comments

The periodicity of this measurement should be annual.

13. Post-transplant mortality with a functioning liver

Definition

Percentage of patients who die with a properly functioning liver.

Justification

Performance indicator that monitors the activity and lifestyle of transplanted patients and allows for focusing the analysis on mortality with this bias.

Formula/Format

Number of transplanted patients who die with normal liver function/number of transplanted patients×100 in a given period.

Explanation of Terms

Includes patients who die from the start of the transplant procedure (operating room, ICU, hospital rooms).

Population

All patients who receive a liver transplant.

Type

Performance indicator. Based on percentages.

Data source
Clinical documentation from the MBDS.
Computer analysis from the admissions department.
Mortality and clinical history commission for the qualitative analysis.

Standard

Unknown.

Comments

The periodicity for this measurement should be annual.

Quality criteria in liver transplants

The working group for Quality and Accreditation of Liver Transplant Programmes defined a first version of the Liver Transplant Quality Criteria. Each criterion also comes with an explanatory guide and checklist, in addition to the description provided. In this document we have only shown the description of each criterion.

1. Criteria related to the documentation of the process

The health care process must be described and documented. The document, accessible and easily located, will compile the main elements needed, including the distribution of responsibilities.

1.1. Definition

The documentation of the process must specify its functional definition and limits for inclusion and exclusion. Additionally, it must define the recipients, objectives, and indicators for evaluation. Each process must have a graphical representation.

2. Responsibility criteria

There must be an official in charge of the systematic management of liver transplants and the continuous improvement of this process with the professional capacities and abilities needed for completing this mission.

3. Transplant resource criteria

3.1. Professionals

3.1.1. Liver transplantation must be supported by the human resources necessary to adequately guarantee each phase of operation. It must be staffed by adequate medical (clinical, surgical, anaesthesiological, radiological, etc.) and nursing staff both in terms of numbers and professional competence.

3.1.2. The health care professionals that participate in the different processes must have their competencies recognised.

3.2. Services

The centre must guarantee the completion of procedures necessary to the study and monitoring of patients. The centre must ensure that the necessary examinations will be completed at the centre or the institution to which services are outsourced.

3.3. Physical space resources

The centre must have access to physical space for the liver transplant as considered convenient in all hospital areas and outpatient monitoring facilities.

3.4. Diagnostic and therapeutic materials

The centre must guarantee the completion of all diagnostic and therapeutic procedures necessary to the study and monitoring of patients. The centre must ensure the completion of necessary examinations, whether at the centre itself or at the institutions to which services are outsourced.

4. Criteria for activities related to the process

The health care activities necessary for a liver transplant must be described along with their characteristics for optimal quality.

4.1. Pre-transplant evaluation

The evaluation of a liver transplant candidate must be described in the procedure for the liver transplant and should be performed such that the majority of patients are evaluated within 30 days.

4.2. Waiting list management

There should be a model for the management of a patient waiting list with well-defined criteria for patient inclusion, the order of transplantation, and the motives for exclusion. The objective of any management model is to reduce waiting list mortality.

4.3. Surgical procedure
There must be a transplant procedure that takes into account all pertinent actions that must be performed when a donor appears that is compatible with a recipient on the waiting list. There must be adequate coordination between the surgical procedures undergone by the donor and the recipient in order to reduce the ischaemia time for the graft.
4.4. Liver transplant postoperative period
The postoperative management of liver transplant recipients is essential in order to achieve good short-term survival, avoiding severe complications and treating them when they do appear in this critical time period.
4.5. Transplant patient follow-up
A good follow-up protocol following discharge from the hospital is correlated with long-term survival and will facilitate placing the survival rate within acceptable limits.
5. Protocol-related criteria
Protocols must be developed, taught, and periodically revised for the diagnosis and treatment of different conditions, to be used by health care professionals.
5.1. Protocol for the detection and treatment of cardiovascular risk factors
Each transplant centre must have an established protocol for the detection, treatment, and follow-up of cardiovascular risk factors that may appear in the post-transplant period (obesity, diabetes, hypercholesterolemia, hypertriglyceridaemia, AHT). From the sixth month post-transplant onwards.
6. Evaluation criteria
The liver transplant process must have a defined quality evaluation system. This system must include the identification and selection of indicators and define a plan for monitoring the process. This plan must at least entail the periodicity of measurements, the information collection system, and the responsibilities inherent to the monitoring system.
7. Information registration criteria
Information for an objective evaluation of the process must be measured and registered.
8. Documentation criteria
The liver transplant must be catalogued in an orderly manner that encompasses its documentation. This catalogue must be continuously updated.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Appendix 1. Participants in the III Consensus Meeting of the Spanish Society of Liver Transplantation

Group 01
Transplant in patients with liver cirrhosis due to hepatitis C virus

Coordinators

Marina Berenguer Haym	Representing AEEH
Ramón Charco Torra	Hospital Universitario Vall d'Hebron
Juan Manuel Pascasio Acevedo	Hospital Universitario Virgen del Rocío

Participants

Rafael Bañares Cañizares	Hospital General Universitario Gregorio Marañón
Fernando Casafont Morencos	Hospital Universitario Marqués de Valdecilla
Lluís Castells Fuste	Hospital Universitario Vall d'Hebron-Barcelona
Valentín Cuervas-Mons Martínez	Clínica Universitario Puerta de Hierro - Majadahonda
Manuel Delgado Blanco	Hospital Universitario Juan Canalejo
Inmaculadada Fernández Vázquez	Hospital Universitario 12 de Octubre
Félix García Pajares	Hospital Universitario Río Hortega
Antonio González Rodríguez	Hospital Universitario Nuestra Señora de la Candelaria
Sara Lorente Pérez	Hospital Clínico Universitario Lozano Blesa
Esther Molina Pérez	Hospital Clínico Universitario de Santiago
Miquel Navasa Anadon	Hospital Universitario Clínic
María Flor Nogueras López	Hospital Universitario Virgen de las Nieves
José Antonio Pons Miñano	Hospital Universitario Virgen de la Arrixaca
Juan Miguel Rodrigo López	Hospital Regional Universitario Carlos Haya
Manuel Rodríguez García	Hospital Universitario Central de Asturias
Milagros Testillano Tarrero	Hospital de Cruces
Xavier Xiol Quingles	Hospital Universitario de Bellvitge

Group 02
Living-donor liver transplant

Coordinators

Juan Carlos García-Valdecasas Salgado	Representing AEC
Paloma Jara Vega	Hospital Universitario La Paz
Fernando Pardo Sánchez	Clínica Universitaria de Navarra

Participants

Itxarone Bilbao Aguirre	Hospital Universitario Vall d'Hebron-Barcelona
Loreto Hierro Llanillo	Hospital Universitario La Paz
Rafael López Andújar	Hospital Universitario La Fe
Manuel López Santamaría	Hospital Universitario La Paz
Alejandro Manrique Municio	Hospital Universitario 12 de Octubre
Javier Nuño Vázquez-Garza	Hospital Universitario Ramón y Cajal

Group 03
Evaluation of the quality of liver grafts

Coordinators

Gloria De la Rosa	Representing the ONT
Javier Briceño Delgado	Hospital Universitario Reina Sofía
Trinidad Serrano Aullo	Hospital Clínico Universitario Lozano Blesa

Participants

José María Álamo Martínez	Hospital Universitario Virgen del Rocío
Manuel de la Mata García	Hospital Universitario Reina Sofía
José Fuster Obregón	Hospital Universitario Clínic
Manuel Gómez Gutiérrez	Hospital Universitario Juan Canalejo
Jorge Ortiz de Urbina López	Hospital de Cruces
Fernando Rotellar Sastre	Clínica Universitaria de Navarra
Belinda Sánchez Pérez	Hospital Reg. Universitario Carlos Haya

Group 04
Quality and accreditation of liver transplant programmes

Coordinators

Juan José Pérez Lázaro	Representing EASP
Gerardo Clemente Ricote	Hospital General Universitario Gregorio Marañón
Evaristo Varo Pérez	Hospital Clínico Universitario de Santiago

Participants

Juan Fabregat Prous	Hospital Universitario de Bellvitge
Agustín García Gil	Hospital Clínico Universitario Lozano Blesa
Daniel Garrote Lara	Hospital Universitario Virgen de las Nieves
Ignacio González-Pinto Arrillaga	Hospital Universitario Central de Asturias
Luis Antonio Herrera Morena	Hospital Universitario Marqués de Valdecilla
José Ignacio Herrero Santos	Clínica Universitaria de Navarra
Jorge Martínez Castro	Hospital Clínico Universitario de Santiago
David Pacheco Sánchez	Hospital Universitario Río Hortega
Martín Prieto Castillo	Hospital Universitario La Fe
Pablo Ramírez Romero	Hospital Universitario Virgen de la Arrixaca
Guillermo Solórzano Peck	Hospital Universitario Infanta Cristina
Arturo Soriano Benítez de Lugo	Hospital Universitario Nuestra Señora de la Candelaria
José Manuel Sousa Martín	Hospital Universitario Virgen del Rocío

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