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REPORTS OF ORIGINAL INVESTIGATIONS

Perioperative clinical practice in liver transplantation: a cross-sectional survey

Pratique clinique périopératoire en transplantation hépatique : un sondage transversal

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Abstract

Purpose *The objective of this study was to describe some components of the perioperative practice in liver transplantation as reported by clinicians.*

Methods *We conducted a cross-sectional clinical practice survey using an online instrument containing questions on selected themes related to the perioperative care of liver transplant recipients. We sent email invitations to Canadian anesthesiologists, Canadian surgeons, and French anesthesiologists specialized in liver transplantation. We used five-point Likert-type scales (from "never" to "always") and numerical or categorical answers. Results are presented as medians or proportions.*

Results *We obtained answers from 130 participants (estimated response rate of 71% in Canada and 26% in France). Respondents reported rarely using transesophageal echocardiography routinely but often using it for hemodynamic instability, often using an intraoperative goal-directed hemodynamic management strategy, and never using a phlebotomy (medians from ordinal scales). Fifty-nine percent of respondents reported using a restrictive fluid management strategy to manage*

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hemodynamic instability during the dissection phase. Forty-two percent and 15% of respondents reported using viscoelastic tests to guide intraoperative and postoperative transfusions, respectively. Fifty-four percent of respondents reported not pre-emptively treating preoperative coagulations disturbances, and 91% reported treating them intraoperatively only when bleeding was significant. Most respondents (48–64%) did not have an opinion on the maximal graft ischemic times. Forty-seven percent of respondents reported that a piggyback technique was the preferred vena cava anastomosis approach.

Conclusion *Different interventions were reported to be used regarding most components of perioperative care in liver transplantation. Our results suggest that significant equipoise exists on the optimal perioperative management of this population.*

Résumé

Objectif *L'objectif de cette étude était de décrire certaines composantes de la pratique périopératoire en transplantation hépatique telles que rapportées par les cliniciens.*

Méthode *Nous avons mené un sondage transversal sur la pratique clinique à l'aide d'un instrument en ligne comportant des questions sur des thèmes sélectionnés liés aux soins périopératoires des receveurs de greffe du foie. Nous avons envoyé des invitations par courriel à des anesthésiologistes canadiens, des chirurgiens canadiens et des anesthésiologistes français spécialisés en transplantation hépatique. Nous avons utilisé des échelles de type Likert à cinq points (de « jamais » à « toujours ») et des réponses numériques ou catégorielles. Les résultats sont présentés sous forme de médianes ou de proportions.*

Résultats *Nous avons obtenu des réponses de 130 participants (taux de réponse estimé à 71 % au Canada et à 26 % en France). Les répondants ont déclaré utiliser rarement l'échocardiographie transœsophagienne de routine, mais l'utiliser fréquemment pour l'instabilité hémodynamique, souvent en utilisant une stratégie de prise en charge hémodynamique peropératoire axée sur les objectifs, et jamais en utilisant une phlébotomie (médianes des échelles ordinales). Cinquante-neuf pour cent des répondants ont déclaré utiliser une stratégie restrictive de gestion liquidienne pour prendre en charge l'instabilité*

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hémodynamique pendant la phase de dissection. Quarante-deux pour cent et 15 % des répondants ont déclaré utiliser des tests viscoélastiques pour guider les transfusions peropératoires et postopératoires, respectivement. Cinquante-quatre pour cent des répondants ont déclaré ne pas traiter préventivement les troubles préopératoires de la coagulation, et 91 % ont déclaré les traiter en peropératoire uniquement lorsque les saignements étaient importants. La plupart des répondants (48-64 %) n'avaient pas d'opinion sur les temps ischémiques maximaux du greffon. Quarante-sept pour cent des répondants ont déclaré qu'une technique de 'piggyback' (anastomose latéroterminale) était l'approche préférée pour l'anastomose de la veine cave.

Conclusion *Différentes interventions ont été signalées pour la plupart des composantes des soins périopératoires dans la transplantation hépatique. Nos résultats suggèrent qu'il existe une incertitude significative concernant la prise en charge périopératoire optimale de cette population.*

Keywords hemodynamic management · liver transplantation · perioperative management · research · Transfusion

Liver transplantation (LT) improves the survival of patients with end-stage liver disease.[1] In recent decades, survival in both patients awaiting transplantation and liver transplant recipients has improved through objective prioritization of the sickest patients and an overall improvement in the quality of care.[2,3] As a result, postoperative morbidity has concomitantly increased as sicker patients are given priority for transplantation.[4–6] To reduce complications and better manage the use of liver grafts, a scarce resource, we must optimize perioperative care.

Liver transplantation is a surgery associated with severe bleeding, hemodynamic instability, coagulopathy, and perioperative multiorgan dysfunctions.[7–12] A higher intraoperative fluid balance, intraoperative hypotension, and exposure to blood products have been associated with worse postoperative outcomes, suggesting that intraoperative fluid and hemodynamic management strategies as well as goal-directed transfusion strategies may be important interventions to reduce postoperative complications.[7,8,11–19] Bleeding and coagulopathy may also be reduced or managed by different techniques, such as the use of a restrictive fluid management strategy, phlebotomies, splanchnic vasoconstrictors, viscoelastic tests, or antifibrinolytics.[11,12,20–24] Many perioperative surgical interventions may also impact postoperative outcomes, such as graft quality, donor type, and surgical approach to vascular anastomose;[25–27] however, there is no high-quality evidence to support the use of any of these techniques. As such, anesthesiologists and surgeons perform most of these interventions based on physiologic paradigms and inferences from low-quality studies.[28–31]

The importance of these interventions in the intraoperative care plan offered by clinicians to liver transplant recipients has not been well described. Previous studies based on data reported by liver transplant anesthesia directors suggested a large variability of the use of different intraoperative interventions across centres.[32–35] Nevertheless, these surveys did not focus on intraoperative goal-directed strategies, did not include many anesthesiologic or surgical interventions that may have important effects on postoperative complications, did not report individual practices, and most did not reflect contemporary practices.

The objectives of this study were to describe some perioperative clinical goals of practice in LT as perceived by Canadian anesthesiologists and surgeons as well as French anesthesiologists, its variability across regions, and the underlying clinical equipoise. We hypothesized that reported perioperative goals of management would be variable, and that equipoise would remain regarding most interventions.

Methods

Design

We conducted a cross-sectional survey on perioperative clinical practice in LT, as perceived by individual anesthesiologists and surgeons involved in LT. This survey was developed according to recognized recommendations on the design of self-administered clinical practice surveys.[36] This study was approved by the research ethics board of the Centre hospitalier de l'université de Montréal (Montreal, QC, Canada), and individual consent was obtained from each participant prior to survey administration.

Survey development

Item generation and reduction

An expert panel that included clinical experts in anesthesiology (F. M. C., S. K.), critical care (F. M. C., C. K., M. C., C. V.), liver diseases (C. K., J. M. G.), LT surgery (E. S., K. D.), nursing (C. V.), measurement and evaluation (C. V.), and epidemiology (F. M. C., M. C.) from different universities participated in the development using a modified web-based Delphi iterative approach.[37] Based on a preliminary list of domains and items proposed by the principal investigator (F. M. C.), the expert panel

first generated new domains and items and classified them using five-point Likert-type scales. Questions considered "important" or "very important" by more than 75% of the experts were selected.[38] The panel then prioritized selected domains and items by order of importance and the most important items were selected by the principal investigator to build a 10–15-min-long survey. The final domain list included hemodynamic management, transfusion management, graft selection and surgical techniques, recipients' risk evaluation and selection, and research goals. Patient representatives (R. F., M. W.) revised this list to ensure they represent items important to patients.

Formatting

Based on the final item list, two investigators (F. M. C., C. V.) developed the survey instrument by creating closed questions on clinical interventions, laboratory thresholds and clinical characteristics, and scenario-based semi-open questions on clinical decision-making. Closed questions required binary, multiple choices, ordinal (five-point Likert-type scale) or open numerical answers and included "other" and "do not know or prefer not to answer" choices to avoid a "floor and ceiling effect", to help identify new items and to minimize break-offs.[39] Some questions were addressed to anesthesiologists, surgeons, or both. We added a final section collecting respondent characteristics (e.g., age, years of practice, etc.). The instrument was finally built online using the REDCap data capture tools, hosted at the Centre de recherche du Centre hospitalier de l'université de Montréal (Montreal, QC, Canada).[40]

Validation

The instrument was pretested among the expert panel, who revised and modified the instrument for content validity (instrument clarity, questions related to selected items, survey objectives met). The instrument was then piloted among representatives of our target population who were not part of the sampling frame (six anesthesiology and five surgery senior residents from the Centre hospitalier de l'Université de Montréal). Participants completed the instrument while investigators (F. M. C., E. A.) observed them and measured the time of completion. Respondents evaluated the clinical sensibility (comprehensiveness, clarity, and face validity) of the instrument using a standardized assessment tool (see Electronic Supplementary Material [ESM] eAppendix 1).[36] We conducted a focus group using a nominal group technique to discuss investigators' observations, clinical sensibility tool answers, instrument flow, ease of administration, and possible redundancy.[41,42] We modified the instrument according to this assessment and asked the same respondents to answer the survey twice over two weeks (test-retest reliability assessment). During a second focus group, we discussed all questions with a percent agreement between 50% and 80% and conducted a complete review of the questions with a percent agreement below 50%. Some questions were modified during this session and changes were unanimously approved by respondents. The final instrument was translated into French and back translated into English by two translators with several iterations until the versions were equivalent. The final French version was revised by three investigators (F. M. C., J. M. G., E. S.) to ensure medical terminology was accurate.[43] Final questions included in the instrument and pertaining to this manuscript can be accessed as supplementary material (ESM eAppendix 2).

Survey administration and data collection

The sampling population included Canadian and French staff anesthesiologists involved in LT and Canadian LT surgeons. Physicians in training (residents, fellows) were excluded. Coinvestigators (J. P., T. O., K. D., N. G. V., S. A. M., S. K., F. M. C., A. C.) sent an invitation letter that included a link to the online instrument to local colleagues (anesthesiologists and surgeons) across the seven Canadian centres in July 2021 (see ESM eAppendix 3). The Canadian Society of Transplantation also sent the invitation letter to its members. The invitation letter was sent to members of the liver transplant interest group (*club foie*) of the Société Française d'Anesthésie-Réanimation in October 2021 by one coinvestigator (A. J.). To ensure that each respondent met the inclusion criteria, a screening section of the questionnaire confirmed eligibility, provided an option to opt out, and requested consent. Four reminders were sent after the initial invitation in Canada and one in France (mid-September 2021 [Canada], end of October 2021 [Canada], mid-December 2021 [Canada], and mid-January 2022 [Canada and France]) to maximize the response rate.[36] No participant received financial compensation. Based on an estimation of 150 potential respondents in Canada (presurvey results; see ESM eTable 1), a 46% response proportion (70 persons) was required to achieve a 95% confidence limit of 8% on a proportion of 50% (a conservative assumption) for any given intervention, using a finite population correction.

Data analyses

We report herein the answers to four of the five domains of the instrument: hemodynamic management, transfusion management, graft selection, and transplantation and research goals (the "recipients' risk evaluation and

selection" domain is not reported in the present manuscript). We report answers as proportions for categorical data, as medians for ordinal data (five-point Likert-type scales) and as means or medians for continuous data. For inference, we estimated score 95% confidence intervals (CIs) for proportions and non-parametric percentiles and bootstrap 95% CIs for ordinal and continuous data using 2,000 iterations (or exact CIs for ordinal data with a very low median).[44] We also report ordinal data as the percentage of answers for each level within figures.

We compared the proportions of use of interventions across six anonymized locations (five Canadian provinces [British Colombia, Alberta, Ontario, Quebec, Nova Scotia] and France), as well as the reported pulse pressure variation and hemoglobin threshold used. We used these locations, rather than centres, since many respondents did not report their centre of practice. We did not compare some answers because of the limited subsample (surgeons only). We used a homogeneity Chi square test by Monte-Carlo simulations using 2,000 replicates for proportions and a Kruskal–Wallis analysis of variance for continuous variables.[45] We did not include answers from unknown locations in these statistical tests but reported the distribution of answers in this group. We set our alpha level at 0.05 and used R software version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) to conduct the analyses.

Results

From a sampling frame of approximately 236 potential Canadian and French respondents, 130 participants answered at least one question of the survey between July 2021 and February 2022 (Table 1, ESM eTables 1 and 2). We estimated that 109 respondents were from Canada and 21 from France (if the 23 respondents who did not declare their country of residence had the same distribution as those who did), which provide a response proportion of 71% in Canada and 26% in France (Table 1 and ESM eTable 1). Of those who started the survey, 107 respondents finished the questionnaire (overall completion proportion of 82%) (ESM eFig. 1).

Table 1 Respondent characteristics

Variable	Result[a]
Specialty	
Anesthesiology	98/130 (75%)
Surgery	32/130 (25%)
Critical care training	
Yes	38/130 (29%)
No	92/130 (71%)
Sex (male)	74/104 (71%)
Years in practice	
< 5	26/106 (25%)
5–9	17/106 (16%)
10–14	15/106 (14%)
15–19	19/106 (18%)
> 19	29/106 (27%)
Country	
Canada	90/107 (84%)
France	17/107 (16%)
Department or service head	13/106 (12%)
Clinician scientist	32/106 (30%)
Centre level of activity	
Low (< 50 LT/year)	22/106 (21%)
Moderate (50–100 LT/year)	53/106 (50%)
High (> 100 LT/year)	31/106 (30%)
Individual cases per year	
Anesthesiologists	10 [5, 20]
Surgeons	23 [15, 35]

[a] Results are reported as *n*/total *N* (%) and as median [first and third quartiles]. Twenty-three respondents did not provide any answer to sociodemographic questions other than the specialty (that was compulsory to start the survey); among them, 35% were surgeons and 65% were anesthesiologists.

Hemodynamic management

This domain was completed by 98 anesthesiologists (one only answered some questions of this domain) and 32 surgeons also answered the question regarding the use of phlebotomy (130 respondents for this domain). Based on five-point ordinal Likert-type scales using medians with 95% CI, transesophageal echocardiography (TEE) was reported to be rarely (95% CI, rarely to sometimes) used routinely but often (95% CI, sometimes to often) used for hemodynamic instability (see ESM eTable 3). A strategy targeted on hemodynamic objectives (goal-directed therapy) was often used (95% CI, sometimes to often) and a phlebotomy never used (95% CI, never to never) (see ESM eTable 3). We also reported the proportion of each level of the answers to the previous questions in Fig. 1. Most anesthesiologists reported using vasopressors to attain their hemodynamic goal; other details on goal-directed therapy and monitoring may be found in ESM eTables 4–7. Seventy-seven percent (95% CI, 68 to 85) of respondents reported using pulse pressure variation (or stroke volume variation) to help decide on fluid administration, with a reported median threshold of 13% (95% CI, 13 to 15) (ESM eTable 8). Faced with hemodynamic instability, reported fluid administration strategies varied between respondents and 81% of them reported adapting their strategy to the surgical phases

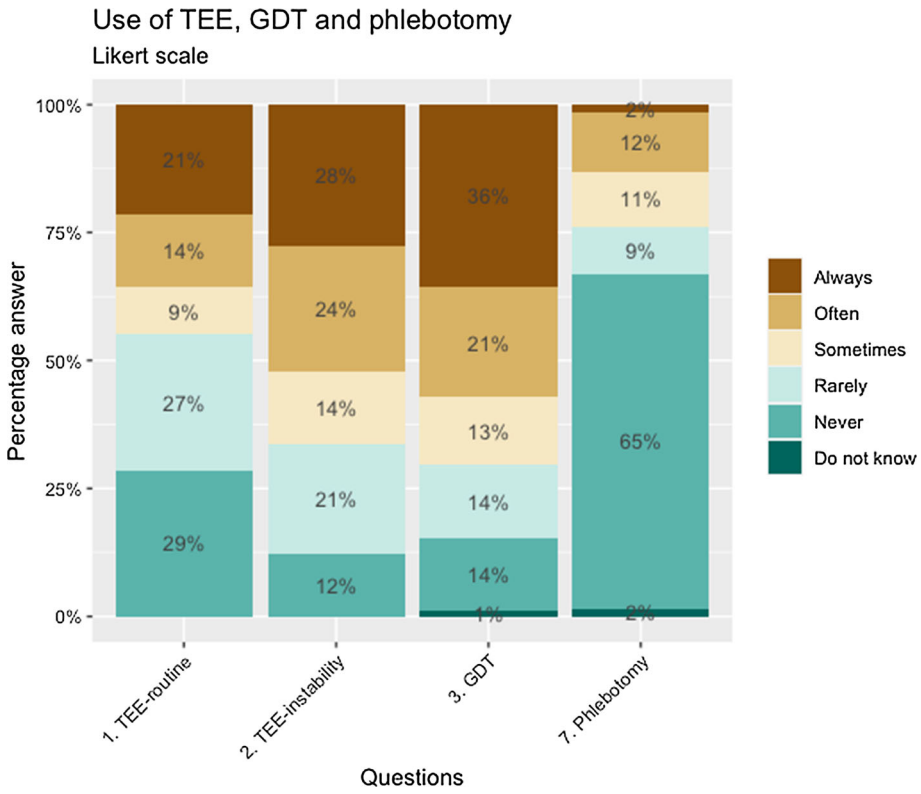

Fig. 1 Use of TEE, GDT, and phlebotomy according to Likert scale results. Results are based on 98 respondents for questions 1,2, and 3 and 130 respondents for question 7 (one missing value from an anesthesiologist). GDT = goal-directed therapy; TEE = transesophageal echocardiography

(Fig. 2 and ESM eTable 9). Among the 57 respondents who reported using a restrictive fluid management strategy during the dissection phase, 33% (95% CI, 22 to 46) also reported using a phlebotomy at least sometimes. Norepinephrine was the most often reported vasopressor (98%; 95% CI, 93 to 99) and vasopressin (or terlipressin) the second (76%; 95% CI, 67 to 84) (see ESM eFig. 2 and eTables 10 and 11). The reported use of most interventions was heterogeneous across locations, except the use of a restrictive fluid management strategy and the pulse pressure variation threshold (ESM eTables 12 and 13 and eFig. 3).

Transfusion management

This domain was completed by 120 participants (ESM eTable 14). The median threshold among the 102 respondents who reported using one was 80 $g{\cdot}L^{-1}$ (95% CI, 70 to 80) (eight participants did not provide an answer and ten participants [9%; 95% CI, 5 to 16] reported never using any threshold to decide on red blood cell [RBC] transfusions) (ESM eTable 15). Most respondents (54%; 95% CI, 45 to 63) reported not treating coagulation disturbances pre-emptively before surgery, but many reported transfusing blood products selectively for certain disturbances (see ESM eTables 16 and 17). Most respondents reported using standard coagulation time values to monitor coagulation either during (45%; 95% CI, 36 to 54) or after surgery (71%; 95% CI, 62 to 78) (see Fig. 3 and ESM eTable 18). Almost all respondents (91%; 95% CI, 84 to 95) reported treating coagulation disturbances during surgery only when bleeding was significant (see Fig. 4 and ESM eTables 19 and 20). The reported use of most interventions was heterogeneous across locations, except the absence of pre-emptive treatment of coagulation disturbances and hemoglobin thresholds used to trigger RBC transfusions (ESM eTable 21 and eFig. 4).

Graft selection and surgical techniques

This domain was completed by 116 participants. A total vena cava replacement technique without veno-venous bypass was the technique most often reported to be used (42%; 95% CI, 34 to 51) (Fig. 5 and ESM eTables 22 and 23). Most respondents did not have an opinion on the acceptable maximum graft ischemic time (ESM eTable 24). The use of partial clamping and the maximal acceptable cold ischemia time were variable across locations (ESM eTable 25 and eFig. 5). Thirty surgeons answered questions on donor characteristics. Age, body mass index (BMI), and agonal time were the main characteristics used to consider a graft in the context of a donation after cardiocirculatory death (DCD) (ESM eTables 26 and 27 and eFig. 6). Portal thrombosis, retransplantation, and arterial anatomy were recipient

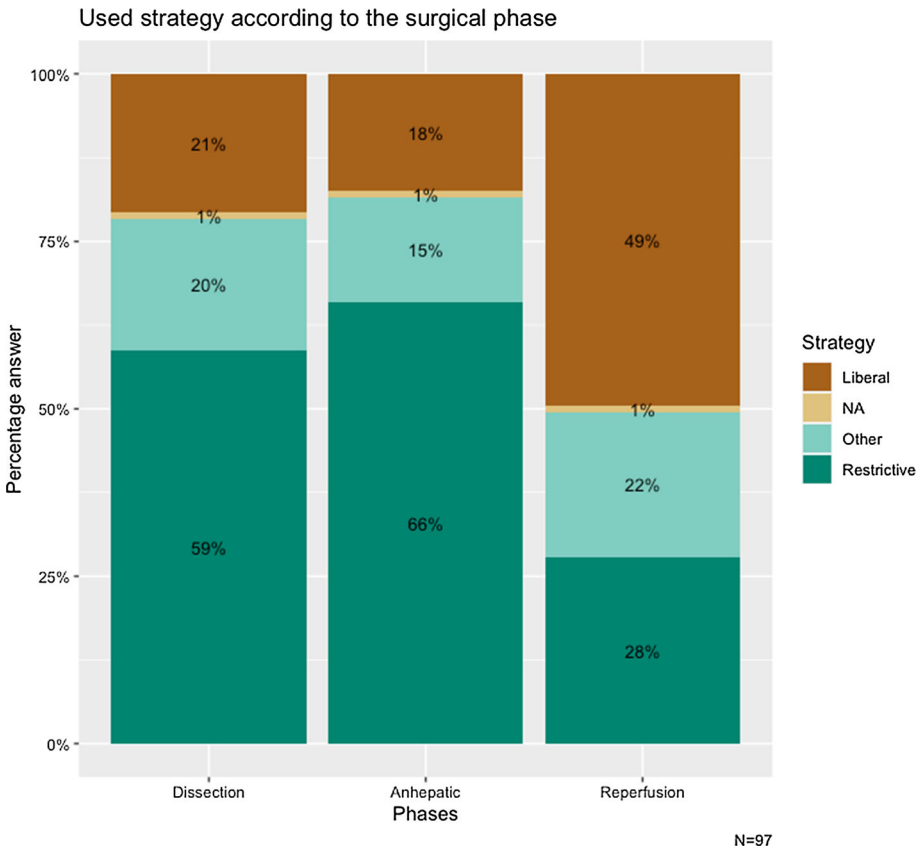

Fig. 2 Fluid management strategy used for hemodynamic instability according to the surgical phase. Results are based on 97 respondents and include respondents who reported using the same strategy during the whole procedure and those who reported adapting their strategy to the surgical phases.
NA = Not available

characteristics most reported to change surgical techniques (ESM eTable 28 and eFig. 7).

Research goals

This domain was completed by 109 participants. Most participants suggested quality of life as a primary outcome for future clinical trials investigating intraoperative management strategies (30%; 95% CI, 22to 39) (ESM eTable 29 and eFig. 8). Primary graft dysfunction, renal complications, and biliary complications were considered the most important complications to include in such a trial (ESM eTable 30 and eFig. 9). In a trial with 60% of the control suffering from at least one severe complication, a median absolute reduction of 6% (95% CI, 3 to 7) on this risk was considered a minimal clinical important difference for any intraoperative intervention (ESM eTable 31).

Discussion

In the present survey study, intraoperative hemodynamic management reported by anesthesiologists suggests clinical equipoise, since practices did not seem to be consistently implemented and were variable across locations, particularly regarding the use of TEE, GTD, and fluid management. Phlebotomy was almost never used, but most often used among respondents who reported using a restrictive fluid management strategy in the dissection phase. Norepinephrine was consistently the first-line vasopressor reported to be used. The approach to coagulation monitoring was not consistent, but the response to coagulation disturbances with factor replacement only when significant bleeding occurred was more consistent. Some donor characteristics were consistently used to select DCD grafts, such as age and BMI, while others were less consistently used. Portal thrombosis consistently modified the surgical approach, but most other recipient characteristics less consistently influenced it. Surgical approach to the vena cava anastomosis was inconsistent and variable, and most

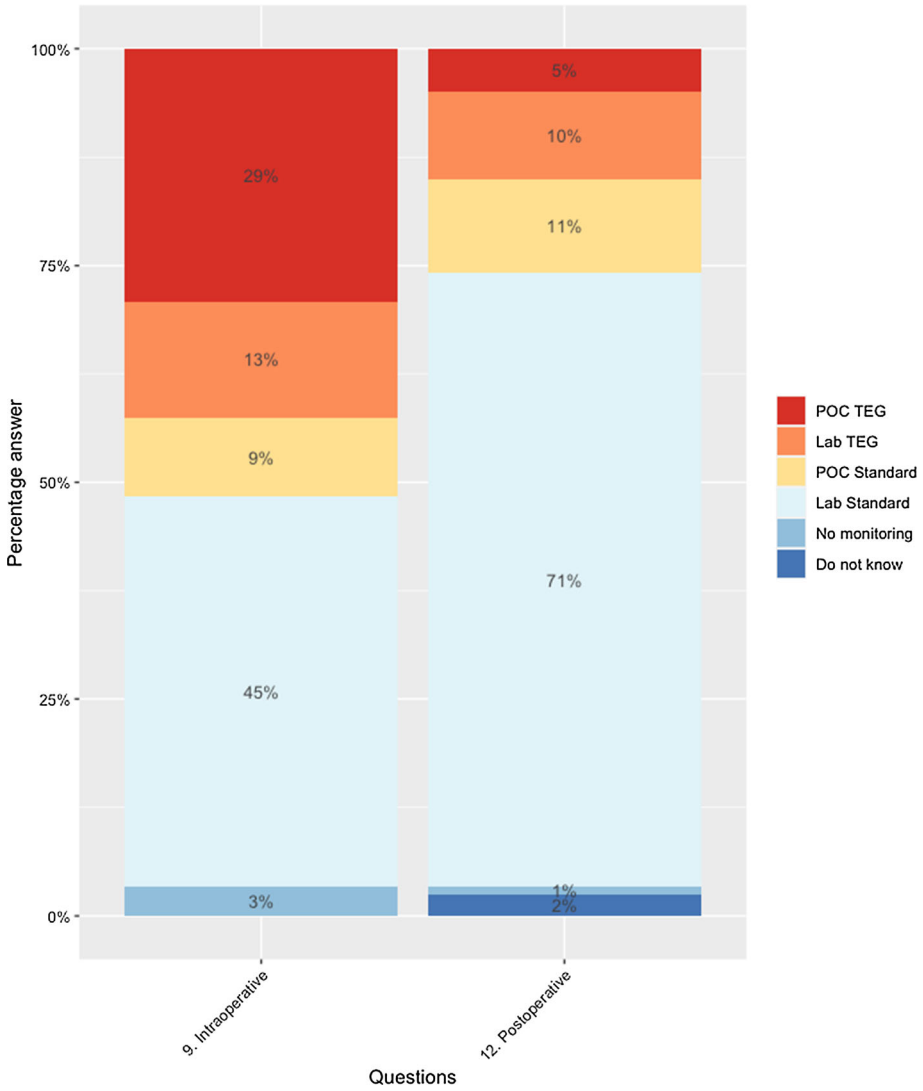

Fig. 3 Coagulation monitoring during and after the transplantation. Results are based on 120 respondents. POC = point-of-care; TEG = yhromboelastrography (or thromboelastometry)

respondents did not have an opinion on maximal ischemia time that should be targeted. Finally, research goals were heterogeneous with no well-recognized primary outcome of intraoperative research in LT, although some complications, such as graft and kidney complications, were more consistently considered important.

Few interventions conducted in the perioperative period of a LT are supported by good evidence. Recent guidelines or reviews on perioperative care for early recovery, hemodynamic management, coagulation management, anesthetic management, and overall management of LT all reported a lack of high-quality evidence.[11,46–49] Clinical perioperative practice is mostly based on low-quality evidence, expert opinion, or historical practice. Our results suggest that equipoise remains on most hemodynamic, transfusion-related, and surgical interventions in Canada and France. Combined with the current state of knowledge, many knowledge gaps and research opportunities remain. Of note, answers on research goals were partly aligned with recently published recommendations suggesting that outcomes other than patient survival should be used in LT research.[50]

Previous surveys on the perioperative care of liver transplant recipients were all conducted among liver transplant anesthesia directors and most were conducted a decade ago.[32–35] The most recent survey was conducted in the USA in 2020–2021 by the Society for the Advancement of Transplant Anesthesia.[35] It focused mostly on care organization but reported data on some themes included in our survey. Interestingly, the use of viscoelastic coagulation testing (95%) was more commonly used at USA centres, while the use of TEE was similar (49%).[35] Nevertheless, this latter study collected institutional data and used broad and subjective categories ("yes" or "no" for the viscoelastic test and four categories for the estimated proportion of cases with TEE); the reasons to

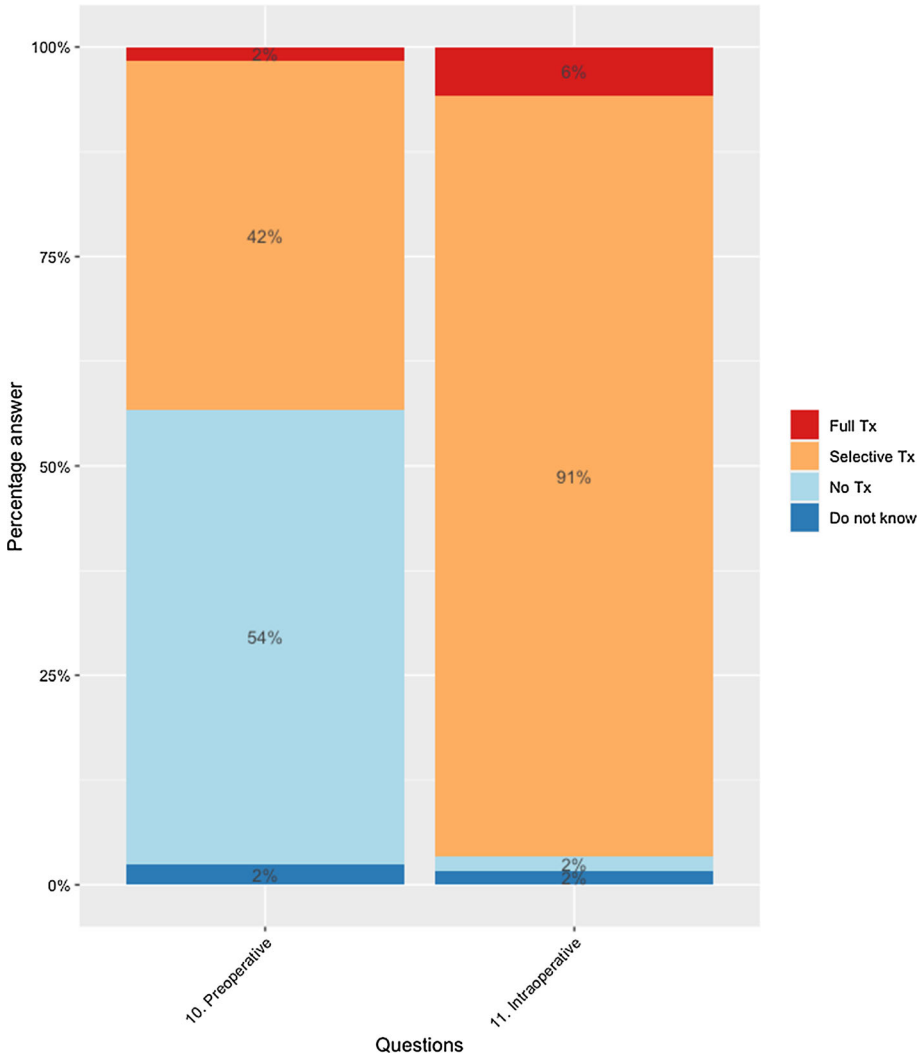

Fig. 4 Treatment of coagulation disturbances with blood products before and during surgery. Results are based on 120 respondents. Full Tx = full treatment (transfusions to treat all abnormal values); No Tx = no treatment (no transfusion to treat abnormal values prior to surgery or no transfusion based on laboratory values during surgery); Selective Tx = selective treatment (transfusions to treat some abnormal values prior to surgery or transfusions to treat some abnormal values when bleeding is significant during surgery)

use TEE or viscoelastic tests perioperatively and most of our other domains and themes were not included.[35] Our results rather circumscribed individual clinicians' perspectives of perioperative practice, including goal-directed interventions.

Our survey was developed following a rigorous method to ensure the validity of the inferences made with our instrument. We involved experts in the field of epidemiology, test theory, anesthesiology, critical care, LT, and patient-partnership to develop domains, items, and questions that met our research objectives. Nevertheless, the validation process had limitations, since the pilot clinical sensibility and reliability testing was performed on a limited number of individuals precluding advanced reliability and agreement measurements.[51] Nevertheless, our goal was strictly to infer on LT perioperative practices and as such, content validation was deemed the most important aspect to support the use of the instrument in our study population. Also, we did not have access to the emails of potential respondents and could not send personalized links. Thus, we cannot exclude that some respondents may have answered more than once. We were also uncertain of the exact denominator of our sampling frame, since the number of potential respondents was estimated from a presurvey conducted in 2019 in Canada and from the number of members of the liver transplantation group of the Société Française d'Anesthésie-Réanimation. Nevertheless, we estimated a

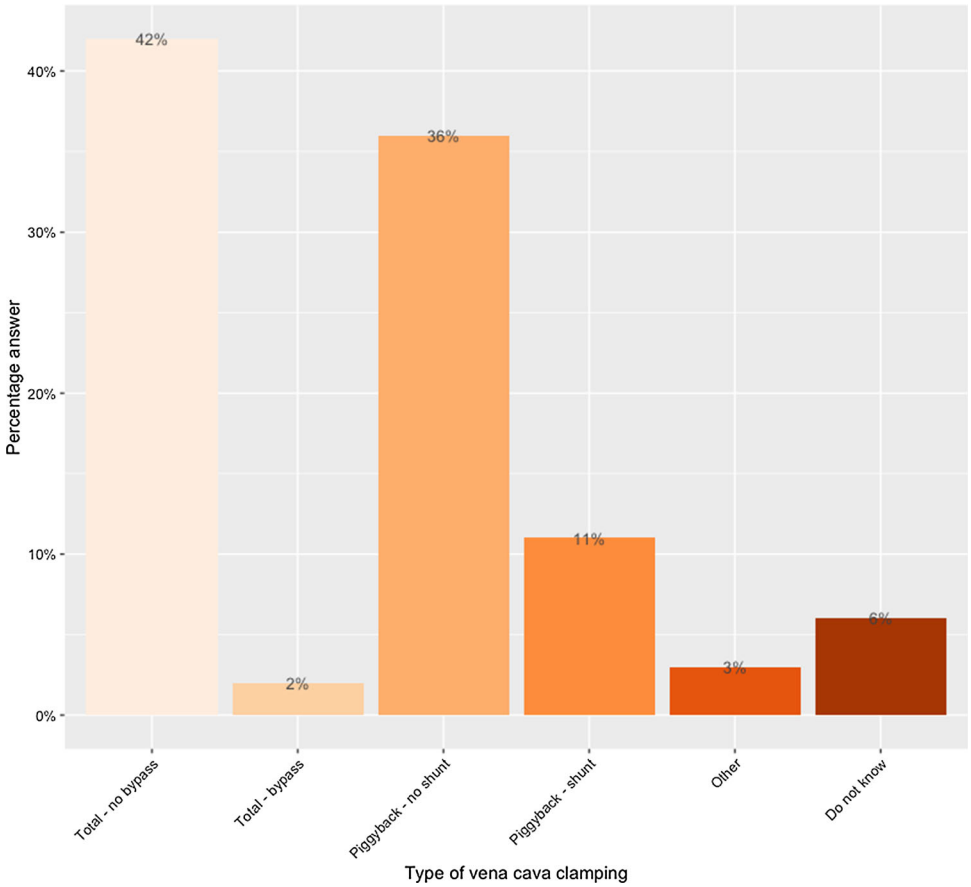

Fig. 5 Vena cava clamping techniques. Results are based on 116 respondents.

response rate of 71% in Canada, suggesting a good representativeness of this community, but only a 26% response rate in France, suggested a more limited international representativeness. The different sampling strategies between countries probably explain these differences.

In conclusion, our survey described the reported practice regarding many interventions reported to be used in the perioperative care of LT recipients in the hemodynamic management, coagulation management, and surgical domains. The perioperative practices seemed variable across centres and clinical equipoise remains on most interventions. These results will inform the design and conduct of high-quality clinical trials evaluating different perioperative interventions in LT recipients.

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