ESOT TLJ3.0
TRANSPLANTATION LEARNING JOURNEY
PRAGUE, 13-15 NOV 2022

Consensus Conference Highlights

TRANSPLANTATION LEARNING JOURNEY
13–15 NOVEMBER 2022

#ESOTTLJ

Contents

About Transplantation Learning Journey (TLJ) 3.0

We are delighted to have welcomed over 250 attendees from 27 countries to TLJ 3.0 in Prague.

TLJ 3.0 was designed in line with the European Society for Organ Transplantation (ESOT) mission 'to improve outcomes for patients with terminal organ disease by means of transplantation, organ regeneration and substitution'. We now celebrate the great success of our most recent meeting, which has brought us another step closer to this goal.

TLJ 3.0 leverages two previous editions of the event and provides a platform to produce methodologically solid, consensus-based guidance documents on clinical practice to improve the care of people with transplants. This leading international event offered the scientific and transplant community a unique opportunity to discuss and build new guidelines and, together with ESOT, shape the future clinical pathway of transplantation.

Following a systematic review, nine key transplantation topics were identified for exploration and investigation at TLJ 3.0. This report focuses on three of these topics, which are highlighted below in bold:

Cardiothoracic topics

- **Machine perfusion in cardiothoracic transplantation**

Liver topics

- **Liver transplantation in patients with primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD)**
- Clinical endpoints in liver transplantation according to value-based care
- Downstaging, bridging and immunotherapy in liver transplantation for HCC

Transversal topics

- Prehabilitation for solid organ transplant candidates
- **Molecular biology testing for non-invasive diagnosis of allograft rejection**

Kidney topics

- Histopathological analysis of pre-implantation donor kidney biopsy: Redefining the role in the process of graft assessment
- The value of monitoring (subclinical) donor specific antibodies (DSAs) for kidney transplant outcomes

Pancreas topics

- Role of pancreas machine perfusion to increase the donor pool for beta-cell replacement

Experts from across the globe convened in Prague to discuss these topics, carry out evidence-based reviews and develop preliminary statements through collaboration and thorough examination. The goal was to reach a robust consensus for the transplant community by debating and finalising a series of consensus reports on these topics that can be submitted for publication. TLJ 3.0 was successful in fulfilling these aims, and the transplant community developed 21 recommendations to direct future research and clinical practice in the field.

TLJ 3.0 Conference Chair, Umberto Cillo, explained, "Throughout TLJ 3.0, there has been great atmosphere of collaboration, [and] exchange of ideas and opinions. Those with incredible expertise in the field have made presentations and have deeply engaged in the discussions, making this meeting very precious."

We would like to extend a huge thank you to everyone who joined ESOT at TLJ 3.0 and supported us on our mission to transform the world of transplantation and improve the lives of people living with transplants.

We are excited to see the impact of these newly formed consensus reports and hope they assist in guiding the future of transplantation. However, we recognise there is still a long way to go. Our work does not stop here, and we look forward to continuing to strive towards a brighter future for transplantation at many more meetings in the years to come.

Consensus methodology

The main purpose of the ESOT TLJ 3.0 Consensus Conference was to provide methodologically solid, evidence-based and best-practice clinical recommendations reflecting the latest knowledge in the field of solid organ transplantation. To support efforts to produce high-quality, evidence-based guidance documents within this field, ESOT has implemented a Guidelines Taskforce that included Umberto Cillo, Ina Jochmans, Liset Pengel, Nuria Montserrat and Nazia Selzner; coordinated by Devi May and Daniele Roppolo. This Taskforce supported the selection of key topics requiring guidelines, applied rigorous methodology around guideline development and ensured conflicts of interest between panel members were monitored.

Prior to the conference, experts in this field carried out evidence-based reviews to develop preliminary statements, with the aim of debating these to reach a consensus on the nine key topics identified. For each of the selected topics, a steering committee was created, comprising members from a range of backgrounds to enable a multidisciplinary expert discussion. For each topic, clinical questions were formulated according to the Population, Intervention, Comparator, Outcome (PICO) methodology. Following the definition of the PICO questions, literature searches were conducted, and experts proposed recommendation statements for each key question. The statements were based on the quality of evidence, and the experts suggested a strength of recommendation for each statement.

During the TLJ 3.0 conference, steering committee members, conference attendees and jury members for each topic discussed the proposed PICO questions and statements to arrive at a group opinion. Steering committee members introduced and presented their topic, provided an overview of evidence for each PICO question and presented the proposed recommendation to an extended panel and conference attendees for them to constructively discuss and provide feedback on suggested changes. The following day, the consensus recommendations underwent a jury vote, with the final result representing the consensus of experts in the field of organ transplantation. Consensus was considered achieved if the agreement rate for the statement was greater than or equal to 75%. All recommendations and consensus statements produced at TLJ 3.0 for the nine topics will be published, along with the evidence-based literature search process for each.

Each statement was marked according to the following legend:

≥75%	CONSENSUS REACHED
<75%	CONSENSUS NOT REACHED

Topic 1 – ENGAGE project

ENGAGE project: Immunomodulation and desensitisation in kidney transplantation

Topic speakers

- Olivier Thaunat (Chair), France
- Lucrezia Furian (Chair), Italy
- Fabio Vistoli, Italy
- Fritz Diekmann, Spain
- Maarten Naesens, Belgium
- Søren Schwartz Sørensen, Denmark
- Klemens Budde, Germany

Introduction and ENGAGE Phase I

The ENGAGE (EuropeaN Guidelines for the mAnagement of Graft rEcipients) project is an ESOT project that aims to capture a general global view of the current management of sensitised kidney recipients and establish a consensus on how desensitisation and immunomodulation strategies should be combined according to a patient's risk of humoral rejection.

Olivier Thaunat (France) opened the educational session at TLJ 3.0 on the ENGAGE project by providing an overview of ENGAGE Phase I, which involved stratifying the risk of humoral rejection in sensitised renal transplant candidates. Olivier explained the different assays used to explore alloimmune serological memory, detect DSA and stratify the risk of rejection. Patients with no detected DSA have a low risk of AMR, meaning transplantation is possible. However, those with CPLT-binding DSA have a very high risk of AMR, meaning transplantation is not possible. There are some patients with non CPLT-binding DSA where translation could be possible, and this formed the basis of some of the consensus statements in ENGAGE Phase II.

The risk stratification methodology, identified in ENGAGE I, was used to categorise patients in ENGAGE II and separate them into five categories according to their risk profile. Søren Schwartz Sørensen (Denmark) emphasised that the ENGAGE project's proposal for humoral risk stratification has provided a basis for methodology that can be applied in the future; this is beneficial because, until now, there has been no uniform definition of risk stratification.

It was explained at TLJ 3.0 how desensitisation and immunomodulation can increase a transplant candidate's access to transplantation, improve transplantation outcomes and decrease known DSA prior to a planned positive crossmatch transplant. Desensitisation strategies can be initiated prior to transplantation to prevent hyperacute rejection in patients with high preformed DSA levels, and the recipient's risk profile can be used to modulate induction and maintain immunosuppression to reduce the risk of AMR and graft loss. However, Fritz Diekmann (Spain) noted that desensitisation strategies do not offer the same graft survival compared with transplants in the absence of DSA and so should only be performed once alternative strategies have been exhausted. Lucrezia Furian (Italy) highlighted the current lack of evidence and need for a consensus among European experts on how desensitisation and immunomodulation strategies should be combined according to a patient's risk of humoral rejection.

ENGAGE Phase II and the Consensus Project

Lucrezia Furian introduced ENGAGE II and the Consensus Project, which discussed outcomes of ENGAGE I and contributed to a debate and consensus. A series of statements relating to clinical practice in the context of sensitised kidney transplant recipients were categorised in relation to the risk stratification proposed by ENGAGE I. The ENGAGE II working group performed a systematic data search to form and then present, discuss and vote on statements on the current management of sensitised kidney recipients; this was done using the Delphi method.

The Delphi method involves two waves of questionnaires with several statements, and panel members are asked to vote on their agreement with the statement. The questions considered risk in relation to transplantation, induction and sensitisation strategies and maintenance immunosuppression. Fabio Vistoli (Italy) highlighted that, in a low-evidence setting, reaching a consensus is an open problem and advised the use of the Delphi method as a reliable approach to measure consensus. In the ENGAGE Consensus Project, this method highlighted strengths and weaknesses in a low-evidence setting.

Following both questionnaire waves, the panellists agreed that a strategy minimising maintenance immunosuppression should be avoided in Category 4 kidney transplant candidates. Moreover, they agreed the withdrawal of steroids or lower than usual doses of CNI/MMF are appropriate in this patient category, depending on the time after transplantation, occurrence of acute rejection and side effects of immunosuppression. However, Klemens Budde (Germany) highlighted the need for more clinical trials on immunosuppression therapy due to weak evidence.

Overall, a high grade of consensus was reached among experts for 41 of 43 statements (95.3%); however, consensus was not reached for two statements relating to the use of complement inhibitors, due to insufficient evidence. Maarten Naesens (Belgium) explained that, according to the expert's opinions, complement inhibitors are not a proven prophylactic therapy to prevent rejection in any of the patient categories and should only be considered to treat AMR episodes where there is evidence of complement activation, and not as prophylaxis before rejection. During this presentation at TLJ 3.0, the speakers agreed that more clinical studies are needed for the treatment of AMR with complement inhibitors.

ENGAGE CONSENSUS

A PROJECT BY THE EUROPEAN SOCIETY FOR ORGAN TRANSPLANTATION (ESOT)

This project is possible thanks to unrestricted grants from Chiesi and Hansa Biopharma

AMR, antibody-mediated rejection; CNI, calcineurin inhibitor; DSA, donor-specific antibody; MMF, mycophenolate mofetil.

Topic 2 – Cardiothoracic

Machine perfusion in cardiothoracic transplantation

Topic chairs

- Arne Neyrinck, Belgium
- Cristiano Amarelli, Italy

Topic steering committee

Marita Dalvindt, Stephan Clark, Massimo Boffini, Clemens Aigner, Bettina Wiegmann, Julien de Wolf, Sandro Sponga, David Gomez de Antonio, Stephan Ensminger, Martin Schweiger, Irene Bello

Introduction to machine perfusion

The machine perfusion of transplantable grafts has emerged as a very promising field in both lung and heart transplantation during the last decade, TLJ 3.0 reported. This presents the potential to assess, preserve or recondition thoracic grafts prior to transplantation. This field of technology has reached a critical turning point, and TLJ 3.0 has advised a consensus is needed on future targets, priorities for development and regional differences within the field of machine perfusion.

Rutger Ploeg (United Kingdom) provided insight into the importance of a cooperative and collaborative approach when carrying out clinical trials, to encourage the involvement of a range of experts. Building a consortium, such as the COPE model, helps ensure this collaboration, and Rutger emphasised the need for all partners to work integrally with a mutually desired outcome. Arne Neyrinck (Belgium) added that a community consortium for machine perfusion could help generate and share ideas, build trust between partners and ensure clarity and clear communication. Additionally, steering committee member, Sandro Sponga (Italy), emphasised the need for the full involvement of all team members to ensure a successful ex vivo perfusion programme. Due to the time-consuming nature of perfusion, Sandro advised ensuring the individual performing the perfusion is different to the transplant surgeon.

Steering committee member, Julien de Wolf (France), provided further detail into machine perfusion within the context of ex vivo lung perfusion in France. He highlighted that machine perfusion successfully increases the graft pool, improves donor matching and expands the indications for lung transplantation. However, Julien noted that this also extends the global procedure time for lung transplantation and there is a risk of cancellation of other surgical procedures to favour this procedure. Importantly, if fewer than three procedures are completed in 1 year, cost becomes an issue; therefore, Julien highlighted the need for European countries to optimise the use of ex vivo lung perfusion and maximise the conversion rate to avoid financial issues.

Bettina Wiegman (Germany) and Irene Bello (Spain) discussed some additional pros and cons of machine perfusion in thoracic transplantation. Machine perfusion reduces time pressure for the organ retrieval team and donor team and increases the time for recipient preparation. Additionally, machine perfusion increases organ imaging performance and improves organ function, donor utilisation, donor acceptance rates and conversion rates. Moreover, machine perfusion decreases waiting times for patients, rates of hospitalisation and the need for immunosuppressive therapy. In contrast to this, some of the cons discussed included the increased salary cost for employing a perfusionist as an additional team member, the expense of the procedure compared with cold storage and the current lack of guidelines for the use of coronary angiography.

For the future of machine perfusion, Arne discussed how registries could allow for the collection of further evidence within the field. These could help sharpen the focus on quality improvement and accommodate post-marketing studies relating to the real-world application of machine perfusion and its broader clinical use. Cost effectiveness has not been included in this TLJ 3.0 consensus discussion, but Arne explained how the use of registries could provide a platform for future comparative cost effectiveness trials. He also noted that it is important in the future to define donor scores to assess donor quality and identify a clear comparator to machine perfusion and a uniform definition of death, particularly in the context of machine perfusion use with DCD donors.

Consensus outcomes

Throughout the discussion session for this topic at TLJ 3.0, the phrasing and format of each of the suggested statements was reviewed by the steering committee members. It was concluded that the use of the word ‘effective’, which had previously been included in the original versions of the statements, should be removed from the statement. This is because it was agreed this term could not be clearly defined in the context of machine perfusion and so was removed and replaced by ‘non-inferior’ or ‘safe’. Additionally, the word ‘sufficient’ was removed or amended to ‘feasible’ across the statements. Where relevant, statements were amended to include additional detail, expanded into multiple parts to improve clarity or removed entirely to instead be included in the discussion section of the official consensus document. Below is an example of how one of the original proposed statements, which was formed prior to TLJ 3.0, was amended live during discussions amongst TLJ 3.0 steering committee members to reach the final statement; this was then voted on to reach consensus.

Before ➡ The use of machine perfusion is safe and effective for heart preservation.

After ➡ **The technique of machine perfusion is safe (non-inferior) for heart preservation in transplantation.**

Members of the steering committee discussed eight PICO questions relating to the use of machine perfusion for cardiothoracic transplantation; four for the lungs and four for the heart. Arne noted the importance of keeping the heart and lung separate at this point in the consensus because, for each organ, machine perfusion will have a different impact – preservation for the heart and reconditioning or assessment for the lung. For each of the PICO questions, the chosen jury members voted on the accompanying recommendation statements to reach a consensus. The final revised PICO questions, their accompanying statements and consensus results for each can be seen below.

Lung transplantation

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 1: In lung transplantation, for which type of lung should machine ex vivo lung perfusion be performed?			
1.1: Compared with cold storage preservation, ex vivo lung perfusion is technically safe for standard donor lungs.	Moderate	Strong for	100% agree **CONSENSUS REACHED**
1.2: Compared with cold storage preservation, ex vivo lung perfusion is technically safe and might lead to increased donor utilisation in non-standard donor lungs.	Moderate	Strong for	100% agree **CONSENSUS REACHED**
2.1: Ex vivo lung perfusion is safe for re-evaluation in situations with impaired/questionable graft function in DCD/DBD grafts.	Low	Weak for	100% agree **CONSENSUS REACHED**
2.2: Ex vivo lung perfusion is safe for logistical reasons.	Low	Weak for	100% agree **CONSENSUS REACHED**
2.3: Ex vivo lung perfusion is safe for standard preservation.	Low	Weak for	70% agree **CONSENSUS NOT REACHED**
2.4: Ex vivo lung perfusion is safe for long expected ischaemic times.	Low	Weak for	100% agree **CONSENSUS REACHED**
PICO 2: In lung transplantation, which protocol/perfusate/ventilation strategy for ex vivo/ex situ lung perfusion leads to optimal outcomes?			
3: The current three major protocols (LUND/TORONTO/OCS) have been validated for clinical use.	Moderate	Strong for	100% agree **CONSENSUS REACHED**
4: Further individualisation of the ex vivo lung perfusion protocols is required.	Low	Strong for	100% agree **CONSENSUS REACHED**
5: The physiological parameters (perfusion/ventilation/gas exchange) have been sufficiently validated to accept/decline a donor lung after ex vivo lung perfusion in clinical practice.	Low	Weak for	100% agree **CONSENSUS REACHED**

Lung transplantation

Statement	Quality of evidence	Recommendation strength	Consensus
6: The assessment of the graft quality to accept/decline the donor lung using physiological parameter cannot be done using one single parameter.	Moderate	Strong for	100% agree **CONSENSUS REACHED**
PICO 3: In lung transplantation, which parameters (physiological, biomarkers) should be used to determine graft quality during ex vivo lung perfusion?			
7: The use of parameters other than the standard physiological parameters should be further developed into clinical practice to define the acceptance/decline of a pulmonary graft.	Moderate	Strong for	100% agree **CONSENSUS REACHED**
PICO 4: In lung transplantation, which recipients should benefit from a lung assessed by ex vivo lung perfusion?			
8: Currently, there is consensus on recipient criteria that might indicate the need to perform machine perfusion.	Very low	Strong for	70% agree **CONSENSUS NOT REACHED**
9: The risk/benefit ratio to transplant the recipient can justify the acceptance of questionable lungs after ex vivo lung perfusion assessment.	Low	Weak for	100% agree **CONSENSUS REACHED**

Overall, 11 (84.6%) of the 13 proposed statements reached consensus for the use of machine perfusion in lung transplantation.

For the two statements that did not reach consensus, according to the expert opinion of the steering committee, ex vivo lung perfusion cannot be considered safe for standard preservation, and they could not confirm consensus on the existence of recipient criteria that might indicate the need to perform machine perfusion.

Heart transplantation

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 1: In heart transplantation, for which type of heart should machine perfusion be performed?			
1: The technique of machine perfusion is safe (non-inferior) for heart preservation in transplantation.	Moderate	Strong for	100% agree **CONSENSUS REACHED**
2: The use of machine perfusion reduced the cold ischaemic time and, therefore, offers the possibility to prolong preservation time.	Moderate	Strong for	100% agree **CONSENSUS REACHED**
3.1: Machine perfusion is a valuable tool in DBD to re-evaluate organ viability before implantation.	Moderate	Strong for	83% agree **CONSENSUS REACHED**
3.2: Machine perfusion is a valuable tool in DCD to assess and re-evaluate organ viability before implantation.	Moderate	Strong for	100% agree **CONSENSUS REACHED**
4: Other devices for advanced graft preservation are under clinical investigation to extend the safe ischaemic time.	Low	Strong for	100% agree **CONSENSUS REACHED**
PICO 2: In heart transplantation, which protocol/perfusate/perfusion strategy for ex vivo/ ex situ heart perfusion leads to the best clinical outcomes post-transplant?			
5.1: The current machine perfusion protocol(s) have been validated for clinical use in adult recipients.	Moderate	Strong for	100% agree **CONSENSUS REACHED**
5.2: The current machine perfusion protocols are feasible for clinical use in paediatric recipients.	Moderate	Strong for	100% agree **CONSENSUS REACHED**
PICO 3: In heart transplantation, which biomarker/parameter is capable of predicting graft survival, graft function and primary non-function during ex vivo heart perfusion?			
6: Angiography is a possible tool to assess coronary arteries of the heart during machine perfusion.	Low	Strong for	100% agree **CONSENSUS REACHED**

Heart transplantation

Statement	Quality of evidence	Recommendation strength	Consensus
7: Lactate is the most commonly used parameter to assess heart preservation during machine perfusion.	Low	Strong for	100% agree **CONSENSUS REACHED**
8: Other biological/functional tools have to be developed to assess heart quality during machine perfusion.	Low	Strong for	100% agree **CONSENSUS REACHED**
PICO 4: In heart transplantation, which recipients will benefit from a heart assessed by machine perfusion?			
9: The use of machine perfusion is non-inferior to perform heart transplantation in VAD patients.	Moderate	Weak for	100% agree **CONSENSUS REACHED**
10: Currently, there is consensus on recipient criteria that might indicate the need to perform machine perfusion.	Very Low	Strong for	100% agree **CONSENSUS REACHED**

Overall, consensus was reached on all 12 proposed statements (100%) for the use of machine perfusion in heart transplantation.

COPE, Consortium for Organ Preservation in Europe; DBD, donation after brain death; DCD, donation after circulatory death; VAD, ventricular assist device.

Topic 3 – Liver

Liver transplantation in patients with primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD)

Topic chairs

- Luca Belli, Italy
- Silvio Nadalin, Germany

Topic steering committee

Marco Carbone, Chiara Mazzarelli, Andrea Della Penna, Eleonora De Martin, Annika Bergquist, Pål Dag Line, James Neuberger, Palak Trivedi

Introduction to liver transplantation in patients with PSC and IBD

In Europe, PSC is closely associated with the presence of IBD, although it is still unclear how each disease influences the pathophysiology of the other. An increased risk of colorectal cancer in IBD and PSC has also been reported. Although liver transplantation represents a standard indication in PSC, TLJ 3.0 has reported the urgent need for a consensus within this field.

Johannes R. Hov (Norway) opened the session by providing an overview of the pathophysiology of PSC and IBD. He explained how PSC is an autoimmune disease in which large bile ducts are chronically inflamed and develop stricturing, with a need for liver transplantation within 13–21 years. He added that there is a significant, yet uncertain, relationship between PSC and IBD, and many patients typically already have IBD at PSC diagnosis. He noted that, in some cases, patients may develop cancer, such as cholangiocarcinoma – a major clinical issue associated with PSC – particularly in the transplant setting. He added that colorectal cancer is more common in patients with both PSC and IBD compared with those with IBD alone. He also noted the importance of recognising that the bile ducts of these patients are not sterile and that detectable microbes within PSC bile, both before and after liver transplantation, could be a driver of disease progression.

Steering committee members, Chiara Mazzarelli (Italy) and Andrea Della Penna (Germany), presented four case studies of patients with PSC and IBD to provide a real-world representation of patients receiving liver transplants. Attendees were then asked questions relating to each case, including what they would recommend as the most appropriate type of donor, whether there are any prevention options for the recurrence of PSC, what they would recommend for preventing and treating IBD, their considerations around re-transplantation and how they would assess the appropriateness of the MELD-based allocation system. This stimulated discussion amongst attendees and encouraged them to provide their expert opinion on each of the cases presented.

Consensus outcomes

The steering committee members discussed the format and content of 18 PICO questions and their accompanying statements relating to liver transplantation for patients with PSC and IBD. Jury members voted on these statements to reach a consensus. Details of the final questions, statements and consensus results can be seen below.

Liver transplantation

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 1: Is the MELD-based allocation scheme a disadvantage in terms of waiting-list mortality for patients with PSC?			
1: MELD score should be used to give priority to PSC liver transplantation candidates, with or without IBD, until a specific metric will be available.	Low	Weak for	100% agree **CONSENSUS REACHED**
2: Because calculated MELD score doesn't reflect the severity of PSC complicated by recurrent cholangitis, refractory pruritus and persistent jaundice, these events should be considered to give priority to PSC liver transplantation candidates.	Very low	Weak for	92% agree **CONSENSUS REACHED**
PICO 2: Is liver transplantation indicated for high-grade dysplasia in suspicious strictures?			
3: Liver transplantation may be considered in people with asymptomatic PSC and high-grade biliary dysplasia confirmed by cytology or ductal histology, according to the local resources. A very strict recall policy is recommended for those on the waiting list.	Very low	Weak for	92% agree **CONSENSUS REACHED**
PICO 3: Is the MELD allocation system suitable for patients with PSC? (PAEDIATRIC)			
4: The MELD system is not suitable for paediatric patients with PSC awaiting liver transplantation.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 4: Is the prophylactic use of rotating antibiotics for recurrent cholangitis safe in view of liver transplantation?			
5: Rotating antibiotics should only be considered following multidisciplinary assessment in highly selected patients due to the risk for multidrug resistance.	Very low	Weak against	92% agree **CONSENSUS REACHED**

Liver transplantation

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 5: Is the prophylactic use of rotating antibiotic for recurrent cholangitis safe in paediatric patients on a waiting list for liver transplantation? (PAEDIATRIC)			
6: Rotating antibiotics for children with bacterial cholangitis listed for liver transplantation cannot generally be recommended.	Very low	Weak for	100% agree **CONSENSUS REACHED**
PICO 6: When should PSC patients on the waiting list be treated with biliary stents?			
7: ERCP may be considered in patients with severe symptoms (i.e. itch, bacterial cholangitis) who are likely to improve following endoscopic treatment after a multidisciplinary meeting or discussion with the liver transplant centre. Stenting should be avoided whenever possible.	Low	Weak for	100% agree **CONSENSUS REACHED**
8: Children with large duct disease and biliary obstruction listed for liver transplantation may be stented to bridge to transplantation. (PAEDIATRIC).	Very low	Weak for	93% agree **CONSENSUS REACHED**
PICO 7: Liver transplantation for PSC: duct-to-duct anastomosis versus Roux-en-Y hepaticojejunostomy?			
9: We recommend duct-to-duct anastomosis to be used as a biliary reconstruction technique in liver transplantation for PSC whenever feasible and technically possible, considering the diagnostic and therapeutical advantages of preserving a normal anatomy.	Moderate	Strong for	92% agree **CONSENSUS REACHED**
PICO 8: Do clinical outcomes differ between duct-to-duct anastomosis versus Roux-en-Y hepaticojejunostomy in paediatric liver transplant recipients who were transplanted for PSC?			
10: No recommendation can be made for the biliary anastomosis in paediatric patients undergoing liver transplantation for PSC. (PAEDIATRIC).	Very low	N/A	93% agree **CONSENSUS REACHED**

Liver transplantation

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 9: Is the use of ECD, including DCD, in PSC associated with higher rate of non-anastomotic stricture compared with other liver transplant indications?			
11: ECD grafts should be used with caution to transplant PSC patients considering risk–benefit balance because of increased risk of inferior outcome and biliary complications post-transplant.	Weak	Strong for	80% agree **CONSENSUS REACHED**
PICO 10: Is the use of ECD, including DCD in paediatric PSC recipients associated with higher rate of non-anastomotic strictures compared with other liver transplantation indications? (PAEDIATRIC).			
12: No recommendation can be made for the use of ECD (marginal donors) in paediatric patients undergoing liver transplantation for PSC.	Very low	N/A	100% agree **CONSENSUS REACHED**
PICO 11: What is the optimal immunosuppression regimen for patients transplanted for PSC?			
13: The optimal immunosuppression regimen needs to be tailored to the need of the individual liver allograft recipient and will depend on many factors, in particular the higher risk of rejection associated with recurrence of disease experience. The panel of experts agrees that in patients with PSC, avoidance of acute rejection is relevant to reduce the risk of rPSC.	High	Strong	100% agree **CONSENSUS REACHED**
14: As acute rejection is associated with rPSC, it is recommended that patients transplanted for PSC should start on triple-immunosuppression regimen based on TAC; because acute, cellular rejection may develop late after transplantation, consideration should be given to maintaining such patients on dual therapy.	Moderate	Weak	92% agree **CONSENSUS REACHED**
15: With regard to rPSC, cyclosporin is associated with a reduced risk of rPSC compared with TAC and no major difference with the choice of antimetabolite. With regard to IBD, use of TAC is associated with progression of IBD and AZT with a better outcome. Mycophenolate and TAC are associated with an increased risk of de novo IBD post-transplant and AZT with a decreased risk. Comment: Despite the marginal benefits of cyclosporin on rPSC and azathioprine on the progression of IBD, we are not recommending the protocol of switching to a cyclosporin-based regimen considering the effect on rPSC because the evidence is weak and the choice of the immunosuppressive regimen will depend on many other factors.	Weak	Weak	71% agree **CONSENSUS NOT REACHED**

Liver transplantation

Statement	Quality of evidence	Recommendation strength	Consensus
16: No recommendation can be made for providing paediatric patients liver transplanted for PSC with standard immunosuppression. (PAEDIATRIC).	Very low	N/A	100% agree **CONSENSUS REACHED**
PICO 12: What is the optimal (safety/efficacy) therapeutic approach for maintaining remission in IBD associated with PSC pre-, peri- and post-liver transplantation?			
17.1: AZT is favoured over mycophenolate post-liver transplantation as maintenance treatment for PSC-associated colitis.	Moderate	Strong	93% agree **CONSENSUS REACHED**
17.2: Anti-<4®7 therapy is recommended as the first-line biologic agent of choice to induce and/or maintain remission of PSC-colitis post-liver transplantation (any degree of inflammation).	Low	Weak	100% agree **CONSENSUS REACHED**
17.3: Anti-TNF < therapy should be used with caution in patients with recurrent acute cholangitis.	Moderate	Strong for	100% agree **CONSENSUS REACHED**
17.4: Anti-TNF-< therapy may be administered post-liver transplantation alongside CNI, provided that AZT/MMF has been stopped.	Low	Strong	100% agree **CONSENSUS REACHED**
17.5: Routine switching of TAC to CSA is not recommended to induce IBD remission.	Low	Weak	100% agree **CONSENSUS REACHED**
PICO 13: Which individuals with PSC-associated colitis should undergo (sub-total) colectomy?			
18.1: We recommend subtotal colectomy in the following situations, among patients who are fit for surgery: Resectable colorectal cancer/neoplasia where colectomy is felt to be a life-extending intervention.	High	Strong	100% agree **CONSENSUS REACHED**

Liver transplantation

Statement	Quality of evidence	Recommendation strength	Consensus
18.2: We recommend sub-total colectomy in the following situations, among patients who are fit for surgery: High-grade colonic dysplasia.	High	Strong	100% agree **CONSENSUS REACHED**
18.3: We recommend sub-total colectomy in the following situations, among patients who are fit for surgery: Low-grade dysplastic lesions with high-risk features (e.g. flat/invisible lesions).	Low	Strong	100% agree **CONSENSUS REACHED**
18.4: We recommend sub-total colectomy in the following situations, among patients who are fit for surgery: Multifocal (synchronous or metachronous) low-grade dysplastic lesions.	Low	Weak	93% agree **CONSENSUS REACHED**
18.5: We recommend sub-total colectomy in the following situations, among patients who are fit for surgery: Fulminant colitis.	High	Strong	100% agree **CONSENSUS REACHED**
18.6: We recommend sub-total colectomy in the following situations, among patients who are fit for surgery: Active colitis refractory to medical therapy.	High	Strong	100% agree **CONSENSUS REACHED**
18.7: We recommend sub-total colectomy in the following situations, among patients who are fit for surgery: Evidence of progressive liver disease (albeit well compensated) and persistent colitis despite 5-ASAs, AZTs (thiopurines) and a single biological agent.	Low	Strong	93% agree **CONSENSUS REACHED**
PICO 14: What is the optimal timing of (sub-total) colectomy?			
19: We recommend that colectomy is performed (for patients who have an indication) prior to the onset of advanced liver disease, specifically to minimise future risks of: a) Native hepatic decompensation (in patients who develop cirrhosis) b) Post-liver transplantation recurrent disease c) Graft loss post-liver transplantation	Moderate	Strong	93% agree **CONSENSUS REACHED**

Liver transplantation

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 15: How does the type of colectomy (i.e. restorative vs non-restorative/IPAA vs ileostomy alone) affect native liver outcomes?			
20: We recommend that patients undergoing sub-total colectomy retain an end ileostomy rather than undergo a restorative procedure. We do not recommend formation of an IPAA among patients with PSC-associated IBD undergoing colonic resection.	Moderate	Strong	86% agree **CONSENSUS REACHED**
21: Paediatric liver transplant recipients with PSC should undergo standard management of their underlying inflammatory bowel disease (PAEDIATRIC).	Very low	Weak for	100% agree **CONSENSUS REACHED**
PICO 16: Should liver transplant recipients for PSC/IBD be monitored with regular histological follow-up (liver and intestine) to capture the first signs of disease reactivation that could be potentially treated with experimental drugs in appropriately designed studies?			
22: A diagnosis of rPSC can be made based on progressive biliary strictures on cholangiography and/or histological findings compatible with PSC occurring >90 days after liver transplantation upon exclusion of other identifiable causes. In particular, given the rise in the usage of marginal grafts (i.e. DCD and high DRI), it is necessary to distinguish between ITBL and rPSC.	Moderate	Strong	**DELETED**
23: Patients transplanted for PSC should undergo protocol MRCP. Liver histology should be performed when clinically indicated. The use of protocol biopsies should be performed only in research protocols to investigate the onset of rPSC and test efficacy and safety of novel drugs.	Very low	Weak	**DELETED**
24: Paediatric patients transplanted for PSC should undergo regular imaging, like MRCP. Liver histology should be performed when clinically indicated. (PAEDIATRIC).	Very low	Strong for	**DELETED**

Liver transplantation

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 17: Are there criteria of futility for re-OLT?			
25: Patients with rPSC and graft failure should be offered re-transplant if expected survival is more than 50% at 5 years, considering local waiting list mortality and surgical issues.	Very low	Strong	100% agree **CONSENSUS REACHED**
PICO 18: Can we identify parameters that support the decision-making process of liver re-transplantation for PSC recurrence in paediatric patients? (PAEDIATRIC)			
26: Paediatric recipients with rPSC and graft failure should be considered for re-transplantation.	Very low	Strong for	77% agree **CONSENSUS REACHED**

Overall, three of the consensus statements (22, 23 and 24) were removed, and it was agreed these would be added to the discussion section of the final consensus document. Of the remaining 22 statements, 21 (95.7%) reached consensus for the use of liver transplantation in patients with PSC and IBD.

The steering committee could not agree on the association of cyclosporin with a reduced risk of rPSC compared with TAC or if there was any major difference with the choice of antimetabolite. In addition, they could not reach a consensus on the association of TAC with the progression of IBD and AZT, or the association of MMF and TAC with an increased risk of de novo IBD post-transplant and AZT with a decreased risk.

5-ASA, 5-aminosalicylic acid; AZT, azathioprine; CNI, calcineurin inhibitor; CSA, chronic cyclosporine; DCD, donation after circulatory death; DRI, Donor Risk Index; ECD, extended criteria donor; ERCP, endoscopic retrograde cholangiopancreatography; IBD, inflammatory bowel disease; ITBL, ischaemic-type biliary lesion; IPAA, ileal pouch anal anastomosis; MELD, Model for End-Stage Liver Disease; MMF, mycophenolate mofetil; MRCP, magnetic resonance cholangiopancreatography; OLT, orthotopic liver transplantation; PSC, primary sclerosing cholangitis; rPSC, recurrent primary sclerosing cholangitis; TAC, tacrolimus; TNF, tumour necrosis factor.

Topic 4 – Transversal

Introduction to molecular biology testing for the non-invasive diagnosis of allograft rejection

Advancements in molecular biology technology have been pivotal to the development of promising biomarkers, such as peripheral blood GEP and dd-cfDNA, for minimally invasive characterisation of allograft rejection and immunosuppression optimisation, TLJ 3.0 reported. Currently, there is no standard recommendation on the usage of this technology. TLJ 3.0 was agreed to be the best platform for a consensus on how to use these biomarkers to non-invasively diagnose rejection.

Graft function monitoring lacks sensitivity and specificity, and allograft biopsies can be considered invasive, costly and prone to sampling error, Dany Anglicheau (France) explained. In addition, the limited improvement in graft survival provides an opportunity for biomarker discovery, implementation and development, Oriol Bestard (Spain) added, and this opportunity for biomarker development provides benefits for solid organ transplantation.

Oriol described how this opportunity for biomarker utilisation can improve characterisation of the pathophysiology of a disease process and can be used as a non-invasive diagnostic tool that outperforms current approaches for early detection of tissue organ damage and/or its recovery. A predictive biomarker can identify patient subgroups who are most likely to respond to therapy, and Oriol described features of two clear groups of predictive biomarkers: 'Early, non-invasive biomarkers of graft damage' and 'biomarkers of alloimmune susceptibility'. Understanding the differences between types of biomarkers is important to underscore their clinical utility.

Early non-invasive biomarkers of graft damage

- ☑ Predictive biomarkers
- ☑ Low specificity for the disease process
- ☑ High negative predictive value for early/subclinical graft damage
- ☑ Avoid unnecessary allograft biopsies
- ☑ Used for safety monitoring of transplant evolution
- ☑ Do not predict whether a graft may be accepted when testing new therapies

  e.g. Urinary chemokines (CXCL9/10), dd-cfDNA, blood GEP

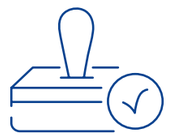
Biomarkers of alloimmune susceptibility

- ☑ Predictive biomarkers
- ☑ High specificity for the disease process
- ☑ Detect ongoing subclinical immune-mediated graft injury
- ☑ Assess the current or future alloimmune status
- ☑ Identify groups of patients who are susceptible of graft acceptance

  e.g. HLA and non-HLA DSA, cellular phenotypes and functional assays

Dany Anglicheau advised to adequately define the context of use for the biomarker, designing extensive validation studies accordingly in a multistep approach, demonstrating meaningful improvements for the patient and designing interventional, multicentre, randomised trials to add clinical value. He also highlighted key features of an ideal biomarker used to guide clinical decision-making in transplantation:

Needs to **perform better than the standard of care**



Should be **thoroughly validated**

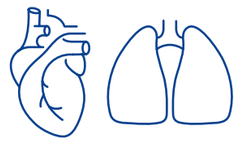
Should **not be too sophisticated** for a physician

Should **not be too expensive**

The two early non-invasive biomarkers of graft damage discussed at TLJ 3.0 – and forming the basis of most of the consensus statements – were dd-cfDNA and blood GEP. This topic on the use of biomarkers to non-invasively diagnose allograft rejection has been separated into three separate discussion topics at TLJ 3.0, depending on the organ:

Kidney
Molecular biology testing or non-invasive diagnosis of allograft rejection

Liver
Molecular biology testing for non-invasive diagnosis of allograft rejection, optimisation of immunosuppression, recurrence of hepatocellular carcinoma and recurrence of primary non-cancer disease



Heart and lung
Molecular biology testing for non-invasive diagnosis of allograft rejection

dd-cfDNA, donor derived cell-free DNA; DSA, donor-specific antibodies; GEP, gene expression profiling; HLA, human leukocyte antigen.

Topic 4.1 – Transversal

Kidney: Molecular biology testing for non-invasive diagnosis of allograft rejection

Topic chair

- John Friedewald, USA

Topic steering committee

Dany Anglicheau, Oriol Bestard, John Friedewald, Claire Tinel, Sook Park, Joana Sellarés

Consensus outcomes: Kidney

John Friedewald (USA) explained how most studies relating to kidney biomarkers have been conducted in adult patients and, therefore, the recommendation statements for the consensus session are most applicable to the adult population. He also noted that the diagnostic tests mentioned in the statements could be affected by sources of non-alloimmune inflammation, such as infections, and should be interpreted in that context.

John provided some analytical considerations for the use of dd-cfDNA, blood GEP and urine chemokines. Currently, for cfDNA, he noted that the donor-derived fraction is the standard measurement used, but some groups have advocated for using both the fraction and the total quantity of dd-cfDNA to improve the detection of clinical acute rejection. John added that there are currently three commercially available assays, and members of the steering committee recommended that further studies are needed to evaluate the available dd-cfDNA assays to cross-check the quality of these and better define their performance compared with one another.

Steering committee members strongly advocate the need for independent prospective studies using GEP for the diagnosis of exclusion of rejection to provide more robust evidence of the value of using GEP to inform the need for biopsies. Some studies have suggested that a combination of GEP and dd-cfDNA biomarkers may increase their predictive value, and John advised this should also be considered. For urine chemokine-based tests, he noted there is a link between the biomarker, the underlying pathological mechanism and the reliance on multiple measurements across different populations. The steering committee recommended further research is needed to validate the use of urinary chemokine-based tests across different platforms.

Members of the steering committee discussed six PICO questions and their accompanying statements relating to the use of these biomarkers in kidney transplant patients. Jury members voted on these statements to reach a consensus. Details of the final questions, statements and consensus results can be seen below.

Kidney transplantation

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 1: In kidney transplant patients with stable allograft function, is dd-cfDNA a reliable diagnostic tool for subclinical acute rejection monitoring compared with standard of care (eGFR/creatinine monitoring or surveillance biopsy)?			
1: We suggest that clinicians consider measuring serial plasma dd-cfDNA in patients with stable graft function to exclude the presence of subclinical antibody-mediated rejection.	Moderate	Weak for	100% agree **CONSENSUS REACHED**
PICO 2: In kidney transplant patients with acute allograft dysfunction, is dd-cfDNA a reliable diagnostic tool for acute rejection monitoring compared with standard of care (eGFR/creatinine monitoring or for cause biopsy)?			
2: We recommend that clinicians measure plasma dd-cfDNA in patients with acute graft dysfunction to exclude the presence of rejection, particularly antibody-mediated rejection.	Moderate	Moderate for	100% agree **CONSENSUS REACHED**
PICO 3: In kidney transplant patients with stable graft function, is blood GEP a reliable diagnostic tool for subclinical acute rejection monitoring compared with standard of care (eGFR/creatinine monitoring or surveillance biopsy)?			
3: We do not yet recommend implementing the use of blood GEP to diagnose or exclude the presence of subclinical rejection.	Low to moderate	Weak against	100% agree **CONSENSUS REACHED**
PICO 4: In kidney transplant patients with acute allograft dysfunction, is blood GEP a reliable diagnostic tool for clinical acute rejection monitoring compared with standard of care (eGFR/creatinine monitoring or for cause biopsy)?			
4: We do not yet recommend the use of blood GEP to diagnose or exclude the presence of acute graft rejection in patients with acute allograft dysfunction.	Low	Weak against	100% agree **CONSENSUS REACHED**

Kidney transplantation

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 5: In kidney transplant patients with acute allograft dysfunction, is urinary chemokine measurement a reliable diagnostic tool for clinical acute rejection monitoring compared with standard of care (eGFR/creatine monitoring or biopsy)?			
5: We recommend the measurement of urinary chemokines CXCL9 and CXCL10 to inform the presence or absence of clinical acute rejection (TCMR or ABMR) in patients with graft dysfunction.	Moderate	Strong for	100% agree **CONSENSUS REACHED**
PICO 6: In kidney transplant patients with stable allograft function, is urinary chemokine measurement a reliable diagnostic tool for subclinical acute rejection monitoring compared with standard of care (eGFR/creatine monitoring or surveillance biopsy)?			
6: We suggest the monitoring of a combination of CXCL9 and CXCL10 in stable patients to exclude subclinical rejection (TCMR or ABMR).	Moderate	Weak for	100% agree **CONSENSUS REACHED**

Overall, all six statements (100%) reached consensus for the use of dd-cfDNA, blood GEP and urinary chemokines as reliable, non-invasive diagnostic tools for allograft rejection in the kidney.

ABMR, antibody-mediated rejection; cfDNA, cell-free DNA; dd-cfDNA, donor derived cell-free DNA; eGFR, estimated glomerular filtration rate; GEP, gene expression profiling; TCMR, T cell-mediated rejection.

Topic 4.2 – Transversal

Liver: Molecular biology testing for non-invasive diagnosis of allograft rejection

Topic chair

- Marina Berenguer, Spain

Topic steering committee

Amelia Hessheimer, Eleonora de Martin, Valeria Mas, Josh Levitsky, Haseeb Zubair, Alina Lutu, Nabeel Wahid, Helena Hernàndez Èvole

Consensus outcomes: Liver

During the discussion, steering committee members adjusted the recommendation strength for statements. The recommendation strength for Statement 1 was originally ‘weak for’, but during the discussion, this was amended to ‘strong’ as the majority of the steering committee members agreed that, due to lack of data, additional studies were required to make a firm recommendation regarding the application of biomarkers to reliably predict or diagnose disease recurrence after liver transplantation.

Members of the steering committee discussed four PICO questions and their accompanying statements relating to the use of the previously discussed biomarkers for liver transplant patients. Jury members voted on these statements to reach a consensus. Details of the final questions, statements and consensus results can be seen below.

Liver transplantation

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 1: Can biomarkers be used to diagnose the recurrence of primary liver diseases after liver transplantation?			
1: Additional studies are needed before any recommendation can be issued regarding the application of biomarkers to reliably predict/diagnose disease recurrence after liver transplantation.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 2: Can biomarkers be used to predict chronic kidney disease in liver transplant recipients?			
2: Based on the available data, we suggest that biomarker assays may be able to help predict chronic kidney disease after liver transplantation.	Very low	Weak for	100% agree **CONSENSUS REACHED**
PICO 3: Can circulating biomarkers be used to predict HCC recurrence following liver transplantation?			
3: While preliminary studies suggest a role for circulating molecular biomarkers in the prediction of HCC recurrence, additional studies are needed before any recommendation can be issued regarding their application in clinical practice, either as predictive factors to select patients for liver transplantation or to guide post-transplant management.	Low to moderate	Weak for	100% agree **CONSENSUS REACHED**
PICO 4: Can biomarkers be used to safely wean immunosuppression (minimisation and/or full withdrawal)?			
4: Based on the available data, we suggest that biomarker assays may be able to help predict safe weaning of immunosuppression.	Moderate	Weak for	100% agree **CONSENSUS REACHED**

Overall, consensus was reached on all four statements (100%) relating to the use of biomarkers in liver transplant patients based on available data. The steering committee members agreed additional data and studies are required in the future.

HCC, hepatocellular carcinoma.

Topic 4.3 – Transversal

Heart and lung: Molecular biology testing for non-invasive diagnosis of allograft rejection

Topic chair

- Luciano Potena, Italy

Topic steering committee

Marisa Crespo Leiro, Kiran Khush, Ingvild Birschmann, Javier Segovia, Andriana Nikolova, Annamaria Minervini, Sean Agbor-Enoh, Robin Vos

Consensus outcomes: Heart and lung

During the voting session, an additional recommendation statement was proposed that applies to the methodology of using molecular biology testing to non-invasively diagnose allograft rejection in all the solid organs discussed. The statement related to ensuring each dd-cfDNA clearly provided a quality measure, such as the coefficient of variance for each clinical threshold, the limit of blank or the limit of detection, as these measures may vary across different assays. The steering committee agreed during the discussion that the statement would not be voted on, but instead, a section would be added to the final consensus document to highlight the need for this information to be made available to those using the clinical tests so they better understand how to interpret the results.

The steering committee noted that current data available for molecular biology testing for diagnosing rejection are based on centralised laboratory analyses. It was also noted that the peripheral blood GEP assay tool, AlloMap®, is not currently available in Europe.

For PICO 1 and 2, questions relating to lung transplant patients, it was suggested to specify what was meant by standard diagnostic methods; therefore, 'surveillance biopsy and surveillance lung function' were added to the PICO questions. For PICO 3 for lung transplant patients, it was noted that the standard clinical classifiers will be specified and added to the final consensus document.

For Statement 3.3 for lung transplant patients, one jury member did not agree with the statement, resulting in 75% agreement for this statement. There was discussion that this could be due to the wording of the statement in relation to the level of supporting evidence, and some members of the steering committee suggested that perhaps no recommendation could be made for this point. The steering committee agreed to amend the wording from 'For patients with respiratory viral infections, dd-cfDNA at time of infection could be used to predict subsequent risk of CLAD and/or CLAD progression' to 'For patients with respiratory viral infections, dd-cfDNA at time of infection might be used to predict subsequent risk of CLAD and/or CLAD progression'.

In total, members of the steering committee discussed four PICO questions relating to the use of biomarkers for heart transplant patients, three PICO questions for lung transplant patients and the accompanying recommendation statements for both. Jury members voted on these statements to reach a consensus. Details of the final questions, statements and consensus results can be seen below.

Heart transplantation

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 1: Are dd-cfDNA and GEP reliable methods to diagnose rejection compared with EMBs?			
1: dd-cfDNA could be used to rule out subclinical rejection (both ACR and AMR) in heart transplant recipients >28 days post-heart transplant.	Low	Weak for	100% agree **CONSENSUS REACHED**
2: Peripheral blood GEP assay (AlloMap®) is a reliable, non-invasive diagnostic tool to rule out acute cellular rejection in stable, low-risk heart transplant recipients >15 years of age who are >55 days post-heart transplant.	Moderate	Strong for	100% agree **CONSENSUS REACHED**
PICO 2: In heart transplant recipients, are GEP and dd-cfDNA reliable surveillance strategies for cardiac allograft vasculopathy?			
3: It is not currently suggested to use dd-cfDNA and GEP (AlloMap®) as surveillance strategy for cardiac allograft vasculopathy post-heart transplant.	Low	Weak against	100% agree **CONSENSUS REACHED**
PICO 3: In heart transplant patients with stable graft function, is dd-cfDNA or GEP a reliable marker to stratify prognosis compared with standard clinical classifiers?			
4: Despite several studies showing associations of dd-cfDNA or GEP with clinical events after heart transplant, we currently do not suggest their use in clinical practice to stratify prognosis.	Very low	Weak against	100% agree **CONSENSUS REACHED**
PICO 4: In heart transplant patients with stable graft function, are cardiac biomarkers (NT-proBNP, BNP, troponin) a reliable surveillance tool for subclinical acute rejection monitoring compared with endomyocardial biopsy?			
5.1: Because of conflicting data, there is not enough evidence to support the routine use of troponin for the diagnosis of acute rejection.	Very low	Weak neutral	100% agree **CONSENSUS REACHED**

Heart transplantation

Statement	Quality of evidence	Recommendation strength	Consensus
5.2: Natriuretic peptides do not appear to be reliable surveillance tools for subclinical acute rejection monitoring in stable heart transplant patients; therefore, we do not suggest their routine use in clinical practice solely for this purpose.	Very low	Weak against	100% agree **CONSENSUS REACHED**

Overall, consensus was reached on all six statements (100%) relating to the use of biomarkers in heart transplant patients.

Lung transplantation

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 1: Is dd-cfDNA a reliable marker to diagnose/monitor clinical and subclinical acute rejection or infection of the graft in lung transplant patients compared with standard diagnostic methods (surveillance biopsy and surveillance lung function)?			
1: Beyond 6 weeks of transplantation, in addition to routine clinical care, dd-cfDNA measurements could be used to rule out clinical and subclinical infection and rejection.	Very low	Weak for	100% agree **CONSENSUS REACHED**
PICO 2: Is dd-cfDNA a reliable therapeutic marker to monitor treatment response for acute rejection or infection of the graft in lung transplant patients compared with standard diagnostic methods (surveillance biopsy and surveillance lung function)?			
2: While dd-cfDNA levels generally decline after treatment for acute rejection or infection is initiated, we currently do not suggest using dd-cfDNA as an indicator of treatment response.	Very low	Weak against	100% agree **CONSENSUS REACHED**
PICO 3: Is dd-cfDNA a reliable marker to stratify prognosis of lung transplant recipients for CLAD compared with standard clinical classifiers?			
3.1: dd-cfDNA levels and trends in the early post-transplant period could be used as a predictive marker for early death and/or CLAD in lung transplant patients.	Very low	Weak for	100% agree **CONSENSUS REACHED**
3.2: In patients with primary graft dysfunction, dd-cfDNA could be used to predict subsequent risk of CLAD.	Very low	Weak for	100% agree **CONSENSUS REACHED**
3.3: For patients with respiratory viral infections, dd-cfDNA at time of infection might be used to predict subsequent risk of CLAD and/or CLAD progression.	Very low	Weak for	75% agree **CONSENSUS REACHED**

Overall, consensus was reached on all five statements (100%) relating to the use of biomarkers in lung transplant patients.

ACR, acute clinical rejection; AMR, acute microbial rejection; BNP, B-type natriuretic peptide; CLAD, chronic lung allograft dysfunction; dd-cfDNA, donor derived cell-free DNA; EMB, endomyocardial biopsy; GEP, gene expression profiling NT-proBNP, N-terminal pro B-type natriuretic peptide.

Consensus summary of the remaining topics discussed at TLJ 3.0

Liver: Clinical endpoints in liver transplantation according to value-based care

Topic chairs

- Umberto Cillo, Italy
- Mario Strazzabosco, United States

Topic steering committee

James Neuberger, Marco Carbone, Agostino Colli, Wojciech Polak, Constantino Fondevila, Anna Forsberg, Sandor Mihaly, Lorenzo Mantovani, Ian Rowe, Alessandra Nardi, Liz Schick, Karen Rockell

Current healthcare systems are still diffusely linked to a pay-per-procedure methodology. Such an approach is associated with a high risk of reducing the efficiency of the systems in achieving their value-based goals. This is particularly relevant in the context of limited resource environments, as in transplantation.

The concept of value-based healthcare has been recently proposed with the ambition of maximising outcomes achieved per resource. The implementation of value-based healthcare is particularly relevant in organ transplantation, which represents a costly procedure offered to a minority of highly selected patients with end-stage organ disease. However, there is no agreed definition of what value means (for whom) in the health context in general and in the transplantation area, including for survival and QALY.

For this session, due to the nature and the complexity of the topics treated and the substantial lack of focused evidence, with particular reference to direct comparisons between different endpoints, the analysis was not developed from PICO questions. More general research questions were formulated to produce a literature search to select relevant evidence and to draft ‘good clinical practice recommendations’.

Consensus outcomes

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 1: Which is the best single measure to evaluate the liver transplantation process as a whole from the VBC perspective? **• Gain in life years (whether QALY adjusted or not)** **• Reduction in life years lost (whether QALY adjusted or not)** **• Others**			
1: From the patient perspective, ITT (from listing) gain in life years, better if quality adjusted, seems to be the best metrics to describe the transplant process as a whole. Such a perspective may be extremely relevant for the patient in the decision process before the transplant, particularly when alternative therapeutic options are taken into consideration.	Low	Strong	100% agree **CONSENSUS REACHED**
2: From the point of view of transplant stakeholders, gain in life years, preferably quality adjusted, represents the most adopted metrics to describe the cost-effectiveness of liver transplantation as a process. Evaluate stratification for aetiology and other factors (age, sex, etc.).	Moderate	Strong	100% agree **CONSENSUS REACHED**
PICO 2: When gain in life years or reduction in years lost are not available/calculable, which is the best measure to describe the transplant process from a VBC perspective?			
3: From a patient and regulator perspective, outcomes from the point of listing (ITT survival) offer a complementary method to assess liver transplant process, taking into account multiple phases, i.e. patient selection, waiting list dynamics, allocation and acceptance of organs and transplant outcome.	Low	Strong	100% agree **CONSENSUS REACHED**
PICO 3: In liver transplant recipients, which is the best tool to adjust for quality of life in life gain of liver transplantation?			
4: Clinicians and researchers should be encouraged to use one of the generic instruments available to measure quality of life in patients with liver disease and after transplantation.	Low	Strong	100% agree **CONSENSUS REACHED**

Consensus outcomes

Statement	Quality of evidence	Recommendation strength	Consensus
5: It is recommended that the EQ5 (see appendix) instrument should be used in preference to other generic instruments. These generic instruments should be used in addition to more disease-specific HRQoL instruments, particularly in trials.	Moderate	Strong	100% agree **CONSENSUS REACHED**
6: Clinicians and researchers should be encouraged to use one of the generic instruments available to measure quality of life in patients with liver disease and after transplantation.	Low	Strong	100% agree **CONSENSUS REACHED**
PICO 4: Which are the unmet needs in defining the critical PROMs and PREMs to be included in liver transplant 'core' evaluation and clinical trial design?			
7: A core outcome set of PROMs should be co-produced with public and patient involvement (including relatives and carers), according to the phase of the transplant journey, that is relevant to both clinical trials and routine healthcare. A general framework for this development includes the following: • PROMs should include information from across the relevant health domains – physical, social and mental • Tools included in the core outcome set should include generic measures of health-related quality of life (e.g. EQ-5D), disease specific tools (e.g. Liver Disease QoL questionnaire) and patient perspective measures that include measures of illness perceptions and patient empowerment (e.g. the Brief Illness Perception Questionnaire and the Patient Empowerment Scale). Inclusion of PREMs should be considered, primarily for use in routine care, to improve the patient experience of liver transplantation across all phases of the transplant journey, with the aim of improving overall outcomes.	Low	Strong	100% agree **CONSENSUS REACHED**

Consensus outcomes

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 5: What is the most appropriate time horizon to describe liver transplant outcomes from a VBC perspective?			
8: From the patient's perspective when describing liver transplantation as a process, the time horizon of comparison should ideally be 10 years to balance urgency and utility.	Low	Weak	82% agree **CONSENSUS REACHED**
PICO 6: In a setting with optimal potential candidate referral and listing process, which is the best measure to evaluate the quality of waiting list management from a VBC perspective?			
9: In discussing the principles of waiting list management in liver transplantation from a VBC perspective, it is fundamental to underscore the importance of: • Inclusion • Diversity • Equity	High	Strong	91% agree **CONSENSUS REACHED**
10: Patient-reported experiences, including managing expectations, providing appropriate information responding to patient needs, efficient care and maintaining communication, should be assessed while patients are waiting for liver transplantation. Centres should promote PAO and their involvement in the process.	Low	Strong	100% agree **CONSENSUS REACHED**

Consensus outcomes

Statement	Quality of evidence	Recommendation strength	Consensus
11: **1.** Wait list events, including mortality, removal for deterioration, removal for improvement, temporary removal and removal for transplant, should be recorded. The yearly dropout rate referred to these metrics is of particular interest. Ideally, all these measures should be further adjusted to account for case mix at the moment of listing. The ability of the centre to accept higher risk patients should also be measured. The local system policy evaluation is relevant when considering these metrics **2.** Probability of being transplanted at 1 year from listing might provide further insights in quality assessment of wait-list management **3.** The proportion of offers that a centre declines, while another centre accepts and transplants, should be recorded representing an offer–acceptance practice metric.	Low	Strong	91% agree **CONSENSUS REACHED**
PICO 7: Which are the best metrics to describe the quality of the early postoperative course?			
12: There is no single metric available describing the quality of the early postoperative course after liver transplantation.	Low	Strong	100% agree **CONSENSUS REACHED**

Consensus outcomes

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 8: Which are the best metrics to describe the quality of the late postoperative course?			
13: There is no single metric available describing the quality of the late postoperative course after liver transplantation. It is suggested to adopt a few simple and comprehensive set of metrics describing late course after liver transplant, that are easy to capture as follows: • 5-year risk-adjusted (ITT and post-liver transplant) survival for adult elective first liver transplant • 10-year risk-adjusted (ITT and post-liver transplant) survival for adult elective first liver transplant • 5-year disease-free survival (autoimmune, viral) • 3- and 5-year disease-free survival (cancer) • Rate of chronic rejection • Rate of renal replacement therapy – days on vs long-term • Rate of new onset diabetes after liver transplant • Rate of cardiovascular events (e.g. stroke, MI) • De novo malignancies e.g. non-melanoma skin, PTLD, head and neck, lung, colorectal, breast, gastrointestinal)	Low	Strong	100% agree **CONSENSUS REACHED**

Overall, consensus was reached on all 13 statements (100%) relating to value-based care in liver transplantation.

HRQoL, heath-related quality of life; ITT, intention-to-treat; MI, myocardial infarction; PAO, patient association organisation; PREM, patient-reported experience measure; PROM, patient-reported outcome measure; PTLD, post-transplant lymphoproliferative disorder; QALY, quality-adjusted life year; QoL, quality of life; VBC; visualisation in biomedical computing.

Consensus summary of the remaining topics discussed at TLJ 3.0

Liver: Downstaging, bridging and immunotherapy in liver transplantation for HCC

Topic chair

- Christian Toso, Switzerland

Topic steering committee

Marco Claasen, Dimitri Sneiders, Gonzalo Sapisochin, Maria Reig, René Adam, Umberto Cillo, Parissa Tabrizian, Sherrie Bhoori, Constantino Fondevilla, Bastiaan Rakke

Over the past two decades, selection criteria to determine eligibility for liver transplantation have been constantly refined, but a fair allocation strategy of liver grafts to patients with HCC remains challenging. In Europe, over a dozen transplantation networks apply different liver transplantation criteria for patients with HCC. Differences sometimes even appear within countries, opening the door to medical tourism and unnecessary competition between centres.

Our aim is to reach a consensus and achieve better homogeneity between centres and networks. The main focus was on downstaging, bridging and immunotherapy.

Consensus outcomes

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 1: Should all eligible patients be transplanted after successful downstaging?			
1: All patients with HCC achieving a successful downstaging to pre-defined transplantable criteria should be considered for liver transplantation as the benefit in terms of both RFS and OS of this approach is significantly higher than any other non-transplant strategy.	High	Strong for	100% agree **CONSENSUS REACHED**
PICO 2: Should all patients outside transplant criteria (all comers) be considered for downstaging?			
2.1: All patients beyond transplant criteria, without extra-hepatic disease, nor macrovascular invasion, and otherwise a candidate should be considered for downstaging, as the original HCC state has demonstrated little impact on post-transplant survival.	Low	Strong for	93% agree **CONSENSUS REACHED**
2.2: The higher the burden of disease (based on morphology and/or biology), the less likely to achieve successful downstaging.	Moderate	Strong for	100% agree **CONSENSUS REACHED**
PICO 3: Should patients with complete response of HCC macrovascular invasion be considered for liver transplantation?			
3: There is insufficient evidence to recommend or not recommend liver transplantation for patients with HCC macrovascular invasion with complete response to therapy.	Low	N/A	**STATEMENT NOT VOTED ON**
PICO 4: Does bridging decrease waiting list dropout?			
4: There is no evidence in the current literature suggesting that bridging therapy over no bridging therapy would reduce waiting list dropout in patients listed with a tumour burden within Milan criteria, within UCSF criteria, or within ETC criteria. However, in view of disease control, waiting list dynamics and regional factors, we recommend that bridging therapy be continued in the usual way by multidisciplinary consultation.	Low	Strong for	**STATEMENT NOT VOTED ON**

Consensus outcomes

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 5: Does bridging improve post-transplant survival?			
5: There are some studies that suggest a positive effect of bridging therapy on long-term post-transplant survival. Therefore, bridging therapy should be considered in patients if feasible.	Low	Strong for	100% agree **CONSENSUS REACHED**
PICO 6: Does the type of response to bridging have an impact on survival?			
6: All patients on the waiting list with an HCC within conventional criteria should undergo locoregional bridging treatments with the aim of achieving a complete response (better if pathological). This has been shown to reduce the rate of post-transplantation tumour recurrence and, therefore, to improve post-transplant survival.	Low	Strong for	85% agree **CONSENSUS REACHED**
PICO 7: What locoregional therapy results in best short-term disease control in patients with HCC without extrahepatic disease?			
7:			
1. When feasible, liver resection, preferably by laparoscopic route and segmental extension, should be considered.	Moderate	Weak for	100% agree **CONSENSUS REACHED**
2. When technically feasible, RFA or MWA are the preferred second-line therapies and are equally effective in obtaining short-term tumour control. When ablation is not obtained or not expected to be obtained, TACE is the preferred therapy.	Moderate	Weak for	100% agree **CONSENSUS REACHED**
3. Intention to treat with combined RFA/MWA and TACE may result in superior short-term tumour control compared with TACE or RFA alone and can be used on indication	Low	Weak for	100% agree **CONSENSUS REACHED**

Consensus outcomes

Statement	Quality of evidence	Recommendation strength	Consensus
7 continued:			
4. Alternatives to TACE or RFA/MWA, including radio-embolisation or SIRT, SBRT, proton-beam radiation therapy or brachytherapy, have shown non-inferior or improved short-term tumour control in preliminary trials and should preferably be used in a research setting.	Low	Weak for	100% agree **CONSENSUS REACHED**
5. RFA or MWA is the preferred first-line therapy and are equally effective in obtaining short-term tumour control.	Moderate	Strong for	100% agree **CONSENSUS REACHED**
6. Intention-to-treat with combined ablation therapy and TACE does not impact short-term tumour control.	Low	Weak for	100% agree **CONSENSUS REACHED**
7. Liver resection, if feasible and indicated, is associated with the higher probability to obtain a complete response on the single HCC.	Low	Weak for	100% agree **CONSENSUS REACHED**
8. Downstaging therapy with TACE is preferred over bland embolisation or chemoinfusion alone.	Low	Weak for	100% agree **CONSENSUS REACHED**
9. Intention to treat with combined RFA/MWA and TACE may result in superior short-term tumour control than TACE alone and can be used on indication.	Low	Weak for	100% agree **CONSENSUS REACHED**
10. Alternatives to TACE, including radio-embolisation or SIRT, SBRT, proton-beam radiation therapy or brachytherapy, have shown non-inferior or slightly improved short-term tumour control in preliminary trials and should preferably be used in a research setting.	Low	Weak for	100% agree **CONSENSUS REACHED**
Note: The sub-statements presented will be combined into one general statement, but this statement is currently not available			
PICO 8: Are patients on immunotherapy prior to liver transplantation at higher risk of rejection?			
8: Liver transplantation in patients previously treated with immune checkpoint inhibitors has shown encouraging results in a small heterogenous cohort despite a potential risk of rejection and publication bias.	Low	N/A	**STATEMENT NOT VOTED ON**

Consensus outcomes

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 9: What is the best way to assess response to immunotherapy?			
9: Immune checkpoint inhibitors have shown some success in induction of pathologic responses in HCC. Limited data exist on the best imaging modality to assess tumour necrosis in response to therapy.	Low	N/A	**STATEMENT NOT VOTED ON**
PICO 10: What is the safety of the combined treatment with immunotherapy and locoregional therapy?			
10: Despite the limited information available, the combined treatment with immunotherapy and locoregional therapy may be safe. There are no data in the context of pre- or post-liver transplantation.	Low	Weak for	**STATEMENT NOT VOTED ON**

Overall, five statements not voted on, but consensus was reached on all of the remaining statements (100%) relating to value-based care in liver transplantation.

ETC, extended Toronto criteria; HCC, hepatocellular carcinoma; MWA, microwave ablation; OS, overall survival; RFA, radiofrequency ablation; RFS, relapse-free survival; SBRT, stereotactic body radiation therapy; SIRT, selective internal radiation therapy; TACE, trans arterial radioembolisation; UCSF, University of California San Francisco.

Consensus summary of the remaining topics discussed at TLJ 3.0

Transversal: Prehabilitation for solid organ transplant candidates

Topic chairs

- Diethard Monbaliu, Belgium
- Sharlene Greenwood, United Kingdom

Topic steering committee

Coby Annema, Stefan De Smet, Maria José Perez Saez, Joost Klaasen, Tania Januadis- Ferreira, Sunita Mathur, Pisana Ferrari, Evangelia Kouidi, Yasna Overloop, Ellen Castle

For transplant candidates, it is important to be in an optimal physical and psychological condition to be able to handle the stress of the upcoming transplant surgery and enhance recovery after transplantation. However, the health status of transplant candidates is often compromised due to disease progression, comorbidities and, in case of kidney disease, adverse effects of dialysis. This may lead to impaired physical functioning, malnutrition and an increased risk of psychological problems.

Prehabilitation, the process of enhancing overall fitness before an operation, may be beneficial for transplant candidates; however, prehabilitation before a transplant warrants a different approach because of the unknown length of the waiting list period. This requires enduring lifestyle changes that fit into the lives of transplant candidates and meet their individual needs and capabilities.

At the moment, some initiatives to establish a prehabilitation program for transplant candidates have been initiated. Within the PreCareTx study (prehabilitation of candidates for renal transplantation), scoping reviews on effective interventions regarding physical intervention, dietary management and psychosocial interventions that can be used in a home-based prehabilitation programme for transplant candidates is in progress. In order to establish guidelines for prehabilitation of transplant candidates, we can build upon the knowledge and experiences of these studies.

Consensus outcomes: Multi-modal prehabilitation

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 1: In candidates for solid organ transplantation, what is the evidence for prehabilitation interventions?			
1: We recommend that high-quality studies (preferably but not exclusively, adequately powered RCTs) with a focus on core outcome measurements and implementation are needed to evaluate the effectiveness of multi-modal prehabilitation interventions in all types of candidates for solid organ transplantation.	N/A	Strong	100% agree **CONSENSUS REACHED**
PICO 2: In candidates for solid organ transplantation, what are the outcome measures relevant to prehabilitation interventions that should be utilised in studies?			
2: In order to make progress in this field, we strongly recommend that a core outcome measurement set is defined for future multi-modal prehabilitation studies in candidates for solid organ transplantation.	N/A	Strong	100% agree **CONSENSUS REACHED**
PICO 3: In candidates for solid organ transplantation, what are the optimal characteristics of multi-modal prehabilitation interventions?			
3: We recommend that high-quality studies (preferably but not exclusively, adequately powered RCTs) are conducted to identify the optimal characteristics and mode of delivery of multi-modal prehabilitation in candidates for solid organ transplantation.	N/A	Strong	100% agree **CONSENSUS REACHED**
PICO 4: In candidates for solid organ transplantation, what is the evidence for the feasibility (enrolment, acceptability, attrition, adherence, fidelity, safety) of multi-modal prehabilitation?			
4: In candidates for solid organ transplantation, the evidence suggests that it is feasible to provide exercise, nutritional and psychosocial prehabilitation.	N/A	Strong	100% agree **CONSENSUS REACHED**

Consensus outcomes: Exercise-based prehabilitation

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 1: In candidates for solid organ transplantation, what is the evidence for exercise-based prehabilitation?			
1: We suggest that exercise-based interventions be included in the prehabilitation care of candidates for solid organ transplantation to improve cardiorespiratory fitness and/or inspiratory muscle strength.	Low	Weak	100% agree **CONSENSUS REACHED**

Consensus outcomes: Nutritional prehabilitation

PICO 1: In candidates for solid organ transplantation, what is the evidence for nutritional interventions pre-transplant?			
1: It is suggested that the use of probiotic therapy might reduce post-transplant infections in candidates for liver transplantation.	Very low	Weak	100% agree **CONSENSUS REACHED**
PICO 2: In candidates for solid organ transplantations, what type(s) of nutritional interventions are recommended in the pre-transplant phase?			
2: In candidates for solid organ transplantation who are underweight, it is suggested that nutritional interventions be utilised to achieve a target weight pre-transplant.	Very low	Weak	100% agree **CONSENSUS REACHED**
3: In candidates for solid organ transplantation who are overweight, it is suggested that nutritional interventions be utilised to achieve a target weight pre-transplant.	Very low	Weak	100% agree **CONSENSUS REACHED**

Consensus outcomes: Psychosocial prehabilitation

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 1: In candidates for solid organ transplantation, what type(s) of psychosocial interventions are recommended pre-transplant?			
1: It is suggested that cognitive behavioural therapy and psychoeducational interventions might be considered when aiming to reduce symptoms of anxiety and depression in candidates for solid organ transplantation.	Very low	Weak	100% agree **CONSENSUS REACHED**
2: In candidates for solid organ transplantation, stress-reducing interventions, such as mindfulness-based stress reduction or relaxation techniques, might be promising to reduce anxiety or stress levels.	Very low	Weak	100% agree **CONSENSUS REACHED**

Overall, consensus was reached on all statements (100%) relating to prehabilitation for solid organ transplant candidates.

RCT, randomised control trial.

Consensus summary of the remaining topics discussed at TLJ 3.0

Kidney: Histopathological analysis of pre-implantation donor kidney biopsy: Redefining the role of the process of graft assessment

Topic chairs

- Lucrezia Furian, Italy
- Gianluigi Zaza, Italy

Topic steering committee

Aiko de Vries, David Cucchiari, Lorna Marson, Michele Rossini, Jan Becker, Albino Eccher, Sandrine Florquins, Jesper Kers, Marion Rabant

Pre-implantation biopsy provides a window on the state of the renal allograft, and it is a valuable decision-making tool in transplantation (mainly in programmes from deceased ECD or high-risk recovered donors). However, although the clinical utility of this procedure is well reported, its introduction in daily clinical practice is still debated and poorly standardised. Currently, there is no consensus about several biopsy-related technical issues, and the real impact of histopathological alterations in kidney compartments as a prognostic factor in graft survival and function is not well defined. Finally, the use of this practice in DCD and the impact of the histological lesions in this clinical setting should be better defined and discussed.

Consensus outcomes

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 1: For the evaluation of chronic lesions in ECD kidneys, is needle core biopsy comparable/inferior/superior to wedge biopsy or punch biopsies in terms of representativity of the entire renal parenchyma?			
1: For the evaluation of chronic lesions in ECD kidneys, needle core biopsy and wedge or punch biopsy are both suitable, even though differences may be found in terms of glomerular and vascular assessment. Punch biopsies have potentially similar suitability, although more evidence is required.	Moderate	Strong for	100% agree **CONSENSUS REACHED**
PICO 2: For the evaluation of chronic lesions in ECD kidneys, is the frozen section comparable/inferior/superior to paraffin-embedded section in terms of the reliability of the reading from pathologists?			
2: For the evaluation of chronic lesions in ECD kidneys the frozen section is inferior to paraffin-embedded section in terms of the reliability of the reading from pathologists. Frozen sections should not be considered as a first option; however, it could be suitable for use in selected cases, like particular urgency or specific contexts.	Moderate	Weak against	100% agree **CONSENSUS REACHED**
PICO 3: For score assessment of pre-implantation kidney biopsy in the evaluation of ECD, is the experienced renal pathologist comparable/inferior/superior to the on-call pathologist in terms of reproducibility and accuracy of the histological report?			
3: For score assessment of pre-implantation kidney biopsy in the evaluation of ECD, the experienced renal pathologist is superior to the inexperienced pathologist in terms of reproducibility and accuracy for the prediction of total parenchyma status.	Moderate	Strong for	100% agree **CONSENSUS REACHED**
PICO 4: In the quantification of the chronic damage in ECD kidneys, is glomerulosclerosis more reproducible in comparison with other parameters (interstitial fibrosis, tubular atrophy, wall/lumen ratio, arteriolar hyalinosis)?			
4: In the quantification of the chronic damage in ECD kidneys, glomerulosclerosis is more reproducible in comparison with other parameters (interstitial fibrosis, tubular atrophy, wall/lumen ratio, arteriolar hyalinosis).	Low	Weak for	100% agree **CONSENSUS REACHED**

Consensus outcomes

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 5: In the quantification of the chronic damage in ECD kidneys, is measurement of histological variables with digital pathology comparable/inferior/superior compared with light microscopy?			
5: In the quantification of the chronic damage in ECD kidneys, measurement of histological variables with digital pathology is potentially comparable with light microscopy.	High	Strong for	100% agree **CONSENSUS REACHED**
PICO 6: In the quantification of the chronic damage in ECD kidneys, is measurement of histological variables with the aid of special staining (periodic-acid Schiff, silver, picro-sirius red, trichrome) comparable/inferior/superior compared with haematoxylin and eosin alone?			
6: In the quantification of chronic damage in ECD kidneys, the use of additional histochemical staining (including, but not limited to, periodic-acid Schiff, silver, trichrome and/or picro-sirius red) is superior to the use of haematoxylin and eosin alone in any diagnostic kidney pathology context but can likely not be performed under time constraints in the context of (on-call) organ utilisation decision-making.	Low	Strong for (expert opinion)	100% agree **CONSENSUS REACHED**
PICO 7: In the quantification of the chronic damage in ECD kidneys, is glomerulosclerosis percentage more representative than other parameters (interstitial fibrosis, tubular atrophy, arteriolar hyalinosis and CV score) to predict the graft survival, graft function and primary non-function?			
7: Even though no studies are available for head-to-head comparison between GS and the other parameters, the degree of GS in procurement of kidney biopsies from ECDs is associated with graft survival.	Moderate	Strong for	100% agree **CONSENSUS REACHED**

Overall, consensus was reached on all seven statements (100%) relating to pre-implantation donor kidney biopsy.

CV, clinical validity; DCD, donation after circulatory death; ECD, extended criteria donor; GS, Gleason score.

Consensus summary of the remaining topics discussed at TLJ 3.0

Kidney: The value of monitoring (subclinical) donor specific antibodies (DSAs) for kidney transplant outcomes

Topic chair

- Aiko de Vries, The Netherlands

Topic steering committee

Marie Paule Emonds, Soufian Meziyerh, Emanuele Cozzi, Dominique Bertrand, Dennis van den Broek, Klemens Budde, Anthony Dorling, Covadonga López del Moral

DSAs are associated with antibody-mediated chronic rejection and poor outcome. The value of a DSA as biomarker for ABMR diagnosis from an indication biopsy (increased creatinine and proteinuria) seems clear. However, the value of subclinical DSAs (without increase in serum creatinine or proteinuria) is less clear.

Subclinical DSAs are thought be an early biomarker of non-adherence or rejection but may also be transient around other clinical issues. The merit of detecting early rejection from routine DSA monitoring is uncertain, as are potential treatment options and changes in prognosis. Subsequently, there is clinical practice variation in routine monitoring of DSAs.

Consensus outcomes

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 1: Does late rejection pose a health problem?			
Sub-PICO: In renal transplant recipients, is late rejection a significant contributor to allograft attrition rates compared with other factors?			
1: Efforts should be made to prevent late renal allograft loss, which is one of the leading causes of ABMR.	High	Strong for	100% agree **CONSENSUS REACHED**
PICO 2: Do we understand the natural history of rejection sufficiently to identify a latent stage?			
2: Clinicians should note that DSAs are associated with a high risk for rejection, primarily ABMR, and subsequent allograft loss.	High	Strong for	100% agree **CONSENSUS REACHED**
PICO 3: Are we able to identify latent rejection through DSA screening before overt dysfunction occurs?			
Sub-PICO: In renal transplant recipients, is the development of dnDSAs or prevalence of pre-formed DSAs associated with subclinical rejection compared with those without DSAs?			
3: DSAs can signal for underlying microscopic injury, indicative of subclinical rejection (ABMR and TCMR), which can be identified through allograft biopsy.	Low	Strong for	100% agree **CONSENSUS REACHED**
4: Upon detection of dnDSAs, the pathogenicity and the impact on prognosis is currently best assessed by doing a biopsy.	Low	Strong for	100% agree **CONSENSUS REACHED**
Sub-PICO: In renal transplant recipients with subclinical DSAs, can allograft biopsy guided by DSA development/evolution identify subclinical rejection in an earlier pathological stage compared with biopsies in the event of more overt dysfunction?			
5: Development of dnDSAs can signal for subclinical TCMR.	Very low	Weak for	0% agree **CONSENSUS NOT REACHED**
6: Allograft biopsies in patients with subclinical DSAs show lower ABMR chronicity scores compared with patients with allograft dysfunction.	Very low	Weak for	23% agree **CONSENSUS NOT REACHED**

Consensus outcomes

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 4: Are current DSA testing methods suitable for DSA screening. and can certain DSA characteristics be used to further guide allograft biopsy decision-making?			
Sub-PICO: In renal transplant recipients, are current DSA assessment methods sufficient to reliably detect anti-HLA antibodies and its donor specificity?			
7: Efforts should be made to standardise testing and reporting of DSAs, including information on MFI, their plausibility and possible cross-reactive antigens/epitopes.	Moderate	Strong for	100% agree **CONSENSUS REACHED**
Sub-PICO: In renal transplant recipients with subclinical DSAs, can DSA characteristics (MFI, class, IgG subclass, complement binding ability) reliably be used to identify patients without rejection compared with allograft biopsy?			
8: Whilst post-transplant monitoring of pre-formed DSAs in patients with stable graft function might be helpful, additional clinical and laboratory parameters should also be considered when deciding if a biopsy should be performed.	Low	Weak against	100% agree **CONSENSUS REACHED**
9: DSA MFI levels or complement binding ability (C1q, C4d, C3d) should not influence decision-making regarding whether a biopsy in patients with subclinical dnDSAs should be performed.	Low	Weak against	69% agree **CONSENSUS NOT REACHED**
PICO 5: Is there a defined treatment for subclinical DSAs or subclinical rejection?			
10: We recommend optimisation of maintenance therapy, including addressing non-adherence in patients who develop subclinical dnDSAs. Additional treatment should only be considered after performing an allograft biopsy.	Low	Strong for	100% agree **CONSENSUS REACHED**

Consensus outcomes

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 6: Is there any evidence of cost-effectiveness of standardised DSA monitoring and treatment of found cases? Sub-PICO: In renal transplant recipients, has monitoring of DSAs been shown to be cost-effective compared with no monitoring?			
11: Cost-effectiveness of DSA monitoring in patients with stable graft function will depend on incidence rate of dnDSAs and, importantly, on the size effect of treatment.	Very low	Weak against	100% agree **CONSENSUS REACHED**
PICO 7: How frequent and until what time should DSA monitoring be conducted? Should monitoring be continued indefinitely? If not, until what time or event should monitoring be continued? Sub-PICO: • Is the incidence rate as a function of time post-transplant defined? • In renal transplant recipients who have developed dnDSAs, is development of additional dnDSAs associated with worse transplant outcome compared with no additional dnDSAs? • In renal transplant recipients who have developed dnDSAs, is disappearance of the dnDSAs associated with better transplant outcomes compared with persistence?			
12: Monitoring for dnDSAs during functional graft life is a continuous process and should not change upon detection of dnDSAs.	Low	Weak against	100% agree **CONSENSUS REACHED**
13: The optimal DSA monitoring scheme has not been established, but a pragmatic approach would be antibody monitoring at 3 to 6 months post-transplant and annually thereafter.	Low	Weak against	78% agree **CONSENSUS NOT REACHED**

Overall, consensus was reached on nine of the statements (69%) relating to the value of monitoring DSAs for kidney transplant outcomes.

ABMR, antibody-mediated rejection; DSA, donor-specific antibody; dnDSA, de novo donor-specific antibody; HLA, human leukocyte antigen; IgG, immunoglobin G; MFI, mean fluorescence intensity; TCMR, T-cell-mediated rejection.

Consensus summary of the remaining topics discussed at TLJ 3.0

Pancreas: Role of pancreas machine perfusion in increasing the donor pool for beta-cell replacement

Topic chair

- Joana Ferrer, Spain

Topic steering committee

Julien Branchereau, Marten A Engelse, Trevor Reichman, Vassilios Papalois, Cinthia Drachenberg, Fabio Vistoli, Steve White, Paul Johnson, Henri G. D. Leuvenink, Benoît Mesnard, Ann Etohan Ogbemudia, Franka Messner, Jason Doppenberg

As a result of donor shortage pressure, an increased number of ECDs are currently used for transplantation. For example, DBD donors of higher age and BMI, or DCD donors. Furthermore, due to this increasing scarcity of pancreases with optimal donor characteristics, islet isolation centres utilise pancreases from ECDs, which are particularly susceptible to prolonged cold ischaemia time.

The advent of hypothermic and normothermic machine perfusion as forms of preservation deemed superior to cold storage for high-risk kidney and liver donor organs have created opportunities in the field of the pancreas surgery. The discussion concerned whether such techniques, when applied to the pancreas, can increase the pool of suitable donor organs for both pancreas and islet transplantation. Recent experimental models of porcine and human ex vivo pancreatic machine perfusion appear promising. Applications of machine perfusion to the pancreas, however, need refinement, such as perfusion protocols and viability assessment tools.

Consensus outcomes

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 1: For whole pancreas transplantation, should hypothermic machine perfusion be performed at a pressure less than 30 mmHg?			
1: For whole pancreas transplantation, hypothermic machine perfusion should be performed up to a pressure of 30 mmHg.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 2: For whole pancreas transplantation, should hypothermic machine perfusion be beneficial if the duration is more than 1 hour and less than 6 hours?			
2: For whole pancreas transplantation, hypothermic machine perfusion should be performed for a duration greater than 1 hour but less than 6 hours.	Very low	Weak for	100% agree **CONSENSUS REACHED**
PICO 3: For whole pancreas transplantation, should hypothermic machine perfusate temperature be maintained at a range between 4°C and 12°C?			
3: For whole pancreas transplantation, non-oxygenated hypothermic perfusate temperature should be maintained at a temperature range between 4°C and 12°C.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 4: For whole pancreas transplantation, should hypothermic machine perfusion be performed with Belzer-MPS or IGL-1?			
4: Hypothermic machine perfusion should be performed with a colloid-based solution clinically licensed for machine use.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 5: For whole pancreas transplantation, could hypothermic machine perfusion be performed by continuous or pulsatile perfusion?			
5: For whole pancreas transplantation, hypothermic machine perfusion can be performed by either continuous or pulsatile perfusion.	Very low	Weak for	100% agree **CONSENSUS REACHED**
PICO 6: Should hypothermic machine perfusion for pancreas transplantation be performed simultaneously through the superior mesenteric artery and the splenic artery?			
6: Ex situ hypothermic machine perfusion for whole pancreas transplantation must be performed simultaneously through the superior mesenteric artery and the splenic artery.	Very low	Strong for	100% agree **CONSENSUS REACHED**

Consensus outcomes

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 7: For whole pancreas transplantation, should hypothermic machine perfusion be performed after a completed back-table preparation to reduce organ leakage?			
7: For whole pancreas transplantation a complete back-table preparation must be performed prior to hypothermic machine perfusion to reduce leakage of the perfusate.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 8: Does the decrease in resistance indices during hypothermic machine perfusion correlate with better preservation of the whole pancreas?			
8: During hypothermic machine perfusion, a decrease in resistance index may be correlated with better preservation of the whole pancreas.	Very low	Strong for	100% agree **CONSENSUS REACHED**

Consensus outcomes: Pancreas ex situ normothermic machine perfusion

PICO 1: Could ex situ normothermic machine perfusion be a method for evaluating the whole pancreas after cold preservation for whole pancreas transplantation?			
1: Preclinical studies suggest ex situ normothermic machine perfusion can be a method for evaluating the whole pancreas after cold preservation.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 2: For whole pancreas transplantation, should ex situ normothermic machine perfusion be performed at temperatures ranging from 34˚C to 37°C, with a perfusate solution containing an oxygen carrier?			
2: For whole pancreas transplantation, ex situ normothermic machine perfusion with a perfusate solution containing an oxygen carrier should be performed within a temperature range of 34–37˚C.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 3: For whole pancreas transplantation, should ex situ normothermic machine perfusion be performed at a maintenance pressure range from 25 to 50 mmHg?			
3: For whole pancreas transplantation, ex situ normothermic machine perfusion should be performed at a maintenance pressure range from 25 to 50 mmHg.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 4: For whole pancreas transplantation, does ex situ normothermic machine perfusion require a balance of pressure and flow to ensure minimal damage to the endothelium?			
4: For whole pancreas transplantation, ex situ normothermic machine perfusion requires a balance of pressure and flow to preserve the endothelium.	Very low	Strong for	100% agree **CONSENSUS REACHED**

Consensus outcomes: Pancreas ex situ normothermic machine perfusion

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 5: In ex situ normothermic machine perfusion for pancreas transplantation, does the addition of an oncotic factor to the perfusate ensure there is an oncotic pressure to minimise oedema formation?			
5: In ex situ normothermic machine perfusion for whole pancreas transplantation, addition of oncotic agents to the perfusate could help to minimise graft oedema.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 6: For whole pancreas transplantation, should ex situ normothermic machine perfusion be beneficial if the duration is more than 1 hour and less than 6 hours?			
6: For whole pancreas transplantation, ex situ normothermic machine perfusion should be performed for a duration longer than 1 hour.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 7: For whole pancreas transplantation, could ex situ normothermic machine perfusion be performed by continuous or pulsatile perfusion?			
7: For whole pancreas transplantation, ex situ normothermic machine perfusion can be performed by either continuous or pulsatile perfusion.	Very low	Weak for	100% agree **CONSENSUS REACHED**
PICO 8: In case of prolonged perfusion, does ex situ normothermic machine perfusion require the management of exocrine secretions to potentially prevent the development of tissue injury?			
8: Ex situ normothermic machine perfusion for whole pancreas transplantation requires diversion of exocrine secretions to prevent tissue injury.	Very low	Weak for	100% agree **CONSENSUS REACHED**
PICO 9: During ex situ normothermic machine perfusion for pancreas transplantation, could the endocrine function of the pancreas graft be assessed by hormone secretion tests?			
9: During ex situ normothermic machine perfusion for whole pancreas transplantation, the endocrine function of the pancreas graft can be assessed by hormone secretion tests.	Very low	Strong for	100% agree **CONSENSUS REACHED**

Consensus outcomes: Pancreas ex situ normothermic machine perfusion

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 10: During ex situ normothermic machine perfusion for pancreas transplantation, could preservation of pancreatic exocrine function be assessed by amylase and lipase levels in the perfusate?			
10: During ex situ normothermic machine perfusion for whole pancreas transplantation, amylase and lipase perfusate levels are not reliable exocrine markers for tissue viability or injury.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 11: Should ex situ normothermic machine perfusion for pancreas transplantation be performed simultaneously through the superior mesenteric artery and the splenic artery?			
11: Ex situ normothermic machine perfusion for whole pancreas transplantation must be performed simultaneously through the superior mesenteric artery and the splenic artery.	Very low	Strong for	100% agree **CONSENSUS REACHED**

Consensus outcomes: Pancreas in situ normothermic regional perfusion

PICO 1: Is in situ normothermic regional perfusion a reliable and reproducible method for donation after controlled circulatory death in the scenario of whole pancreas transplantation?			
1: In situ normothermic regional perfusion is a reliable and reproducible method for donation after controlled circulatory death in the scenario of whole pancreas transplantation.	Low	Strong for	100% agree **CONSENSUS REACHED**
PICO 2: For whole pancreas transplantation, is in situ normothermic regional perfusion in the setting of controlled DCD compatible with the procurement of liver and kidneys?			
2: For whole pancreas transplantation, in situ normothermic regional perfusion in the setting of controlled DCD is compatible with the procurement of liver and kidneys.	Strong	Strong for	100% agree **CONSENSUS REACHED**
PICO 3: For whole pancreas transplantation, is in situ normothermic regional perfusion in the setting of controlled DCD compatible with the procurement of heart and lungs?			
3: For whole pancreas transplantation, in situ normothermic regional perfusion in the setting of controlled DCD is compatible with the procurement of heart and lungs.	Very low	Strong for	100% agree **CONSENSUS REACHED**

Consensus outcomes: Pancreas in situ normothermic regional perfusion

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 4: Should post-mortem in situ normothermic regional perfusion in the setting of controlled DCD be run for a duration of 1–4 hours in the context of whole pancreas transplantation?			
4: In the context of whole pancreas transplantation, in situ normothermic regional perfusion in the setting of controlled DCD should be maintained between 1 and 4 hours.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 5: Should valid parameters (machine perfusion-monitoring flow and temperature, analytical/biochemical parameters and functional warm ischaemia time) be defined to assess the quality of the pancreatic graft before deciding the suitability/validity of the organ for whole pancreas transplant?			
5: In the context of whole pancreas transplantation after in situ normothermic regional perfusion of controlled DCD, valid assessment parameters of graft quality still need to be defined.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 6: Could in situ normothermic regional perfusion in donation in the setting of controlled DCD improve graft and patient outcomes compared with in situ cooling and rapid procurement in pancreas transplantation?			
6: For whole pancreas transplantation, in situ normothermic regional perfusion in the setting of controlled DCD might improve the graft and patient outcomes when compared with in situ cooling and rapid procurement.	Low	Weak for	100% agree **CONSENSUS REACHED**
PICO 7: Does in situ normothermic regional perfusion in the setting of controlled DCD have the potential to expand the donor pool for whole pancreas transplantation?			
7: In situ normothermic regional perfusion in the setting of controlled DCD has the potential to expand the donor pool for whole pancreas transplantation.	Low	Weak for	75% agree **CONSENSUS NOT REACHED**

Consensus outcomes: Islets ex situ hypothermic perfusion

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 1: Should ex situ hypothermic perfusion of the pancreas for islet isolation be performed in the same manner as for vascularised pancreas transplantation with regards to temperature, pressure, perfusate composition, oxygenation, duration and timing?			
1: Ex situ hypothermic perfusion of the pancreas for islet transplantation should be performed in the same manner as for whole pancreas transplantation with the addition of oxygenation.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 2: In islet transplantation, could ex situ hypothermic perfusion be used to increase cellular energy reserves, especially in donation after circulatory death procedures?			
2: In the pancreas for islet transplantation, oxygenated ex situ hypothermic perfusion could be used to increase cellular ATP levels, especially in controlled donation after circulatory death.	Low	Strong for	100% agree **CONSENSUS REACHED**
PICO 3: Could ex situ hypothermic perfusion be used to avoid night-time islet isolations?			
3: In the pancreas for islet transplantation, oxygenated ex situ hypothermic machine perfusion has the potential to prolong cold preservation times, which may be helpful for logistical considerations in islet isolation and transplantation.	Very low	Strong for	75% agree **CONSENSUS NOT REACHED**

Consensus outcomes: Islets ex situ normothermic machine perfusion

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 1: Could ex situ normothermic machine perfusion be a reliable method for evaluating whole pancreases after cold preservation in islet transplantation?			
1: Ex situ normothermic machine perfusion has the potential for evaluating the donor pancreas after cold preservation for islet transplantation.	Low	Weak for	100% agree **CONSENSUS REACHED**

Consensus outcomes: Islets ex situ normothermic machine perfusion

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 2: In islet transplantation, should ex situ machine perfusion be performed at physiologic temperature, with perfusate solution containing an oxygen carrier to sustain the metabolic activities of the cells?			
2: In the pancreas for islet transplantation, ex situ normothermic machine perfusion with a perfusate solution containing an oxygen carrier should be performed within a temperature range of 34–37˚C.	Low	Strong for	100% agree **CONSENSUS REACHED**
PICO 3: In islet transplantation, should ex situ normothermic machine perfusion be performed at a maintenance pressure range from 25 to 50 mmHg?			
3: If ex situ normothermic machine perfusion of the pancreas for islet transplantation is to be performed, it should be carried out at a maintenance pressure ranging between 25 and 50 mmHg.	Low	Weak for	100% agree **CONSENSUS REACHED**
PICO 4: In islet transplantation, does ex situ normothermic machine perfusion require a balance of pressure and flow to ensure minimal damage to the endothelium?			
4: In ex situ normothermic machine perfusion of the pancreas for islet transplantation, consideration of pressure and flow is necessary to minimise injury to the endothelium.	Low	Strong for	100% agree **CONSENSUS REACHED**
PICO 5: In ex situ normothermic machine perfusion for islet transplantation, does the addition of an oncotic factor to the perfusate ensure there is an oncotic pressure to minimise oedema formation?			
5: In ex situ normothermic machine perfusion of the pancreas for islet transplantation, the addition of oncotic agent/s to the perfusate could help to minimise graft oedema.	Low	Strong for	100% agree **CONSENSUS REACHED**
PICO 6: In islet transplantation, should ex situ normothermic machine perfusion be beneficial if the duration is more than 1 hour and less than 6 hours?			
6: Ex situ normothermic machine perfusion of the pancreas for islet transplantation should be performed for a duration longer than 1 hour.	Very low	Strong for	100% agree **CONSENSUS REACHED**

Consensus outcomes: Islets ex situ normothermic machine perfusion

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 7: In islet transplantation, could ex situ normothermic machine perfusion be performed by continuous or pulsatile perfusion?			
7: In the pancreas for islet transplantation, ex situ normothermic machine perfusion can be performed by either continuous or pulsatile perfusion.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 8: In the case of prolonged perfusion, does ex situ normothermic machine perfusion require the management of exocrine secretions to prevent the development of tissue injury?			
8: In the pancreas for islet transplantation, ex situ normothermic machine perfusion requires diversion of exocrine secretions to prevent tissue injury.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 9: During ex situ normothermic machine perfusion for islet transplantation, could the endocrine function of the pancreas graft be assessed by hormone secretion tests?			
9: During ex situ normothermic machine perfusion of the pancreas for islet transplantation, the endocrine function of the pancreas graft can be assessed by hormone secretion tests.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 10: During ex situ normothermic machine perfusion for islet transplantation, could preservation of pancreatic exocrine function be assessed by amylase and lipase levels in the perfusate?			
10: During ex situ normothermic machine perfusion of the pancreas for islet transplantation, amylase and lipase perfusate levels are not reliable exocrine markers for tissue viability or injury.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 11: Should ex situ normothermic machine perfusion for islet transplantation be performed simultaneously through the superior mesenteric artery and the splenic artery?			
11: Ex situ normothermic machine perfusion of the pancreas for islet transplantation must be performed simultaneously through the superior mesenteric artery and the splenic artery.	Very low	Strong for	100% agree **CONSENSUS REACHED**

Consensus outcomes: Islets in situ normothermic regional perfusion

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 1: Is in situ normothermic regional perfusion in the setting of controlled DCD a reliable and reproducible method for donation after controlled circulatory death in the scenario of islet transplantation?			
1: In situ normothermic regional perfusion is a reliable and reproducible method for donation after controlled circulatory death in the scenario of the pancreas for islet transplantation.	Low	Strong for	100% agree **CONSENSUS REACHED**
PICO 2: For islet transplantation, is in situ normothermic regional perfusion in the setting of controlled DCD compatible with the procurement of other abdominal organs (kidneys, liver)?			
2: In the pancreas for islet transplantation, in situ normothermic regional perfusion in the setting of controlled DCD is compatible with the procurement of liver and kidneys.	Low	Strong for	100% agree **CONSENSUS REACHED**
PICO 3: For islet transplantation, is in situ normothermic regional perfusion in the setting of controlled DCD compatible with the procurement of thoracic organs (heart, lungs)?			
3: In the pancreas for islet transplantation, in situ normothermic regional perfusion in the setting of controlled DCD is compatible with the procurement of heart and lungs.	Low	Strong for	100% agree **CONSENSUS REACHED**
PICO 4: Should post-mortem in situ normothermic regional perfusion in the setting of controlled DCD be run for a duration 1–4 hours in the context of islet transplantation?			
4: In the context of the pancreas for islet transplantation, in situ normothermic regional perfusion, in the setting of controlled DCD, should be maintained between 1 and 4 hours.	Low	Strong for	100% agree **CONSENSUS REACHED**
PICO 5: Valid parameters (machine perfusion, laboratory analysis and function warm ischaemia time) should be defined to assess the quality of the pancreatic graft before deciding the suitability/validity of the organ for islet transplant?			
5: In the context of the pancreas for islet transplantation after in situ normothermic regional perfusion of controlled DCD, valid assessment parameters of graft quality still need to be defined.	Low	Strong for	100% agree **CONSENSUS REACHED**

Consensus outcomes: Islets in situ normothermic regional perfusion

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 6: Could in situ normothermic regional perfusion in donation after circulatory death improve isolation outcomes (yield, function and viability) and post-transplantation outcomes compared with in situ cooling and rapid procurement in islet transplantation?			
6: In the pancreas for islet transplantation, in situ normothermic regional perfusion in donation after controlled DCD may improve islet isolation and transplantation outcomes compared with in situ cooling and rapid procurement.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 7: Does in situ normothermic regional perfusion in the setting of controlled DCD have the potential to expand the donor pool for islet transplantation?			
7: In situ normothermic regional perfusion in the setting of controlled DCD has the potential to expand the donor pool of pancreases for islet transplantation.	Very low	Strong for	75% agree **CONSENSUS NOT REACHED**

Consensus outcomes: Islets persufflation

PICO 1: In islet transplantation, should persufflation be performed using a humidified gaseous flow of 40% oxygen and 60% nitrogen?			
1: In the pancreas for islet transplantation, persufflation should be performed using a humidified gaseous flow of 40% oxygen.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 2: Should persufflation be performed at a temperature of 4–8°C in an organ preservation solution?			
2: In the pancreas for islet transplantation, persufflation should be performed at a temperature of 4–8°C in an organ preservation solution.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 3: Should persufflation be performed using a gaseous flow rate of 20–25 mL/h?			
3: In the pancreas for islet transplantation, persufflation should be performed using a gaseous flow ate of 20–25 mL/h.	Very low	Strong for	100% agree **CONSENSUS REACHED**

Consensus outcomes: Islets persufflation

Statement	Quality of evidence	Recommendation strength	Consensus
PICO 4: Should persufflation be performed by canulation of the superior mesenteric artery and the splenic artery and optionally the pancreaticoduodenal artery?			
4: In the pancreas for islet transplantation, persufflation can be performed by cannulation of both the superior mesenteric artery and the splenic artery, and optionally the gastroduodenal artery.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 5: Should arterial leakages be closed until the gaseous outflow is mainly venous when starting persufflation?			
5: In the pancreas for islet transplantation, before persufflation a back-table preparation must be performed to stop arterial gaseous leaks.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 6: Can persufflation be used to prevent further cold ischaemic damage for up to 24 hours?			
6: In the pancreas for islet transplantation, persufflation has the potential to prolong cold preservation up to 24 hours.	Very low	Strong for	100% agree **CONSENSUS REACHED**
PICO 7: Can persufflation be performed during organ transport or as an end-ischaemic strategy?			
7: In the pancreas for islet transplantation, persufflation can be performed during organ transport or as an end-ischaemic strategy.	Very low	Strong for	100% agree **CONSENSUS REACHED**

Overall, consensus was reached on 51 of the 54 statements (94%) relating to the role of pancreas machine perfusion in increasing the donor pool for beta-cell replacement.

ATP, adenosine triphosphate; BMI, body mass index; DBD, donation after brain death; DCD, donation after circulatory death; ECD, extended criteria donor.

The patient perspective at TLJ 3.0

As we strive to build new guidelines and shape the future clinical pathway of transplantation, ESOT recognise how important it is to hear first-hand from patients what should be done to improve the processes involved in transplantation. Therefore, at TLJ 3.0, we ensured patients were at the heart of the meeting as we understand that it is just as crucial to hear from their personal experiences as it is to hear from the experiences of transplant professionals.

We appreciate the value of enhancing the transplant patient experience through strengthening the relationship between the patient community and transplant professionals. This is why we encourage open communication and collaboration between all those involved in transplantation. TLJ 3.0 offered another opportunity to further these relationships and align more closely with our Patient Inclusion Initiative.

The increased conversation and transparency between transplant patients and transplant professionals help to improve clarity within the field as we strive to achieve increasingly tailored and personalised care for patients.

To learn about their own experiences at TLJ 3.0, here is what some of our patients and patient representatives had to say:

"My participation as a patient at ESOT TLJ 3.0 was one of the most rewarding experiences of the last period. At first, I was afraid that I would not be taken seriously enough, given the complexity of the topics covered, but from my very first speech, it was clear to me that a patient has a unique point of view that clinicians and scientists sorely need. I had the impression that there is a lot of mutual interest and that we are only at the beginning of a collaboration that will lead to important goals."

STEFANO PAVANELLO – *lung transplant recipient and President of the Lung Transplant Union of Padua*

"I had a very good experience at ESOT TLJ 3.0. In the sessions I attended, I found the topics fascinating and inspiring and felt listened to and included. It was good to see the enthusiasm for patient involvement, but also concerning to hear that public contribution in research or service improvement varies across Europe. I hope those who had not experienced public voice before will go back to their transplant units and endeavour to instigate public patient involvement in their work in future."

KAREN ROCKELL – *patient advocate and Co-Director / Patient and Public Involvement and Engagement Strategy Lead of the UK Organ Donation and Transplantation Research Network*

"For collaborative patient-centred care to be a reality, it is important that patients/patient advocates understand the perspectives of healthcare professionals and vice versa. TLJ 3.0 offered a great forum to share experiences, priorities and hopes for the future, both in the structured sessions and the informal networking opportunities. ESOT's commitment to patient engagement is real and very encouraging. I am looking forward to ESOT Congress 2023 in Athens and being part of a growing patient voice within the society."

COLIN WHITE – *President of the European Transplant and Dialysis Sports Federation and ESOT Ambassador/ European Transplant Patient Organisations representative.*

EU-TRAIN Statistical Course

On 15 November, the attendees of TLJ 3.0 were invited to attend the EU-TRAIN (EUropean TRAnsplantation and INnovation consortium: for improving diagnosis and risk stratification in kidney transplant patients) Statistical Course, which took place onsite in Prague. The course on prediction models was chaired by Alexandre Loupy and Oriol Bestard, who coordinated the session and facilitated the smooth running of the course.

Prediction models are developed to assist healthcare providers in estimating the probability or risk that a specific disease or condition is present (diagnostic models) or the likelihood that it may occur in the future (prognostic models) to inform decision-making. Detailed and clear reporting on all aspects of a prediction model is crucial to fully assess the risk of bias and the potential usefulness of the model. This statistic course aimed to provide key guidelines to ensure prediction models can be developed, validated and reported effectively.

A total of 49 professionals from different scientific areas registered for the course. The session welcomed physicians, researchers and transplant scientists from all specialities within the field, as well as patients. The wide variety of attendees aided the mission of encouraging widespread understanding of the importance of prediction models in transplantation.

Multiple examples were used throughout the course to illustrate the use of biomarker-based predictive models and molecular classifiers, which are both widely developed fields of research in transplantation.

At the start of the course, Oriol Bestard, Head of the Department of Nephrology and Kidney Transplantation at Vall d'Hebron University Hospital (HUVH), welcomed attendees and introduced Alexandre Loupy, Professor of Nephrology and Epidemiology at the Kidney Transplant Department of Necker Hospital in Paris and the Principal Investigator of EU-TRAIN. Oriol Bestard proceeded to highlight the objective of the session, which was to improve diagnosis and prognosis in solid organ transplantation through teaching on how to design, develop, validate and transparently report prediction models.

The first session was run by Silvia Pineda, Assistant Professor of Biostatistics at the Statistics and Data Science Department in University Complutense, Madrid, which focused on leveraging big data using machine learning techniques in solid organ transplantation. Silvia Pineda explained that we are now in an era of big data, which enables us to carry out extensive statistic testing in the medical field.

The key messages highlighted by Silvia Pineda included the importance of detecting which statistical problem you want to solve – which involves identifying and understanding the biological you are looking for. You can then harness this to build an accurate model and find the method that is best suited to your particular data. She also explained that machine learning approaches enable the prediction of clinical outcomes, patient responses and therapy responses as well as the discovery of novel mechanisms, novel biomarkers and therapy responses. When the number of variables is very large, machine learning techniques may help in solving statistical problems. However, it is important to remember to start off simple to eventually construct a more complex model.

Next, Marc Raynaud, Senior Scientist at the Paris Transplant Group, led the group in a talk about the development and validation of prognostic models. He took the participants through the 20 TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) guideline rules that should lead the way when we want to develop and validate a prediction model. Marc Raynaud explained that these guidelines, published in 2015, are the most complete and famous statistical guidelines for prognostic research, offering a method to homogenise report results and improve the quality of prognostic research.

20 TRIPOD rules:

1. Which outcome is to be predicted?
2. In which population?
3. What is the literature around this topic?
4. Explain the rationale for developing and validating the multivariable prediction model.
5. Which data do we have, and how many patients?
6. Do we have, or can we obtain external validation cohorts?
7. Explain the study design.
8. Explain the key study dates and the locations of centres.
9. Explain the sources of data. We need a clear definition of the predictors used and how and when they were measured.
10. Explain the eligibility criteria for the patients.
11. Provide a clear definition of the outcome and how it was assessed.
12. For missing data, what were the numbers and how were they handled?
13. Which model do we use?
14. Describe how the prediction performances were handled.
15. Describe the flow of participants and the prevalence/incidence of the outcome.
16. Describe the baseline characteristics of the patients of the development and validation cohorts.
17. Present the full prediction models with regression coefficients.
18. Present the full prediction performances of the final models.
19. Assess the prediction performances in different clinical scenarios.
20. Explain how to use the prediction model.

The final talk, titled 'Development and validation of diagnostic models', was led by Dina Zielinski, also a Senior Scientist, at the Paris Transplant group, who guided the group through the key challenges and criteria in the field. She proceeded to demonstrate how a diagnostic model should be developed based on histology, which has very low reproducibility and can make it challenging to properly assess models. She guided attendees through five key steps in the development and validation of diagnostic models, which included study design, model development, evaluating model performance, validating the model in external cohorts and transparent reporting through initiatives such as the TRIPOD rules explained in Marc Raynaud's previous session.

A Q&A took place after each session, offering attendees the opportunity to ask questions on the information presented. There was an open discussion between the speakers and attendees, allowing for increased clarity on the topic.

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Visit: **https://eu-train-project.eu/**

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- The European Liver and Intestine Transplant Association (ELITA)
- The European Pancreas and Islet Transplant Association (EPITA)
- The European Kidney Transplant Association (EKITA)
- The European Cardio Thoracic Transplant Association (ECTTA)
- The European Transplant Allied Health Professional (ETAHP)
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