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REVIEW ARTICLE

What is the optimal anesthetic monitoring regarding immediate and short-term outcomes after liver transplantation?—A systematic review of the literature and expert panel recommendations

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Abstract

Background: Liver transplant centers vary in approach to intraoperative vascular accesses, monitoring of cardiac function and temperature management. Evidence is limited regarding impact of selected modalities on postoperative outcomes.

Objectives: To review the literature and provide expert panel recommendations on optimal intraoperative arterial blood pressure (BP), central venous pressure (CVP), and vascular accesses, monitoring of cardiac function and intraoperative temperature management regarding immediate and short-term outcomes after orthotopic liver transplant (OLT).

Methods: Systematic review following PRISMA guidelines and recommendations using the GRADE approach derived from an international expert panel. Recommendations made for: (1) Vascular accesses, arterial BP and CVP monitoring, (2) cardiac function monitoring, and (3) Intraoperative temperature management (CRD42021239908).

Results: Of 2619 articles screened 16 were included. Studies were small, retrospective, and observational. Vascular access studies demonstrated low rates of insertion complications. TEE studies demonstrated low rates of esophageal hemorrhage. One study found lower hospital-LOS and 30-day mortality in patients monitored with both PAC and TEE. Other monitoring studies were heterogenous in design and outcomes. Temperature studies showed increased blood transfusion and ventilation times in hypothermic groups.

Conclusions: Recommendations were made for; routine arterial and CVP monitoring as a minimum standard of practice, consideration of discrepancy between peripheral and central arterial BP in patients with hemodynamic instability and high vasopressor requirements, and routine use of high flow cannulae while monitoring for extravasation and hematoma formation. Availability and expertise in PAC and/or TEE monitoring is strongly recommended particularly in hemodynamic instability, portopulmonary HT and/or cardiac dysfunction. TEE use is recommended as an acceptable risk in patients with treated esophageal varices and is an effective diagnostic tool for emergency cardiovascular collapse. Maintenance of intraoperative normothermia is strongly recommended.

KEYWORDS

central venous access, cardiac output or hemodynamic monitoring, pulmonary artery catheter, transesophageal echocardiography, PiCCO, hyperthermia, LiDCO, monitoring, or FloTrac, hypothermia, thermoregulation, liver transplantation, venous or arterial access

1 | INTRODUCTION

The intraoperative management of the liver transplant recipient varies among transplant centers. Variation exists in number and location of arterial lines, vascular accesses, cardiac monitoring, and temperature management. Practice is often based on local protocols, resource availability and institutional culture. There is little scientific evidence for which modalities optimize immediate and short-term clinical outcomes.

Extensive variability exists regarding use of intra-operative TEE. Once considered relatively contraindicated due to risk of bleeding in patients with esophageal varices, it is now more established with increasing use.[1–7] Of particular benefit is its ability to diagnose life-threatening causes of hemodynamic instability such as intracardiac thrombus, ventricular dysfunction and out-flow tract obstruction.[7]

Pulmonary artery catheters remain the only monitor capable of direct measurement of pulmonary artery pressures. Despite concerns around safety and benefits, they are considered by some liver transplant anesthesiologists as the standard monitor of cardiac function.

Less invasive devices (e.g., PiCCO) obtain hemodynamic data through transpulmonary thermodilution and pulse contour analysis. They have shown acceptable reliability as a measure of cardiac output and other hemodynamic metrics in orthotopic liver transplant (OLT).[8]

Minimally invasive monitors assessing arterial pulse wave (e.g., LiDCO) and pulse contour (e.g., Vigileo, FloTrac) analysis offer information on volume status via stroke volume variation and other metrics. These have yet to prove reliable in OLT.[9–12] Other minimally invasive monitors based on esophageal doppler, thoracic bioreactance or determining extravascular lung water and pulmonary vascular indices are considered experimental.

Intraoperative temperature control during OLT can be challenging due to multiple factors. The detrimental effects of hypothermia are well established in the general surgical population, for example, increased risk of surgical site infection, sepsis, coagulopathy, bleeding and decreased myocardial contractility.[13,14] Hypothermia-induced pulmonary vasoconstriction may contribute to worsening pulmonary arterial hypertension and RV dysfunction. The OLT patient is at increased risk of these sequelae due to pre-existing immunocompromise, coagulopathy and cardiac dysfunction.

Our panel's objective is to systematically review the literature and provide expert recommendations on: optimal intraoperative vascular access, arterial blood pressure (BP) and central venous pressure (CVP) monitoring, cardiac function monitoring and temperature management to improve immediate and short-term outcomes after OLT.

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 review protocol was registered in advance with PROSPERO ID: CRD42021239908

TABLE 1 Eligibility criteria of the systematic review

	Included	Excluded
Population	Adults with ESLD who underwent deceased donor orthotopic liver transplantation	Children Split livers Living donor recipients
Intervention	Use of: -Cerebral blood flow monitoring -Cerebral Oximetry -Cardiac Output monitoring -Pulmonary artery catheter -Transesophageal echocardiography -Esophageal Doppler -Transthoracic Impedance monitoring -Active thermoregulation	-Veno–Venous Bypass -Continuous Veno–Venous Hemofiltration
Control	No use of the above monitoring	
Observation	Perioperative complications Morbidity and mortality ICU length of stay Hospital length of stay Hospital readmission rates	Any other observations

2.2 | Eligibility criteria

The eligibility criteria for the systematic review are listed in Table 1.

2.3 | Information sources

The following bibliographic databases were searched: Ovid MEDLINE, Embase, Scopus, Google Scholar, Clinical.Trials.gov and the Cochrane Central Register of Controlled Trials. The search date was set to March 10, 2021. No study authors were contacted for details of additional studies.

2.4 | Search

The generic search string below was used, and adapted to individual databases (e.g., by expanding MESH terms) by professional medical librarians from the University of Zurich:

Search keywords: (monitoring AND [anesthesia OR anaesthesia]) OR ([venous OR arterial] AND access) OR "central venous access" OR "intraoperative hemofiltration" OR "intraoperative haemofiltration" OR CVVH OR "cerebral blood flow monitoring" OR "cerebral oximetry" OR "near infra-red spectroscopy" OR (["cardiac output" OR heart OR hemodynamic OR haemodynamic] AND [monitor OR monitoring]) OR "pulmonary artery catheter" OR ([transesophageal OR transoesophageal] AND [echocardiography OR echocardiogram]) OR ([esophageal OR oesophageal] AND doppler) OR "transthoracic impedance" OR (PiCCO OR LiDCO OR FloTrac) OR ([hypothermia OR hyperthermia OR thermoregulation] AND [intra-operative]) AND ([liver OR hepatic] AND [transplant OR transplantation]).

2.5 | Study selection

Studies were screened in abstract for eligibility using Endnote v.10, then downloaded for full text review and inclusion, by two reviewers independently (LJ and MZ). Disagreements about inclusion were arbitrated by a third reviewer (DAR).

2.6 | Quality of studies and recommendations grading

The "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) approach was used for grading quality of evidence (QOE) and strength of recommendations.[15] The GRADE system was designed to provide a comprehensive and structured approach to the rating 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.[16] 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.[17,18]

3 | RESULTS

3.1 | Study selection

Twenty relevant studies were selected for inclusion after duplicate removal and screening. This included one additional study added by the expert review panel due to relevance to the topic. Four studies were excluded by the panel for reasons described in Figure 1. Sixteen studies were included in final qualitative synthesis. Studies related to VVB were covered elsewhere in the ERAS4OLT.org project and hence not included.

3.2 | Study characteristics

Subquestions and characteristics of included studies are listed in Tables 2–4.

3.3 | Results of individual studies

The outcomes of the selected studies are listed in Tables 5–7.

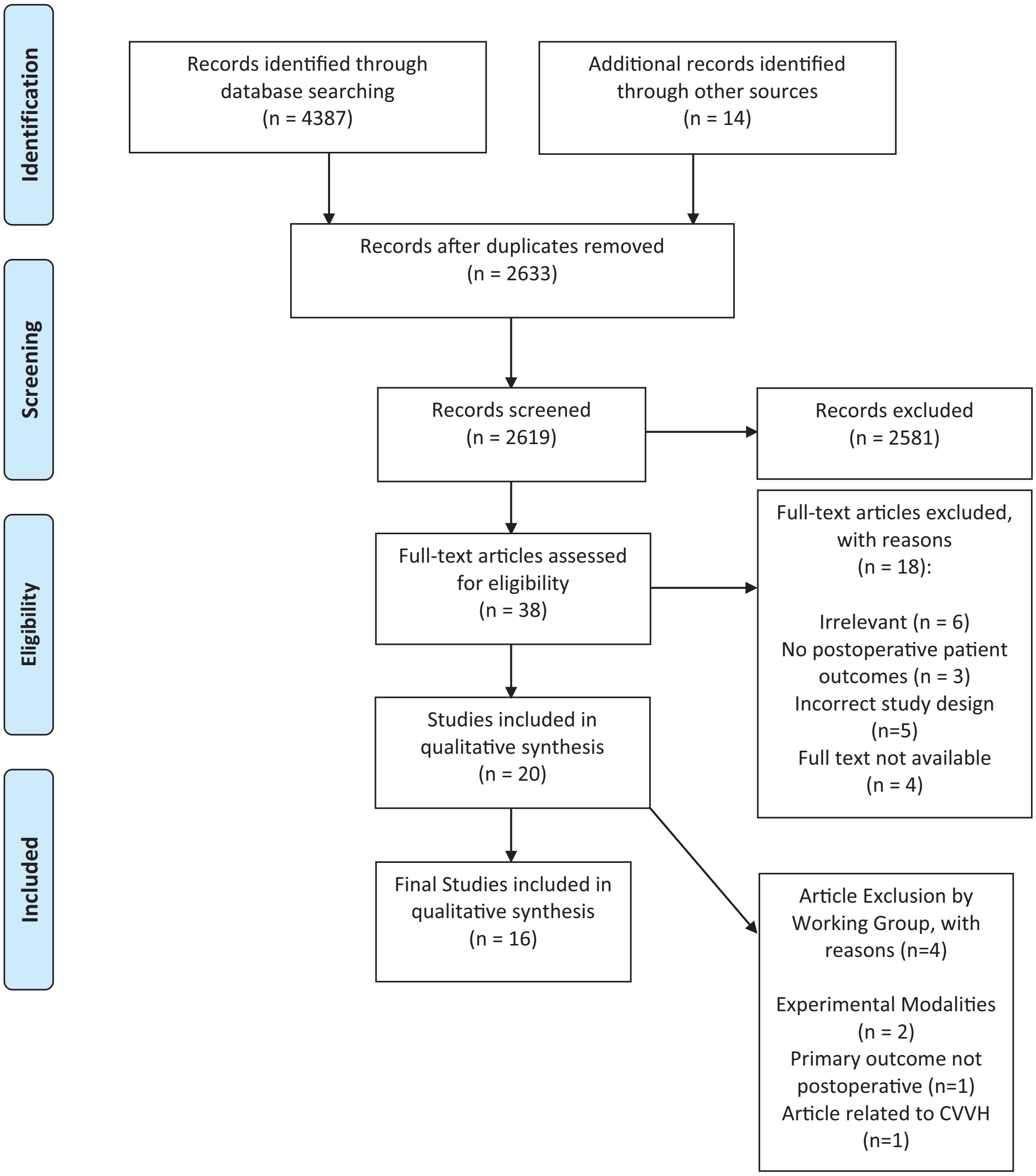

FIGURE 1 Systematic review flow diagram

TABLE 2 Study characteristics

	Study type	No. of patients	Main outcomes assessed
Lu 2013	Retrospective observational	1206	• Arterial line complication • Central venous line complication • PAC line complication
Torgay 2005	Retrospective observational	45 Subclavian 22 Internal Jugular 23	• Central venous line complication
Porter 2021	Retrospective observational	839	• Rapid infusion line complication

Note: Which vascular access and intraoperative monitoring of blood pressure and central venous pressure are optimal with regard to immediate and short-term outcomes after liver transplantation?

TABLE 3 Study characteristics

	Study type	No. of patients	Main outcomes assessed
Siniscalchi 2013	Prospective observational study	82	• Early mortality • ICU care • Graft failure • Hospital length of stay
Perilli 2012	Prospective observational	38	• ICU care • Graft failure
Milan 2011	Prospective observational study	• 124 patients undergoing OLT • 24 not included • 100 patients undergoing OLT	• Early mortality
Prasad 2015	Retrospective single center study	55	• Early mortality
Prasad 2017	Retrospective observational	101	• Early mortality
Villa 2019	Retrospective single center case/ control study	209 PA catheter, $n = 109$ No PA catheter, $n = 100$	• Early mortality • ICU care • Graft failure • Hospital length of stay
Hofer 2020	Retrospective observational	316 38 TEE 200 PAC 78 Both	• Early mortality • ICU care • Hospital length of stay
Pai 2015	Retrospective observational	1811 232 TEE	• Esophageal hemorrhage
Burger-Klepp 2012	Retrospective single center case/ control study	$n = 396$ Esophageal varices $n = 287$ No esophageal varices $n = 109$	• Early mortality • Esophageal hemorrhage
Markin 2015	Retrospective observational	116	• Esophageal hemorrhage
Myo Bui 2015	Retrospective	433 TEE 223 No TEE	• Esophageal hemorrhage
Lu 2013	Retrospective observational	1206	• Esophageal hemorrhage

Note: Which modality for intraoperative monitoring of cardiac function is optimal with regard to immediate and short-term outcomes after liver transplantation?

TABLE 4 Study characteristics

	Study type	No. of patients	Main outcomes assessed
Ying Sun 2018	Retrospective observational	107 Normothermia, $n = 67$ Hypothermia, $n = 40$	• Blood transfusion • Ventilation Time • Bacterial infection • ICU length of stay
Fazakas 2011	Retrospective observational	54 Normothermia, $n = 29$ Hypothermia, $n = 25$	• Blood transfusion • Ventilation Time • Bacterial infection • ICU length of stay

Note: What is the optimal intraoperative temperature management regarding immediate and short-term outcomes after liver transplantation?

3.4 | Quality of evidence

The summary of findings for the main outcomes, including the QOE assessment according to the GRADE approach are summarized in Tables 8–10.

3.5 | Recommendations

This panel recommends routine use of arterial and CVP monitoring as a minimum standard of practice in all transplant recipients. In patients with significant hemodynamic instability and high

TABLE 5 Study outcomes

	Arterial line complication	Central venous line complication	PAC line complication	Rapid infusion cathetercomplication
Lu 2013	Radial 2/1206 (.17%) Femoral 7/1206 (.58%)	Internal Jugular 4/1206 (.33%)	0/1206	
Torgay 2005		Internal Jugular Hematoma 2/23 (8.7%) Arterial Puncture 2/23 (8.7%) Infection 4/23 (17.4%) Subclavian Hematoma 1/22 (4.5%) Infection 3/22 (13.6%) Arterial puncture 0/22		
Porter 2021				14/839 (1.7% 95% CI 1%–2.78%) Infiltration 11/839 (1.3%) Hematoma 3/839 (.36%)

Note: Which vascular access and intraoperative monitoring of blood pressure and central venous pressure monitoring is optimal with regard to immediate and short-term outcomes after liver transplantation?

vasopressor requirements we recommend consideration of potential discrepancy between peripheral and central arterial BP measurements. We recommend routine use of high flow intravenous cannulae placed centrally or peripherally under US guidance and appropriate sterility. Regular review of insertion sites is recommended to monitor for extravasation and hematoma (QOE; very low | Grade of Recommendation; High) (Table 11).

The panel recommends availability and expertise in use of PAC and/or TEE monitoring particularly in high risk, hemodynamically unstable patients and those with existing porto-pulmonary hypertension and/or cardiac dysfunction. We recommend use of TEE in patients with treated esophageal varices as an acceptable risk. In emergency cardiovascular collapse we recommend early use of TEE by appropriately trained anesthesiologists as an effective diagnostic tool (QOE; Low | Grade of Recommendation; High) (Table 12).

The maintenance of intraoperative normothermia is strongly recommended (QOE; Low | Grade of Recommendation; High) (Table 13).

4 | DISCUSSION

Orthotopic liver transplantation is often characterized by periods of hemodynamic instability. Despite experiencing similar challenges, heterogeneity exists among transplant centers regarding chosen vascular accesses and modality of cardiac function monitoring. Additionally, patients are susceptible to hypothermia and subsequent detrimental clinical sequelae. Evidence is limited for which vascular accesses, cardiac function monitoring and temperature management provide optimal immediate and short-term outcomes following liver transplantation

4.1 | Subquestion 1

Which vascular access and intraoperative monitoring of blood pressure and central venous pressure monitoring are optimal with regard to immediate and short-term outcomes after liver transplantation?

Invasive arterial and central venous access allow monitoring of BP, CVP, blood sampling and delivery of vasoactive medications. The evidence for benefit of a particular type of vascular access on immediate and short-term outcomes is limited, however, it is the opinion of this panel that insertion of such lines should be routine and a minimum standard of monitoring in patients undergoing OLT.

Vascular access and line selection often reflects decisions based on local protocols, for example, the need for rapid infusions (RIC lines), PAC monitoring (PAC introducer sheaths) and facilitation of VVB (femoral sheaths, RIC lines, large bore venous return cannulae). Where pressurized high flow infusions are administered via large bore cannulae, insertion sites should be routinely monitored to ensure extravasation injury is not encountered. VVB access cannulae carry associated risk of life-threatening complications, for example, hemomediastinum, hemothorax, air embolism.[19,20] VVB was deemed outside the scope of this subquestion and is addressed elsewhere in the ERAS4OLT project.

The literature review yielded a small number of retrospective, single center studies assessing line complications. Ultrasound use was not identified as an independent factor reducing insertion complications. It should be utilized to increase first-pass success and minimize complications.[21]

Generally, a low rate of line-related complications has been published. However, potential under- and non-reporting along with publication bias mean the incidence of complications is undoubtedly higher than reported in the literature. For example, Lu et al. looked at complications related to invasive monitors in OLT and found zero complications out of 1206 PAC insertions.[2] Case reports however

TABLE 6 Study outcomes

	Early mortality	ICU care	Graft failure	Hospital length of stay	Esophageal hemorrhage
Siniscalchi 2013	Patients with severe Hyperdynamic Circulation had greater incidence of early ICU death (before day 15) 14% versus 2% ($p = .042$)	No statistically significant difference between patients with severe Hyperdynamic Circulation and without (five days vs. eight days)	Patients with severe Hyperdynamic Circulation had higher incidence of re-transplantation due to primary graft non-function ($p = .034$)	No statistically significant difference between patients with severe Hyperdynamic Circulation and those without (eight days vs. four days)	
Perilli 2012		11.5 + 6.2 versus 5.8 + 2.4 days (PGD vs. No PGD) Mean ± SD	7 versus 31 (PGD vs. No PGD) *Patients*		
Milan 2011	89 survivors versus 11 deaths (No *p*-values)				
Prasad, 2015	Greater mean absolute deviation of SBP, SVV < 10% predicted 180-day survival				
Prasad 2017	MAD CVP, *p* .045 RBC exposure, *p* .008 Intraoperative Area CVP > 5 mmHg, P(0 .048) Platelet exposure, P(.022) Intraoperative Area SVI, P(.024) Whole blood exposure, P(.002)				
Villa 2019	0% versus 1% $p = .966$	(PAC vs. no PAC) 2 days versus 1 $p = <.011$	No difference (PAC vs. no PAC) 2% versus 5% $p = .376$	No difference (PAC vs. no PAC) 13 days versus 14 days $p < .083$	
Hofer 2020	TEE 12.8% versus PAC 3.5% versus TEE+PAC 1.3%, P(.047)	TEE 1.8 versus PAC 1.5 versus TEE+PAC 1.4 days P(.68)		TEE 10.6 days versus PAC 9.1 days versus TEE+PAC 8.6 days P(.03)	
Pai 2015					1/232 (.4%) Esophageal hemorrhage
Burger-Klepp 2012	16/396 (4%) died within first 30 days post OLT				1/287 (.3%) Major hemorrhage*(Not definitely caused by TEE)*
Markin 2015					1/116 (.86%) Incidence of major bleed
Myo-Bui 2015					1/433 (.2%) Incidence of major bleed 11/433 (2.54%) Bloody NG Output
Lu 2013					4/1206 (.33%) Esophageal hemorrhage

Note: Which modality for intraoperative monitoring of cardiac function is optimal with regard to immediate and short-term outcomes after liver transplantation?

TABLE 7 Study outcomes

	Blood transfusion	Ventilation time	Bacterial infection	ICU length of stay
Ying Sun 2018	10 versus 12 units $p = .019$ (Normothermia vs. hypothermia)	5.9 versus 7.1 h (Normothermia vs. hypothermia)	13.43% versus 32.50%, $p = .03$ (Normothermia vs. hypothermia)	Moderate correlation between hypothermia and ICU stay ($r = .48$, $p = .002$)
Fazakas 2011	10 ± 6 versus 18 ± 8, $p = .01$ (Normothermia vs. hypothermia)	86 ± 74 versus 204 ± 135 h, $p = .05$ (Normothermia vs. hypothermia)	Urinary 1/29 versus 3/25 Catheter related 5/29 versus 2/25 Pneumonia 0/29 versus 2/25 NS (Normothermia vs. hypothermia)	4 ± 1/29 versus 4 ± 1.3/25. NS (Normothermia vs. hypothermia)

Note: What is the optimal intraoperative temperature management regarding immediate and short- term outcomes after liver transplantation?

TABLE 8 Summary of findings leading to the quality of evidence assessment according to the GRADE approach

***Which vascular accesses and intraoperative monitoring of blood pressure and central venous pressure monitoring are optimal with regard to immediate and short-term outcomes after liver transplantation?* Summary of findings**									
Number of studies			**Effect from comparative studies**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Quality of Evidence (GRADE)**
RCT	**Observational comparative**	**Observational non-comparative**							
Outcome 1: ***Arterial Line complication (Radial or Femoral)***									
0	0	1	Nil comparative studies	Serious	Not serious	Not serious	Serious	Likely	Very low ●○○○
Outcome 2: ***Central Venous Line complication (IJ, Subclavian)***									
0	0	1	Nil Comparative studies	Very Serious	Not serious	Not serious	Very Serious	Likely	Low ●●○○
Outcome 3: ***Pulmonary Artery Catheter complication***									
0	0	1	Anecdotal and case reports for OLT literature Very few events	Serious	Not serious	Not serious	Very serious	Likely	Very low ●○○○
Outcome 4: ***Rapid Infusion Catheter complication***									
0	0	1	Nil Comparative studies	Serious	Not serious	Not serious	Serious	Likely	Low ●●○○

Note: Question 1. Vascular and arterial access.

demonstrate rare but significant complications associated with PAC insertion in the liver transplant population. Gwak et al found OLT to be an independent risk factor for ventricular arrhythmias during PAC line insertion with an incidence of 37%.[22] A comprehensive review of PAC complications in the general population identified complications of arrhythmias, pulmonary infarction, catheter knotting and PA rupture.[23] Further evidence of this has been found in prospective RCT's such as the PAC-Man study.[24] Overall, however, the incidence of PAC-related complications remains low with insertion benefit outweighing risk when clinically indicated.

The location and number of arterial lines inserted varies among transplant centers. The radial artery presents an easy access, low complication site. The brachial artery lacks collateral circulation and can be associated with risk of thrombosis and nerve injury. The femoral artery correlates more closely to central arterial pressure however may pose increased risk of kinking, infection and pseudoaneurysm. Large series and reviews however demonstrate acceptably low and comparable incidence of major complications from arterial lines across all sites of insertion.[2,25,26]

The limitations of peripheral arterial vs central arterial pressure monitoring during liver transplantation should be considered when selecting the optimal location. A discrepancy between central and peripheral arterial pressure measurements may exist, particularly during caval clamping, reperfusion, severe arteriolar vasodilation or periods of high vasopressor requirement[27] (See Supplement: Figure S1). RABP may underestimate FABP measurements with a systolic FABP to systolic RABP gradient.[27–29] NIBP has also been shown to approximate FABP more accurately than RABP.[28] One study, however, found that

TABLE 9 Summary of findings leading to the quality of evidence assessment according to the GRADE approach

Which modality for intraoperative monitoring of cardiac function is optimal with regard to immediate and short-term outcomes after liver transplantation?Summary of findings									
Number of studies			Effect from comparative studies	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Quality of Evidence (GRADE)
RCT	Observational comparative	Observational non-comparative							
Outcome 1: ***Early Mortality***									
0	3	4	Similar, very few events	serious	Not serious	Not serious	Serious	Not likely	Very low ●○○○
Outcome 2: ***ICU Care(ICU LOS/Ventilation)***									
0	2	2	Similar, very few events	Serious	Not serious	Not serious	Serious	Not likely	Low ●●○○
Outcome 3: ***Graft Failure***									
0	1	2	Similar, very few events	Serious	Not serious	Not serious	Very Serious	Not likely	Very low ●○○○
Outcome 4: ***Hospital Length of Stay***									
0	2	1	Lower in combined TEE & PAC group in one study, no effect in other studies	Serious	Not serious	Not serious	Serious	Not likely	Low ●●○○
Outcome 5: ***Esophageal Hemorrhage***									
0	2	3	Similar, very few events	Serious	Not serious	Not serious	Very serious	Not likely	Low ●●○○

Note: Question 2. Cardiac function monitoring.

TABLE 10 Summary of findings leading to the quality of evidence assessment according to the GRADE approach

What is the optimal intraoperative temperature management regarding immediate and short-term outcomes after liver transplantation? Summary of Findings								
Number of studies			**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Quality of Evidence (GRADE)**
RCT	**Observational comparative**	**Observational non-comparative**						
Outcome 1: ***Blood transfusion***								
0	2	0	Not Serious	Not Serious	Not Serious	Serious	Likely	Low ●●○○
Outcome 2: Ventilation time								
0	2	0	Not Serious	Not Serious	Not Serious	Serious	Likely	Low ●●○○
Outcome 3: Bacterial infection								
0	2	0	Not serious	Not Serious	Not Serious	Serious	Likely	Low ●●○○
Outcome 4: ICU stay								
0	2	0	Not Serious	Not Serious	Not Serious	Serious	Likely	Low ●●○○

Note: Question 3. Temperature management.

radial MAP correlates well with femoral MAP during reperfusion.[30] Some centers conclude that radial arterial pressure monitoring alone is unreliable during transplantation, with central arterial pressure better estimating organ perfusion.[31] There is no universal consensus on this and a lack of evidence for improved immediate or short-term outcomes of one monitoring site over another.

4.2 | Subquestion 2

Which modality for intraoperative monitoring of cardiac function is optimal with regard to immediate and short-term outcomes after liver transplantation?

TABLE 11 Evidence to recommendation framework according to the GRADE approach

Which vascular accesses and intraoperative blood pressure and central venous pressure is optimal with regard to immediate and short-term outcomes after liver transplantation?			
	Judgement		
Decision domain	Yes	No	**Reason for Judgement**
Balance between desirable and undesirable outcomes (estimated effects), with consideration of values and preferences (estimated typical) *Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?*	√		OLT requires mandatory intra-arterial BP and CVP monitoring as a minimum. Limited evidence is available for optimal vascular accesses. Overall, there is a low incidence of complications with line insertion, particularly when using US guidance by experienced practitioners. The limitations of peripheral vs central arterial monitoring should be considered especially in critically unwell patients with hemodynamic instability and high vasopressor requirement as radial arterial pressure may significantly under-read. The impact of multiple lines, multi-puncture and larger bore access should be considered. US guidance should be utilized along with regular monitoring for extravasation and hematoma.
Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes) *Is there high, moderate or low-quality evidence?*		√	There is a lack of high-quality evidence on optimal vascular accesses for OLT. Available studies are limited, retrospective and non-comparative. While low in incidence, many complications of vascular access are presumably anecdotal, underreported and unpublished.
Confidence in Values and Preference, and their Variability *Are you confident about the typical values and preferences and are they similar across the target population?*	√		OLT patients require optimal vascular access and arterial monitoring to manage potential hemodynamic instability, vasopressors and large, rapid volume requirements. The ability to reliably predict this is often limited. Author consensus is that appropriate practitioner experience, use of ultrasound and judicious line selection lead to an overall low incidence of complications with balance toward beneficial patient outcome.
Resource implications *Are the resources worth the expected net benefit from following the recommendation?*	√		Resources allocated to optimal vascular access and intraoperative BP and CVP monitoring are generally widely available and acceptable in cost. Considerable practice variability exists across transplant centers regarding the optimal site, number and size of vascular accesses and BP monitoring. Clinicians should be aware of the clinical implications of their choice of site and type of BP/CVP monitoring and vascular access selection
Overall Quality of Evidence: Very Low			
Recommendations: ***Strong for routine use of invasive arterial and CVP monitoring as a minimum standard of practice.*** ***Strong for consideration of discrepancy between peripheral and central arterial monitoring in patients with hemodynamic instability and high vasopressor requirements.*** ***Strong for use of high flow intravenous cannulae placed centrally or peripherally under US guidance while monitoring for extravasation and hematoma.***			

Note: Question 1. Vascular access.

The ideal cardiac function monitor would provide real-time, minimally invasive assessment of cardiovascular parameters allowing the diagnosis and management of hemodynamic instability and life threatening conditions. No single modality provides all these parameters. The interpretation of monitored data and subsequent patient management also requires a high level of expertise and training to optimize patient outcomes.

Systematic review of literature relevant to cardiac function monitoring in OLT resulted in a paucity of articles showing clear evidence of any monitors benefit on immediate and short-term outcomes. Articles related to experimental or rarely used techniques were eliminated from review. These included Transcranial Doppler and Near Infrared Spectrometry assessment of cerebral autoregulation to reduce post-op brain injury[32] and extravascular lung water and pulmonary vascular index as a predictor of prolonged mechanical ventilation.[33]

Much has been written comparing TEE to PAC[34–37] with debate continuing whether TEE could replace the PAC as a sole monitor. Criticisms of TEE include its operator-dependent nature and inability to be continuously used post-operatively in the ICU. Despite this, utilization and experience of TEE in OLT is increasing. A 2018 survey on TEE use in American transplant centers found 42% of surveyed transplant anesthesiologists held basic or advanced perioperative TEE certification, with another 11.5% in the certification process. Over 90% of responding centers had at least one team member who utilized TEE.[6]

The Society for Advancement of Transplant Anesthesia reviewed the safety and benefit of TEE in OLT surgery. They found it to be an effective form of monitoring with safety profile similar to that in

TABLE 12 Evidence to recommendation framework according to the GRADE approach

Which modality for intraoperative monitoring of cardiac function is optimal with regard to immediate and short-term outcomes after liver transplantation?			
	Judgement		
Decision domain	Yes	No	**Reason for Judgement**
Balance between desirable and undesirable outcomes (estimated effects), with consideration of values and preferences (estimated typical) *Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?*	√		Despite multiple options the optimal modalities of intraoperative monitoring of cardiac function remain unclear. Expertise in assessment and availability of the chosen monitoring is recommended. Current literature indicates an overall low incidence of complications and minimal harm associated with their insertion.
Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes) *Is there high, moderate or low-quality evidence?*		√	Study design did not provide the required level of evidence for linking use of monitors with reduction of stated outcomes.
Confidence in Values and Preference, and their Variability *Are you confident about the typical values and preferences and are they similar across the target population?*	√		Scientific evidence and literature is lacking on optimal modality for intraoperative monitoring of cardiac function during OLT. Our expert opinion is a combination of PAC and/or TEE for intraoperative monitoring provide optimal and comprehensive real-time assessment of cardiac function. This combination was described in 1 included paper (Hofer et al 2019) with respect to reduction in hospital LOS and 30-day mortality.
Resource implications *Are the resources worth the expected net benefit from following the recommendation?*	√		Variability exists across transplant centers regarding availability of TEE and accreditation/expertise in its use. Intraoperative TEE and PAC monitoring carry a not insignificant cost per resource unit. Our opinion is that these modalities should be available in all transplant centers. The ability of TEE and/or PAC to aid diagnosis/treatment of cardiovascular collapse make them worthwhile resource allocations particularly as the prevention and treatment of cardiovascular collapse leads to an overall net reduction in resource cost.
Overall Quality of Evidence: ***Low***			
Recommendation: ***Strong for the availability and expertise in use of PAC and/or TEE monitoring particularly in high risk hemodynamically unstable patients and those with portopulmonary HT and/or cardiac dysfunction.*** ***Strong for use of TEE in patients with treated esophageal varices as acceptable risk. Strong for early use of TEE as an effective diagnostic tool in emergency cardiovascular collapse.***			

Note: Question 2. Cardiac function monitoring.

cardiac surgery.[7] Major complications were attributed to TEE in .47% of the 2706 patients included in their meta-data.[7]

TEE studies included in our search were retrospective, single-center and mostly regarding esophageal hemorrhagic complications.[1–5] The incidence of hemorrhagic complications from TEE use in patients undergoing OLT was acceptably low and consistent among most studies (.2%–.4%). One study had a higher incidence of major gastroesophageal bleed (.86%), however, a lower sample size.[5] Only one included study reported mortality in a patient with TEE-related variceal hemorrhage, however, this was attributed to primary graft non-function and multi-organ failure.[1]

A 1-year prospective large scale multicenter study of TEE safety in cardiac patients found a low overall incidence of major complications of .08%, however, a mortality incidence of .03%. This indicates a high probability of death (~40%) when a major TEE-related complication is encountered.[38] This important finding should be remembered in the OLT setting with TEE performed by appropriately trained and experienced clinicians.

Shilcutt et al. described TEE findings during all phases of liver transplantation and their relation to post-operative MACE.[39] This study was not included in the GRADE process due to the primary outcomes being intraoperative TEE findings rather than immediate or short-term post-operative outcomes. The findings highlight the effectiveness and

TABLE 13 Evidence to recommendation framework according to the GRADE approach

What is the optimal intraoperative temperature management regarding immediate and short- term outcomes after liver transplantation?			
	Judgement		
Decision domain	Yes	No	**Reason for Judgement**
Balance between desirable and undesirable outcomes (estimated effects), with consideration of values and preferences (estimated typical) *Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?*	√		The risks of targeting normothermia during OLT are minimal whereas the potential benefits of this strategy are large in comparison. There are significant benefits in reducing ventilation duration, ICU LOS, bleeding and infection. Normothermia (36.0°C–37.5°C) should be aimed for.
Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes) *Is there high, moderate or low-quality evidence?*	√		Despite the low quality of evidence with limited patient numbers, there is reasonable confidence in the positive benefits of normothermic temperature management during liver transplantation. There are relatively few downsides and resources needed for the intervention
Confidence in Values and Preference, and their Variability *Are you confident about the typical values and preferences and are they similar across the target population?*	√		There is reasonable confidence in the typical values across the population, with minimal variability. The method for determining these values is satisfactory for the population. There are no contradictory studies.
Resource implications *Are the resources worth the expected net benefit from following the recommendation?*	√		The intervention is feasible and generally available, with minimal resource implications. There is minimal variability in resource requirements across different healthcare settings. The cost is minimal compared to the benefits, for example, better outcomes and reduced subsequent healthcare costs.
Overall Quality of Evidence: ***Low***			
Recommendation: ***Strong for the maintenance of intraoperative normothermia (36.0°C--37.5°C) during liver transplantation***			

Note: Question 3. Temperature monitoring.

diagnostic utility of TEE. At least one abnormal intraoperative TEE finding was noted in 88% of patients during all phases of OLT. The most common findings were; microemboli (44%), RV dysfunction (31%), and intracardiac thromboemboli (27%). The reperfusion phase carried the highest incidence of abnormal findings (77%). Patients with intraoperative biventricular dysfunction or intracardiac thromboemboli were more likely to experience MACE and death.[39]

It is recommended liver transplant anesthesiologists complete formal training and certification in order to utilize intraoperative TEE.[7] There is also the need for regular evaluation of operator expertise. Simpler abbreviated TEE protocols may increase accessibility for non-expert TEE practitioners. A five-view focussed TEE protocol targeting five diagnoses (Table 14) during OLT is sufficient to detect critical findings and guide management changes when standard monitoring is insufficient. Additionally, a protocol-based rescue TEE in acute cardiovascular collapse found new diagnoses in 62% of cases.[40] All findings correlated with intraoperative management changes.

Very few studies directly assess the advantages of PAC over TEE with respect to clinical outcomes after OLT. Hofer et al. retrospectively assessed clinical outcomes in patients who underwent OLT with TEE or PAC alone versus TEE and PAC concurrently.[41] The combined TEE and PAC group had the shortest hospital-LOS and lowest 30-day mortality rate. They received the lowest volume of fluid intraoperatively but also had the highest incidence of new postoperative dialysis. There were no significant differences in survival rates or hospital-LOS between TEE versus no TEE.[41] These findings highlight the possibility of an outcome benefit through combined use of TEE and PAC over either device in isolation.

TABLE 14 Abbreviated TEE protocol adapted for liver transplantation[40]

Diagnosis	OLT TEE protocol (five views)
LV or RV dysfunction Hypovolemia Tamponade	Mid-esophageal 4-Chamber
SAM/LV outflow tract obstruction	Mid-esophageal LV Long-Axis
Patent Foramen Ovale Pulmonary Embolism	Mid-esophageal Bicaval
RV Dysfunction Intracardiac Thrombus Pulmonary Embolism	Mid-esophageal RV inflow/outflow
Hepatic Vein Stenosis	Hepatic Vein

Adapted from Vanemann et al.[40]

Advantages of TEE over PAC include its ability for real-time assessment of cardiac function, contractility, volume status and rapid diagnosis of life-threatening cardiac pathology such as acute RV failure, intracardiac thrombus, hypertrophic obstructive cardiomyopathy, LV out-flow tract obstruction, Takotsubos cardiomyopathy, tamponade and pulmonary embolism. Where most PAC devices carry a lag-time until return of cardiac output data, TEE can provide immediate and dynamic assessment. TEE can also directly assess ventricular preload including dynamic changes associated with treatment. PCWP however is a poor estimate of true LV volumes.[31,42]

Some transplant centers no longer use a PAC as standard for every OLT case, instead utilizing TEE. Others only use TEE as needed. The PAC does provide valuable trends to guide treatment including; PAP, cardiac output, PCWP and mixed venous oxygen saturation. Many PAC monitoring modules also provide information on End Diastolic Volume, RV Ejection Fraction, Stroke Volume and Stroke Volume Variation.

The PAC is the gold-standard monitor in patients with portopulmonary hypertension, being able to directly measure pulmonary artery pressures. This enables diagnosis of prohibitive mean pulmonary pressures and pulmonary vascular resistance (>50 mmHg and >250 dynes.s.cm^{-5}) above which proceeding to transplantation carries unacceptable mortality risk.[43] When moderate pulmonary hypertension is encountered TEE assessment of satisfactory RV function should be considered to help determine suitability to proceed.[31]

The PiCCO device is a less invasive monitor requiring central venous and arterial cannulation. It uses a combination of transpulmonary thermodilution and pulse contour analysis to obtain hemodynamic data. While its measurement of cardiac output and other metrics have shown acceptable reliability it is unable to measure pulmonary arterial pressures or SvO2 continuously.[8] This limits its use in patients with pulmonary hypertension. Its ability to improve patient-centered outcomes in OLT has yet to be demonstrated.

Our systematic review returned only one comparative study using minimally invasive cardiac output monitors assessing arterial pulse contour analysis. Villa et al. retrospectively evaluated post-operative OLT outcomes utilizing the PAC versus FloTrac/Vigileo.[44] They found no significant difference between the two groups in ICU-LOS, graft failure, hospital-LOS and mortality. FloTrac/Vigileo reliability has been questioned in low SVR, high CO states such as Child-Pugh grade B and C patients.[11] Villa et al. acknowledge this as a study limitation given the FloTrac/Vigileo was used only in Child-Pugh A, low MELD patients with low-grade portal HT.

Numerous validation studies have assessed the utility of minimally invasive systems in accurately determining cardiac output in OLT.[9–12,45–49] These often lack assessment of impact on clinical outcomes. While calibrated devices (e.g., LiDCO) have demonstrated accuracy in some validation studies,[9] uncalibrated devices (e.g., LiDCOrapid, Vigileo, FloTrac) have demonstrated conflicting results.[10–12] They largely show poor correlation and interchangeability with the PAC in OLT.[45–47] Their reliability and validity are therefore questionable.

These devices may offer information on volume status via assessment of SVV. SVV has been shown to be a reliable indicator of preload and RV end diastolic index during liver transplantation.[50,51] This has yet to show a significant positive difference on clinical outcomes when guiding fluid management in the liver transplant population. Wang et al. looked at fluid administration directed by SVV (using FloTrac/Vigileo) versus CVP and outcomes of acute kidney injury, 30-day and 1-year survival rates for living donor transplants. Outcomes were similar across the two groups showing that use of SVV is at least feasible.[52] Choi et al. found that maintenance of a high SVV (10%–20% SVV compared with <10%) reduced blood transfusion requirements in OLT recipients without significant impact on acute kidney injury, ICU/hospital-LOS or 1-year survival.[53]

Non-invasive finger cuff devices calculate cardiac output and BP by analyzing the pressure and waveform of digital arteries. A pooled meta-analysis showed that arterial pressure and cardiac output measurements using finger cuff technology and reference methods were not interchangeable in surgical or critically ill patients.[54] A trial of non-invasive finger cuff (ClearSite™) measurement of cardiac output and SVR as a substitute for the PAC in recipients of living donor transplants is currently registered with clinicaltrials.gov.[55] Once again, it is a validation and accuracy study lacking assessment of clinical outcomes.

Currently, the minimally invasive monitors do not represent a reliable substitute for the PAC or TEE. Further developments in their technology are needed.

4.3 | Subquestion 3

What is the optimal intraoperative temperature management regarding immediate and short-term outcomes after liver transplantation?

Liver transplant recipients are at increased risk of intraoperative hypothermia due to prolonged abdominal surgery, extensive blood loss and transfusion. As the liver is a contributor to temperature regulation and thermogenesis, a decrease in temperature occurs during the anhepatic or any non-functional period. There is also a drop in the patient temperature following reperfusion of the implanted cold-stored liver. This will then increase with a well-functioning graft.

Our systematic review found a small number of studies relevant to OLT temperature management and short-term clinical outcomes. While retrospective, small numbered and low quality, the studies still highlight the benefits of normothermia, with hypothermic OLT patients requiring increased blood transfusion rates and longer ICU ventilation.[56,57]

Maintenance of normothermia can be achieved by pre-warming patients, increasing ambient temperature while exposed and through active warming devices such as; forced air warmers, active heating mattresses and active fluid warming.[58] The use of regular core temperature monitoring should be undertaken throughout the perioperative period.

Although the evidence is of low quality, there is reasonable confidence in the positive benefits of normothermic temperature maintenance during liver transplantation. There are relatively few downsides and resources needed for this intervention. From the available evidence and expert opinion, the maintenance of normothermia leads to: a reduction in coagulopathy and blood transfusion; reduced ventilation time and ICU-LOS and reduced infective complications. Normothermia also reduces pulmonary vasoconstriction, and optimizes cellular, metabolic and ventricular function.

The impact of machine organ reperfusion and VVB on intraoperative temperature management was beyond the scope of this review however may have an impact on control of the patient's temperature.

5 | LIMITATIONS

With regard to all sub-questions, there was limited evidence in the literature relevant to immediate and short-term outcomes. Studies were small, non-randomized, retrospective, and observational.

6 | CONCLUSION

Significant variation in practice remains regarding approaches to vascular access, intraoperative BP and cardiac function monitoring. Many studies in the literature relate to complications of use rather than impact on postoperative outcomes. Despite this, the working group were able to make the following recommendations;

Subquestion1

Routine use of invasive arterial BP and CVP monitoring as a minimum standard of care.

Consideration of potential discrepancy between peripheral and central arterial BP during significant hemodynamic instability.

Routine use of high flow venous cannulae placed under US guidance, monitoring for extravasation and hematoma.

(Quality of Evidence Very Low, Grade of Recommendation Strong)

Subquestion 2:

The availability and expertise in use of the PAC and/or TEE during OLT.

Use of TEE in patients with treated esophageal varices as an acceptable risk

TEE is an effective diagnostic tool in emergency cardiovascular collapse.

(Quality of Evidence Low, Grade of Recommendation Strong)

Subquestion 3:

Normothermia should be maintained during the perioperative period.

(Quality of Evidence Low, Grade of Recommendation Strong)

Our expert working panel suggest a number of areas for future research and development.

As technology and accuracy of minimally invasive monitors improves, well-constructed, prospective trials assessing their utility and impact on post-operative clinical outcomes are necessary.

With the increasing use of TEE in the liver transplant community, global consensus of a "TEE for OLT" protocol would prove useful. Furthermore, universal agreement on necessary standards of training, regular evaluation of operator expertise and requirements for maintenance of accreditation would ensure ongoing TEE proficiency among liver transplant anesthesiologists leading to better intraoperative care.

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The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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