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ORIGINAL ARTICLE

Optimal anesthetic conduct regarding immediate and short-term outcomes after liver transplantation – Systematic review of the literature and expert panel recommendations

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Abstract

Background: In the era of enhanced recovery after surgery, there is significant discussion regarding the impact of intraoperative anesthetic management on short-term outcomes following liver transplantation (LT), with no clear consensus in the literature.

Objectives: To identify whether or not intraoperative anesthetic management affects short-term outcomes after liver transplantation.

Data Sources: Ovid MEDLINE, Embase, Scopus, Google Scholar, and Cochrane Central.

Methods: A systematic review following PRISMA guidelines was undertaken. The systematic review was registered on PROSPERO (CRD42021239758). An international expert panel made recommendations for clinical practice using the GRADE approach.

Results: After screening, 14 studies were eligible for inclusion in this systematic review. Six were prospective randomized clinical trials, three were prospective nonrandomized clinical trials, and five were retrospective studies. These manuscripts were reviewed to look at five questions regarding anesthetic care and its impact on short term outcomes following liver transplant. After review of the literature, the quality of evidence according to the following outcomes was as follows: intraoperative and postoperative morbidity and mortality (low), early allograft dysfunction (low), and hospital and ICU length of stay (moderate).

Conclusions: For optimal short term outcomes after liver transplantation, the panel recommends the use of volatile anesthetics in preference to total intravenous anesthesia (TIVA) (Level of Evidence: Very low; Strength of Recommendation: Weak) and minimum alveolar concentration (MAC) versus bispectral index (BIS) for depth of anesthesia monitoring (Level of Evidence: Very low; Strength of Recommendation: Weak). Regarding ventilation and oxygenation, the panel recommends a restrictive oxygenation strategy targeting a PaO_2 of 70–120 mmHg (10–14 kPa), a tidal volume of 6–8 ml/kg ideal body weight (IBW), administration of positive end expiratory pressure (PEEP) tailored to patient intraoperative physiology, and recruitment maneuvers. (Level of evidence: Very low; Strength of Recommendation: Strong). Finally, the panel recommends the routine use of antiemetic prophylaxis. (Level of evidence: low; Strength of Recommendation: Strong).

KEYWORDS
bispectral index (BIS), depth of anesthesia, liver transplantation, minimum alveolar concentration (MAC), oxygen management, positive end-expiratory pressure (PEEP), total intravenous anesthesia, ventilation, volatile or inhalational anesthesia

1 | INTRODUCTION

Enhanced recovery after surgery (ERAS) programs have been developed to improve patient outcomes and recovery following surgery through improvements in the quality of peri-operative care. Anesthetic conduct during the intraoperative period is a well-recognized component of ERAS pathways.[1] Several studies have focused on understanding the importance of different components of routine anesthetic care including type, depth and monitoring of anesthesia,[2–4] and intraoperative mechanical ventilation settings.[5] Reviews as well as specific recommendations have been published for certain types of abdominal surgery.[6,7]

In this study, we provide an updated review of the literature focused on understanding the optimal anesthetic conduct regarding immediate and short-term outcomes specifically for patients undergoing liver transplantation (LT). In particular, we aim to answer the following questions:

1. Does the type of anesthesia (Total Intravenous Anesthetic (TIVA) vs. Volatile) affect immediate and short-term outcomes after liver transplantation?
2. Does the type of depth of anesthesia assessment (EEG based awareness monitoring such as Bispectral Index (BIS) vs. Minimum Alveolar Concentration (MAC)) affect immediate and short term outcomes after liver transplantation?
3. Does a liberal versus restrictive O2 management affect immediate and short-term outcomes after liver transplantation?
4. Do intraoperative ventilation strategies (positive end-expiratory pressure (PEEP), tidal volumes, recruitment maneuvres) affect immediate and short-term outcomes after liver transplantation?
5. Does antiemetic prophylaxis affect immediate and short-term outcomes after liver transplantation?

Based on the findings of this literature review, we provide expert panel recommendations for the optimal anesthetic conduct in patients undergoing liver transplantation.

This work was conducted in preparation for the ILTS – ERAS4OLT.org Consensus Conference on Enhanced Recovery for Liver Transplantation, January 2022, Valencia, Spain.

2 | METHODS

2.1 | Protocol and registration

The PROSPERO protocol ID is CRD42021239758.

2.2 | Eligibility criteria

The population being studied in this review was adults with end-stage liver disease who were listed for and underwent deceased donor orthotropic liver transplantation. Split-livers and patients undergoing living donor liver transplantation were excluded. The interventions and controls being studied include: TIVA versus volatile anesthesia, depth of anesthesia assessment using BIS versus MAC, liberal versus restrictive oxygen administration, use of intraoperative ventilatory strategies such as low tidal volume ventilation, PEEP, and recruitment manoeuvres, and use or avoidance of antiemetic prophylaxis.

2.3 | Information sources and search

The following bibliographic databases were searched: Ovid MEDLINE, Embase, Scopus, Google Scholar, Clinical.Trials.gov and the Cochrane

Central Register of Controlled Trials. Any study published prior to March 7, 2021 was eligible for inclusion. There were no language limitations. Studies reporting on pediatric populations as well as case reports or conference abstracts were excluded. The search strategy involved searching the terms liver or hepatic and transplantation with the following keywords: (1) total intravenous and anesthesia or anesthesia, (2) TIVA, propofol, isoflurane, sevoflurane, desflurane, fentanyl, remifentanil, sufentanil, volatile, inhalational (3) depth of anesthesia, bispectral index, BIS, minimum alveolar concentration, minimal alveolar concentration, and (4) oxygen management, ventilation, end-tidal concentration, positive end-expiratory pressure, PEEP. The search was performed by expert University of Zurich librarians and Junior Research Committee members.

2.4 | Study selection

Types of studies that were reviewed include both comparative and single cohort studies, retrospective or prospective, describing outcomes in patients that received different anesthetics conducts during liver transplantation.

2.5 | Quality of studies and recommendations grading

The "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) approach was used for grading quality of evidence and strength of recommendations.[8] The GRADE system was designed to provide a comprehensive and structured approach to rating the quality of evidence (QOE) for systematic reviews, and to grade the strength of recommendations for development of guidelines in health care. We applied the modified GRADE approach for QOE assessment derived from systematic reviews using estimates summarized narratively.[9] The QOE was rated separately for each outcome. The direction and strength of recommendation was assessed individually by all authors and disagreements resolved by consensus.[10,11]

3 | RESULTS

3.1 | Study selection

Initial search of the databases revealed 3374 records, which was reduced to 1670 after duplicates were removed. After screening for eligibility, 23 records remained, with nine excluded due to lack of outcome data, lack of data regarding operative data, studies related to living donors rather than recipients, or being a case presentation or abstract. This resulted in 14 records which were taken forward for analysis (Figure 1).

3.2 | Study characteristics

The characteristics of the included studies are available in Table 1.

3.3 | Results of individual studies

The outcomes of the included studies are listed in Table 2.

3.4 | Quality of evidence

After review of the literature, we assessed its quality based on the questions presented in the introductions with specific focus at the following short-term outcomes: intraoperative morbidity and mortality, postoperative morbidity and mortality, early allograft dysfunction, length of intensive care unit (ICU) and hospital stay.

The summary of findings for the main outcomes, including the quality of evidence (QOE) assessment according to the GRADE approach are summarized in Table 3.

3.5 | Recommendations

Despite moderate to low QOE across the main outcomes, the expert working group issued the following recommendations for optimal short-term outcomes following LT (Table 4 for evidence framework):

1. The use of volatile anesthesia with consideration of TIVA in patients at risk of, or with raised intracranial pressure.
2. The use of MAC rather than EEG based awareness monitoring such as BIS to measure depth of anesthesia during LT when using volatile agents.
3. A restrictive oxygen strategy titrated to PaO_2 70–110 mmHg (10–14 kPa).
4. Ventilatory strategies: tidal volumes 6–8 ml/kg IBW, PEEP titrated to patient physiology, recruitment maneuvres.
5. The routine use of antiemetic prophylaxis.

4 | DISCUSSION

This systematic review focuses on establishing the literature and expert panel opinion supporting intraoperative anesthesia technique and its association with intermediate and short term outcomes after LT.

When comparing the use of TIVA versus volatile in LT, one study showed a faster wake-up time with Propofol versus Desflurane, but no other outcome impact.[18] An additional study showed a lower

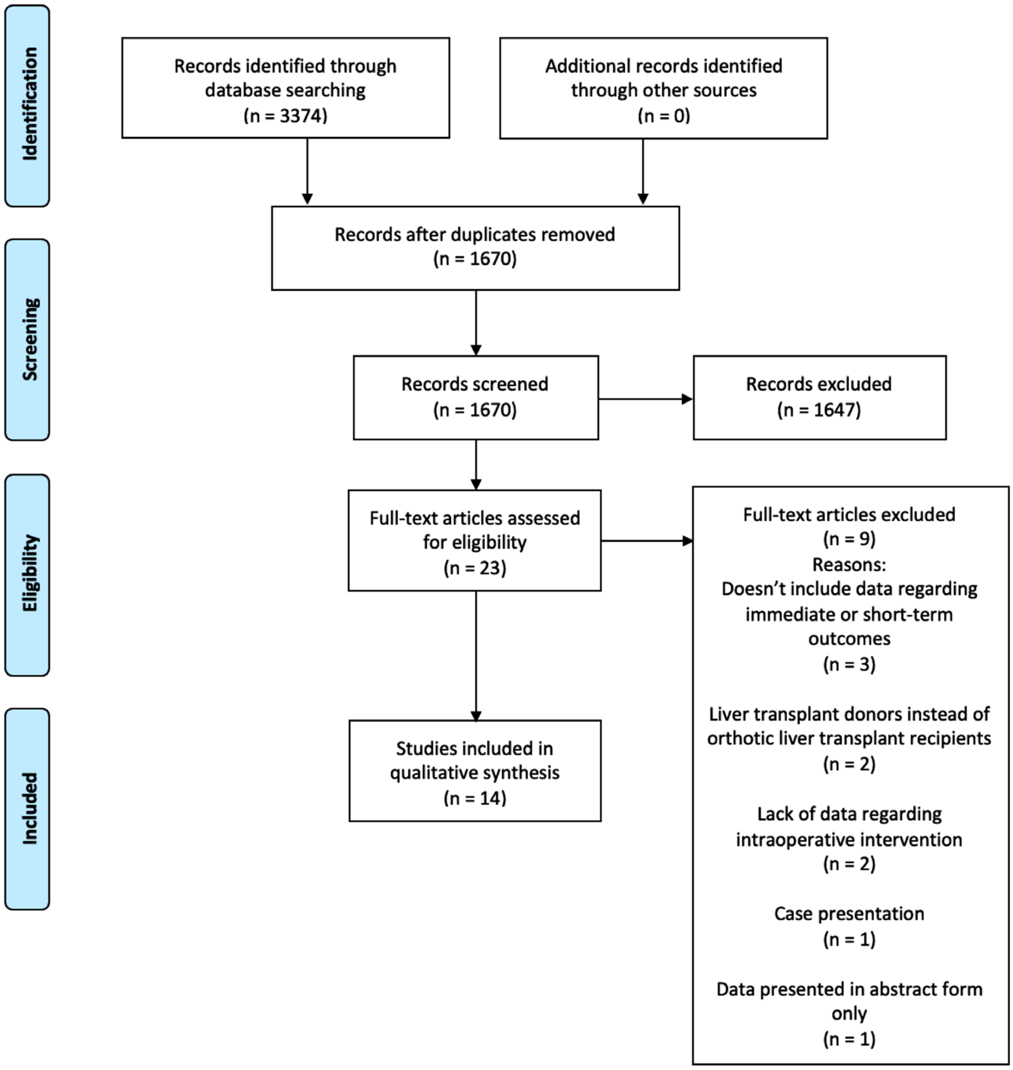

FIGURE 1 Study flow diagram

postreperfusion MDA (marker of ischemic reperfusion injury) levels in the Propofol versus the non-Propofol groups, but no other effects on hemodynamics.[23] Propofol may also be beneficial in the acute liver failure, acute on chronic liver failure, or other transplant populations at risk for increased ICP.[30] Conversely, the panel noted the impact of hepatic and renal function on Propofol metabolism. Although there are no studies specific to LT, the increased cost of certain volatile agents coupled with their negative environmental impact due to increased greenhouse gas emissions is well known.[31]

Based on this information reviewed, the panel can make a weak recommendation supporting the use of volatile anesthesia, with a secondary recommendation to consider total intravenous anesthetics in populations at risk for increased ICP. There is no recommendation regarding the use of a particular volatile anesthetic as the panel feels appropriate intraoperative utilization can be left to the provider.

In the comparison of EEG based monitors versus MAC as a marker of anesthetic depth, one paper showed no difference in incidence of postoperative cognitive dysfunction when utilizing BIS versus control[13]; one reference assessed BIS versus MAC in patients with hepatic encephalopathy, however no difference in time to return of consciousness was found.[22] While there are some referenced potential benefits to EEG based anesthetic depth monitoring in the surgical population[26] its practice may be limited by availability and cost internationally. It should be noted as well that EEG awareness monitoring is not a standard monitor as recommended by the American Society of Anesthesiologists.[32] It is the opinion of this panel for a weak recommendation supporting MAC utilization over EEG based anesthetic depth monitoring.

There is also no evidence in the liver transplant literature reviewed regarding liberal versus restrictive O_2 use, specific ventilatory strategies, and antiemetic prophylaxis. However, the panel felt despite the lack of evidence, strong recommendations could be made in these specific domains based on established literature from other surgical arenas. Regarding the use of liberal versus restrictive O_2 use in

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TABLE 1 Study characteristics

Author, year (Reference)	Study type	Number of participantsinclusion and exclusion criteria	Main outcomes assessed
Najafi et al. (2019)[12]	Single-center, randomized	78 Propofol: 39 Sevoflurane: 39	• Hemodynamic parameters, coagulation, hepatic and renal function
Cao et al. (2017)[13]	Combined prospective and retrospective case control	60 EEG based awareness monitoring (BIS): 33 Control: 27	• incidence of POCD Day 7 post LT
Beck-Schimmer et al. (2015)[14]	Multi-center, double-blinded, randomized	98 Propofol: 48 Sevoflurane: 50	• Peak postop AST • EAD • In-hospital complications • Hospital and ICU LOS Secondary outcomes: postop ALT, early allograft dysfunction (INR > / = 1.6, ALT > 2000, bilirubin > / = 10 mg/dl at day 7 post-LT), in-hospital complications (Clavien-Dindo complication score), ICU length of stay, hospital length of stay
Gucyetmez (2016)[15]	Single center, randomized, blinded	70 Control: 35 Treatment group: 35	• Postoperative tramadol requirements • ICU and hospital LOS
Gajate Martin (2016)[16]	Single center, retrospective	201 Propofol: 143 Sevoflurane: 58	• Primary graft dysfunction
Ali Sahmeddini (2012)[17]	Single center, randomized, blinded	40 Norepinephrine: 20 Acupuncture: 20	• Haemodynamic parameters
Ali Sahmeddini, 2012	Randomized blinded unicentric 20 acupunture 20 NE	40	MAP in hepatectomy-anhepatic-neohepatic
Lu (2016)[18]	Single center, retrospective	111 total patients TIVA: 66 Desflurane: 45	• Haemodynamic parameters • Extubation time • INR, ALT 24 h • Hospital and ICU LOS.
Mangus (2018)[19]	Single-center retrospective study	1291 total cases Isoflurane: 797 Desflurane: 102 Sevoflurane: 392	• IRI • ALT and bilirubin up to Day7 • Peri-operative mortality and graft loss • 1-year mortality ad graft survival • EAD • Hospital LOS
Toprak (2011)[20]	Single center, prospective, non-randomized,	50 patients	Primary outcome: End-tidal Isoflurane concentration at the 3 phases of LT • Haemodynamic parameters
Pan (2016)[21]	Single center, prospective, non-randomized, un-blinded	53 patients MELD < 9: 32 MELD > 10: 21	• Haemodynamic parameters • Haemodynamic instability

(Continues)

TABLE 1 (Continued)

Author, year (Reference)	Study type	Number of participantsinclusion and exclusion criteria	Main outcomes assessed
Kim (2019)[22]	Single center, retrospective, observational	64 Non-severe HE, Grade 1-2): 26 Severe HE, Grade 3-4: 38	• Postop recovery of consciousness
Tsai (2012)[23]	Single center, prospective, randomized, unblinded	20 Control: 10 Propofol group: 10	• IRI
Sorensen (2014)[24]	Single center, retrospective	49	• Cerebral oxygenation and $ETCO_2$ during LT
Jowkar (2020)[25]	Single center, randomized	100	• Changes in liver and renal biochemistry and coagulation from day 1–7 post LT • Extubation time • Hospital and ICU LOS

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, asparatate transaminase; BIS, bispectral index; BUN, blood urea nitrogen; CO, cardiac output; CVP, central venous pressure; EAD, early allograft dysfunction; $ETCO_2$, end tidal carbon dioxide, HE: hepatic encephalopathy, GA: general anesthesia, HR: heart rate, INR: international normalized ratio, IRI: ischemic reperfusion injury; MAP, mean arterial pressure; MDA, malondialdehyde; MPAP, mean pulmonary artery pressure; NSE, neuron specific enolase; LOC, loss of consciousness; LOS, length of stay; LT, liver transplant; MELD, model for end stage liver disease; POCD, postoperative cognitive dysfunction; PT, prothrombin time; PTT partial thrombin time; S100B, calcium-binding protein B; TCI, target controlled infusion; TIVA, total intravenous anesthesia.

abdominal sugery, there are studies showing increased risk of mortality, increased cancer incidence, increased incidence of atelectasis, and increased cardiac injury markers with utilization of higher O_2 concentrations perioperatively.[33–36] There appears to be minimal evidence for higher O_2 concentrations contributing to an increased risk of surgical site infections.[37–39] From a resources standpoint, reducing the amount of oxygen needed per patient could lead to improved costs with reduced ventilator and ICU time in liver transplantation patients, with the caveat that data has been extrapolated. Looking at the harms of liberal O_2 and potential benefits of lower oxygen concentrations, the panel feels it can propose a strong recommendation for restrictive oxygen administration with a FiO_2 to maintain a PaO_2 of 70–110 mmHg (10–14 kPa).

Considering specific ventilatory strategies, there is significant literature supporting low-tidal volume ventilation in abdominal surgery in overall improved mortality and reduction in pulmonary complications.[40–42] Similarly, there are multiple studies showing improved oxygenation and reduction in postoperative hypoxemic events when PEEP is utilized.[43,44] While PEEP itself is recommended, the panel cannot recommend a specific PEEP value or range of values. Instead, intraoperative PEEP should be tailored and optimized to individual patient requirements dependent on their body habitus, oxygen requirements, and where possible flow volume loops. Along similar lines, the use of recruitment maneuvers has very little evidence in abdominal surgery and liver transplantation,[45] but their benefit is well proven to improve oxygenation and lung function, particularly in the ICU population. As a result, the panel feels a strong recommendation can be proposed for the use of low tidal volume ventilation of 6–8 ml/kg ideal body weight (IBW), use of PEEP tailored to patient physiology, and recruitment maneuvers in liver transplantation.

Regarding antiemetic prophylaxis, there is well supported consensus opinion regarding the management of postoperative nausea and vomiting.[46] The utility of routine of antiemetic prophylaxis may be low given that a large number of centers do not routinely extubate in the operating room, but within a specified number of hours postoperatively. However, with increasing implementation of fast-track liver transplantation pathways and the favorable benefit to risk ratio of antiemetic prophylaxis (an important risk being the potential QT prolongation associated with most antiemetics, which may provide an issue in the setting of cardiomyopathy), the panel feels that a strong recommendation can be proposed for the use of antiemetic prophylaxis during liver transplantation.

5 | LIMITATIONS

This review has several limitations. Firstly, there is a distinct lack of evidence for intraoperative anesthetic care in liver transplantation and short term outcomes, therefore extrapolation from other high-quality studies not specific to liver tranplantation as well as a heavy reliance

TABLE 2 Study outcomes

Author, year (Reference)	Intra-operative morbidity and mortality	Post-operative morbidity and mortality	Early allograft dysfunction	ICU and hospital length of stay
Najafi et al. (2019)	–	No significant difference between 2 groups in hemodynamic parameters, coagulation, hepatic and renal function	–	–
Cao et al. (2017)	EEG based awareness monitoring (BIS) guided anesthesia could avoid hypotension during surgery through reduced consumption of Propofol	No significant difference in incidence of POCD between the 2 groups (*p*-value = 0.089) -	–	–
Beck-Schimmer et al. (2015)	–	No significant difference in liver biochemistry (ALT, AST, bilirubin) between both groups No significant difference in major in-hospital complications between both groups (*p*-value = 0.23) No significant difference in overall morbidity rate between both groups (p-value = 0.42)	No significant difference in incidence of EAD in both groups (*p*-value = 0.45)	No significant difference in ICU LOS (*p*-value = 0.64) or hospital LOS (*p*-value = 0.77) between both groups
Gucyetmez (2016)	–	24-h total tramadol requirement lower in the study group 4.1 ± 0.07 versus 3.7 ± 0.05 mg/kg/h Time to first tramadol longer in the study group 3.2 ± 0.7 versus 17.5 ± 2.5 h Reduced duration of mechanical ventilation in the study group in multivariate analysis (p-value < 0.001) -	–	Similar ICU and hospital LOS between both groups
Gajate Martin (2016)	–	–	No significant difference in incidence of primary graft dysfunction between both groups. (OR 0.76, CI 0.42–1.47; p-value = 0.45).	–
Ali Sahmeddini (2012)	No differences in hemodynamic variables (MAP, HR, CVP) during LT between both groups	–	–	–
Lu (2016)	Statistically significantly lower dose of norepinephrine during reperfusion in TIVA versus Desflurane group (*p*-value = 0.012) No significant difference in haematological (INR) and biochemical (ALT) markers 24 h post LT	Awake time was significantly faster in the TIVA group versus Desflurane (*p*-value = 0.034) No significant differences in extubation time	–	No significant difference in ICU or total hospital LOS
Mangus (2018)	No significant differences in perioperative death	No significant differences in death at 1 year post LT Greatest perioperative IRI occurred in Isoflurane group	No significant difference in EAD	No significant difference in hospital LOS between all 3 groups

(Continues)

TABLE 2 (Continued)

Author, year (Reference)	Intra-operative morbidity and mortality	Post-operative morbidity and mortality	Early allograft dysfunction	ICU and hospital length of stay
Toprak (2011)	Significant changes in MAP, MPAP, $ETCO_2$, EEG based awareness monitoring (BIS), and body temperature across all 3 phases of LT (all values remained clinically acceptable) No difference in HR across the 3 phases of LT.	-	–	–
Pan (2016)	Significant difference in hypotension (MAP) seen at 30 min (p-value = 0.027) No significant difference in bradycardia No significant difference in quantity of vasoactive agents (atropine and phenylephrine) used	–	–	–
Kim (2019)	–	Time to recovery of consciousness significantly longer in severe HE group vs. non-severe group (2.8 days vs. 1.2 days, p-value = 0.002) Multivariate analysis: MELD score and GCS at 24 h were associated with increased consciousness recovery time: (MELD: hazard ratio 1.09, p-value = 0.02) (GCS: hazard ratio 0.692, p-value < 0.001) -	-	–
Tsai (2012)	No significant difference in perioperative hemodynamic data between groups No significant difference in mean MDA levels between both groups before reperfusion Mean MDA significantly lower in Propofol group versus control group at 3, 5, 0, and 60 min after reperfusion (all time points: p-value < 0.05)	-	-	–
Sorensen (2014)	Cerebral oxygenation and $ETCO_2$ reduced by 4.3% and 0.3 kPa respectively in the anhepatic phase (p-value < 0.0001) Cerebral oxygenation and $ETCO_2$ increased by 5.5% and 0.7 kPa respectively during reperfusion of the liver	–	–	–

(Continues)

TABLE 2 (Continued)

Author, year (Reference)	Intra-operative morbidity and mortality	Post-operative morbidity and mortality	Early allograft dysfunction	ICU and hospital length of stay
Jowkar (2020)	–	No significant difference in postoperative liver biochemistry (AST, INR, bilirubin) Patients who received remifentanil had statistically significant, but clinically insignificant, changes in ALT No change in renal function over 7 days post LT No significant difference in extubation time	–	No significant difference in ICU LOS (p-value = 0.75) and hospital LOS (p-value = 0.23)

Outcomes are presented in the same order as in Table 1.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, asparatate transaminase; BIS, bispectral index; BUN, blood urea nitrogen; CI, confidence interval; CO, cardiac output; CVP, central venous pressure; EAD, early allograft dysfunction; $ETCO_2$, end tidal carbon dioxide; FFP, fresh frozen plasma; HE, hepatic encephalopathy; GA, general anesthesia; GCS, Glasgow coma scale; HR, heart rate; INR, international normalized ratio; IRI, ischemic reperfusion injury; LT, liver transplant; MAC, minimum alveolar concentration; MAP, mean arterial pressure; MDA, malondialdehyde; MPAP, mean pulmonary artery pressure; NSE, neuron specific enolase; LOC, loss of consciousness; LOS, length of stay; LT, liver transplant; MELD, model for end stage liver disease; OR, odds ratio; PCC, prothrombin complex concentrate; POCD, postoperative cognitive dysfunction; PT, prothrombin time; PTT, partial thrombin time; S100B, calcium-binding protein B; TCI, target controlled infusion; TIVA, total intravenous.

TABLE 3 Summary of findings leading to the quality of evidence assessment according to the GRADE approach

Summary of findings								
Number of studies								
RCT	Observational comparative	Observational non-comparative	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence (GRADE)
Outcome 1: Intraoperative morbidity and mortality								
2	5	1	Serious	Not serious	Serious	Serious	Not likely	Low ●●○○
Outcome 2: Postoperative morbidity and mortality								
4	3	0	Serious	Not serious	Serious	Serious	Not likely	Low ●●○○
Outcome 3: Early allograft dysfunction								
1	2	0	Not serious	Not serious	Not serious	Serious	Not likely	Low ●●○○
Outcome 4: ICU length of stay								
3	1	0	Not serious	Not serious	Not serious	Serious	Not likely	Moderate ●●●○
Outcome 5: Hospital length of stay								
3	2	0	Not serious	Not serious	Not serious	Serious	Not likely	Moderate ●●●○

on expert opinion has been utilized to make recommendations. Secondly, the questions have several financial, resource, and environmental implications which pose a challenge to making strong recommendations that are widely applicable, given that LT is a worldwide procedure occurring in environments with different resource constraints. For example, certain anesthetic resources like EEG based awareness monitoring such as BIS, or target controlled propofol infusions are associated with increased costs and subsequently variable access; volatile agents have been shown to have a detrimental effect on the environment and are expensive, but remain widely used. Thirdly, an element of conflict exists within subsequent questions, as demonstrated by the first question which compares type of anesthesia (TIVA vs. volatile) and the second question which examines MAC, implying the use of volatile anesthesia, versus EEG based awareness monitoring.

TABLE 4 Evidence to recommendation framework according to the GRADE approach

Decision domain	Judgement: Yes	Judgement: No	Reason for Judgement
Question 1: Does the type of anaesthesia (TIVA vs. Volatile) affect immediate and short-term outcomes after liver transplantation?			
Balance between desirable and undesirable outcomes (estimated effects), with consideration of values and preferences (estimated typical)	✓		The literature reviewed showed a small amount of evidence supporting faster wakeup and markers of decreased ischemic reperfusion injury in patients receiving TIVA when compared to volatile anaesthesia In general, when assessing volatile agents as an anesthesia type, their desirability lies in their ability to provide amnesia at a measurable level and lack of dependence on hepatic or renal metabolism, which outweighs their undesirable effects such as postoperative nausea and vomiting, and environmrntal impact particularly with desflurane When generally assessing TIVA as an anesthetic type, its desirability as an agent is due to more rapid emergence, improved profile in patients with increased intracranial pressure (ICP), and lower incidence of PONV are outweighed by the need for metabolism by the liver and non-validated means of confirming amnesia intraprocedurally, especially in the setting of rapid blood loss.
Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		✓	The evidence is low when looking at TIVA versus volatile anesthesia in terms of their contribution to important outcomes post-liver transplantation
Confidence in Values and Preference, and their Variability		✓	There is inconsistency between the studies analyzed in the manner in which TIVA versus volatile was administered. In certain studies, target controlled infusions for TIVA were utilized versus anesthesiologist titration to BIS or discretion, which was also similar to the volatile administration parameters
Resource implications *Are the resources worth the expected net benefit from following the recommendation?*	✓		There are increased costs and potential environmental effects depending on the agent used. For TIVA, resource implications include the cost of propofol vials, as well as the resources needed for target controlled infusions and non-validated depth of anaesthesia monitoring techniques technologies
Overall Quality of Evidence: Very Low			
Recommendation of the Panel: Weak for the use of volatile anesthesia for use in liver transplantation for optimal short term outcomes, with consideration of TIVA in patients at risk for or with increased intracranial pressure.			
Question 2 : Does the type of depth of anaesthesia assessment (EEG based awareness monitoring vs. MAC) affect immediate and short term outcomes after liver transplantation?			
Decision domain	**Judgement: Yes**	**Judgement: No**	**Reason for Judgement**
Balance between desirable and undesirable outcomes (estimated effects), with consideration of values and preferences (estimated typical)	✓		In general, there is some data supporting the use of EEG based awareness monitoring for reduction of anesthetic delivered, improved hemodynamics, and improved survival, and has been shown to be of similar reference value in cirrhotic patients[26]
Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)			The evidence is low regarding the use of EEG based awareness monitoring versus MAC contributing to important outcomes post-liver transplantation

(Continues)

TABLE 4 (Continued)

Decision domain	Judgement: Yes	Judgement: No	Reason for Judgement
Question 2 : Does the type of depth of anaesthesia assessment (EEG based awareness monitoring vs. MAC) affect immediate and short term outcomes after liver transplantation?			
Decision domain	**Yes**	**No**	**Reason for Judgement**
Confidence in Values and Preference, and their Variability	✓		BIS values have been shown to be consistent in the cirrhotic population, with MAC requirements shown to be reduced in cirrhotics undergoing liver transplantation[27,28]
Resource implications	✓		There is an increased cost associated with the utilization of EEG based awareness monitoring monitoring relative to the use of MAC during the intraoperative phase of case
Overall Quality of Evidence: Very Low			
Recommendation: Weak for the use of MAC as a measure of anesthetic depth during liver transplantation for optimal short term outcomes			
Question 3: Does a liberal versus restrictive O_2 management affect immediate and short-term outcomes after liver transplantation?			
Decision domain	**Yes**	**No**	**Reason for judgement**
Balance between desirable and undesirable outcomes (estimated effects), with consideration of values and preferences (estimated typical)	✓		In the literature reviewed, there is no data supporting varying oxygen concentrations. However, there is significant data supporting the use of lower oxygen concentrations as well as data showing the harms of liberal oxygen use in other surgical populations
Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)	✓		The evidence is low to support different levels of oxygen administration for important outcomes after liver transplantation
Confidence in Values and Preference, and their Variability		✓	The concentration of O_2 for restrictive O_2 concentrations is not well defined. Liberal O_2 concentration is defined as a FiO_2 of 80–100%
Resource implications	✓		There is a cost associated with oxygen to centers, so there is a benefit with restrictive O_2 management techniques
Overall Quality of Evidence: Very Low			
Recommendation: Strong for restrictive O_2 administation titrated to a PaO_2 of 70–110 mmHg (10–14 kPa) should be utilized during liver transplantation for optimal short term outcomes.			
Question 4: Do intraoperative ventilation strategies (PEEP, tidal volumes, recruitment manoeuvres) affect immediate and short-term outcomes after liver transplantation?			
Decision domain	**Yes**	**No**	**Reason for Judgement**
Balance between desirable and undesirable outcomes (estimated effects), with consideration of values and preferences (estimated typical)	✓		Low tidal volumes (TV) as defined 6–8 ml/kg IBW, use of PEEP, and recruitment maneuvers all are beneficial to patients with minimal undesirable outcomes associated with their utilization
Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)	✓		There is low-quality evidence supporting the use of low tidal volume ventilation, PEEP, and recruitment maneuvers for improving outcomes postliver transplantation

(Continues)

TABLE 4 (Continued)

Question 4: Do intraoperative ventilation strategies (PEEP, tidal volumes, recruitment manoeuvres) affect immediate and short-term outcomes after liver transplantation?			
Decision domain	**Judgement**		**Reason for Judgement**
	Yes	**No**	
Confidence in Values and Preference, and their Variability	✓		The defintion of low TV is well defined as 6–8 ml/kg. Optimal PEEP has not been defined and varies by patient factors. The definition of recruitment maneuver is also varied depending on literature[29]
Resource implications	✓		Although not defined in the evidence, there could be a potential resource saving in reduced need for mechanical ventilation or ICU days
Overall Quality of Evidence: Very Low			
Recommendation: Strong for the use of tidal volumes of 6-8 ml/kg IBW, PEEP titrated to patient intraoperative physiology, and recruitment maneuvers in liver transplantation for optimal short-term outcomes.			
Question 5: Does antiemetic prophylaxis affect immediate and short-term outcomes after liver transplantation?			
Decision domain	**Judgement**		**Reason for Judgement**
	Yes	**No**	
Balance between desirable and undesirable outcomes (estimated effects), with consideration of values and preferences (estimated typical)	✓		The benefits of antiemesis outweigh the risk of QT prolongation associated with most common antiemetic agents.
Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)	✓		The evidence is low for the support of antiemetic prophylaxis contributing to important outcomes in liver transplantation
Confidence in Values and Preference, and their Variability		✓	n/a
Resource implications?	✓		No resource difference in patients receiving PONV prophlaxis
Overall Quality of Evidence: Very low			
Recommendation: Strong for the use of antiemetic prophylaxis in liver transplantation for optimal short term outcomes			

6 | CONCLUSION

When considering optimal anesthetic management and its contribution to short-term outcomes after liver transplantation, the panel was able to come to the above conclusions about the five proposed questions. However, more importantly, this review demonstrates significant deficiencies in the anesthesia literature. More outcome focused research is needed to identify the most beneficial anesthetic techniques for liver transplant patients in the perioperative period, such research should also consider the resource implications of specific techniques.

Panel suggestions for key areas of future research:

1. A core outcome set (https://www.comet-initiative.org) to define key outcomes that should be reported in any study focusing on intraoperative anesthetic management in liver transplantation.
2. Volatile Anesthetics: studies comparing the use of different volatiles on short term outcomes after LT including: time to extubation, EAD, comparison of cost relative to hospital and ICU length of stay.
3. International multicenter RCTs comparing volatile agents versus TIVA focusing on:
   a. Cardiovascular stability and intraoperative vasopressor, inotrope, and fluid requirements
   b. Ability to extubate early (on-table and within a specified number of hours postoperatively on ICU)
   c. Postoperative cognitive dysfunction
   d. Early Allograft Dysfunction
4. Multi-center RCTs comparing liberal versus restrictive oxygenation strategies focusing on:
   a. Ischaemia-reperfusion injury (given the theory that IRI is partly driven by an increase in oxygen free radicals)

b. Postoperative pulmonary complications such as atelectasis, pneumonia, and pulmonary edmea.
c. Early allograft dysfunction

5. Explanatory studies to assess: Depth of anesthesia monitoring: correlation of MAC with EEG based awareness monitoring in LT recipients

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AUTHORSHIP

All authors qualify for authorship as per the International Committee of Medical Journal Editors (ICMJE) guidelines.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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