



## Fluid and pain management in liver surgery (MILESTONE): A worldwide study among surgeons and anesthesiologists <sup>☆</sup>



Timothy H. Mungroop, MD<sup>a,b</sup>, Bart F. Geerts, MD<sup>b</sup>, Denise P. Veelo, MD<sup>b</sup>, Timothy M. Pawlik, MD<sup>c</sup>, Aurélie Bonnet, MD<sup>d</sup>, Mickaël Lesurtel, MD<sup>e</sup>, Koen M. Reytjens, MD<sup>f</sup>, Takehiro Noji, MD<sup>g</sup>, Chao Liu, MD<sup>h</sup>, Eduard Jonas, MD<sup>i</sup>, Christopher L. Wu, MD<sup>j</sup>, Eduardo de Santibañes, MD<sup>k</sup>, Mohammed Abu Hilal, MD<sup>l</sup>, Markus W. Hollmann, MD<sup>b</sup>, Marc G. Besselink, MD<sup>a</sup>, Thomas M. van Gulik, MD<sup>a,\*</sup>

<sup>a</sup> Department of Surgery, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, the Netherlands

<sup>b</sup> Department of Anesthesiology, Amsterdam UMC, University of Amsterdam, the Netherlands

<sup>c</sup> Department of Surgery, the Ohio State University Wexner Medical Center, Columbus, OH

<sup>d</sup> Department of Anesthesiology, Croix Rousse University Hospital, University of Lyon, France

<sup>e</sup> Department of Surgery and Liver Transplantation, Croix Rousse University Hospital, University of Lyon, France

<sup>f</sup> Department of Anesthesiology, University Medical Center Groningen, University of Groningen, the Netherlands

<sup>g</sup> Department of Gastroenterological Surgery II, Faculty of Medicine Hokkaido University, Sapporo, Japan

<sup>h</sup> Department of Surgery, Sun Yat-sen Memorial Hospital, Guangzhou, China

<sup>i</sup> Department of Surgery, University of Cape Town/Groote Schuur Hospital, Cape Town, South Africa

<sup>j</sup> Department of Anesthesiology, the Hospital for Special Surgery/Weill Cornell Medical College; New York, NY

<sup>k</sup> Department of Surgery, Hospital Italiano de Buenos Aires, Argentina

<sup>l</sup> Department of Surgery, University of Southampton NHS, Southampton, UK

### ARTICLE INFO

#### Article history:

Accepted 12 August 2018

Available online 9 October 2018

### ABSTRACT

**Background:** Fluid and pain management during liver surgery (eg, low central venous pressure) is a classic topic of controversy between anesthesiologists and surgeons. Little is known about practices worldwide. The aim of this study was to assess perioperative practices in liver surgery among and between surgeons and anesthesiologists worldwide that could guide the design of future international studies.

**Methods:** An online questionnaire was sent to 22 societies, including 4 international hepatopancreatobiliary societies, the American Society of Anesthesiologists, and 17 other (inter-)national societies.

**Results:** A total of 913 participants (495 surgeons and 418 anesthesiologists) from 66 countries were surveyed. A large heterogeneity in fluid management practices was identified, with 66% using low central venous pressure, 22% goal-directed fluid therapy, and 6% normovolemia. In addition, large heterogeneity was found regarding pain management practices, with 49% using epidural analgesia, 25% patient-controlled analgesia with opioids, and 12% regional techniques. Most participants assume that there is a relation between perioperative pain management and morbidity and mortality (78% of surgeons vs 89% of anesthesiologists;  $P < .001$ ). Both surgeons and anesthesiologists have the highest expectations for minimally invasive surgery and enhanced recovery pathways for improving outcomes in liver surgery. No clear differences between continents were found.

**Conclusion:** Worldwide there is a large heterogeneity in fluid and pain management practices in liver surgery. This survey identified several areas of interest for future international studies aiming to improve outcomes in liver surgery.

© 2018 Elsevier Inc. All rights reserved.

### Introduction

Liver surgery is high-risk surgery with morbidity rates around 40%<sup>1-3</sup> and mortality rates of 1% to 5%, depending on the extent of the resection.<sup>4,5</sup> Because the liver is one of the best perfused organs of the human body, major liver surgery is associated with significant risk of blood loss.<sup>6</sup> The correlation between the amount of

<sup>☆</sup> Funding for this study was provided by departmental sources of the Amsterdam UMC, University of Amsterdam.

\* Corresponding author: Department of Surgery, Cancer Center Amsterdam Amsterdam UMC, University of Amsterdam, IWO IA.1-118, Meibergdreef 9, PO Box 22660, 1100 DD Amsterdam, the Netherlands. Tel.: +31 20 566 9111

E-mail address: [t.m.vangulik@amc.nl](mailto:t.m.vangulik@amc.nl) (T.M. van Gulik).

blood loss and the risk of adverse outcomes in liver resections has been well established in several studies.<sup>7,8</sup> To improve outcomes, standards in perioperative care have been formulated.<sup>9</sup> Not all aspects of perioperative care in liver surgery, however, have been standardized. For instance, fluid and pain management have been classic areas of controversy among surgeons and anesthesiologists.

Arguably the most common topic of controversy is the use of restrictive fluid practices—that is, low central venous pressure (CVP). The potential short-term beneficial effects of low CVP on the surgical field seem to be in conflict with numerous randomized controlled trials (RCTs) on the benefits of goal-directed fluid therapy (GDFT) in other types of surgery.<sup>10,11</sup> Furthermore, epidural analgesia is widely used for pain management, although recent RCTs have found that there are effective alternatives.<sup>12–14</sup> For example, continuous wound infiltration with preperitoneal catheters, placed by surgeons, may offer some secondary advantages such as a reduced incidence of hemodynamic instability, placement during surgery, and no need for prolonged use of urinary catheters.<sup>14</sup>

The aim of this study was to assess current practices regarding perioperative fluid and pain management in liver surgery. These results can guide the choice of topics for future international studies and focus on the topics of controversy.

## Methods

### Study design and participants

An online, secure, anonymous survey with 23 questions was created in collaboration with the multidisciplinary MILESTONE study group. The content of the questionnaire was optimized and validated in consultation with a senior methodologist who has experience in performing and analyzing surveys. The survey was pilot tested and improved multiple times before launch. Internet protocol addresses were captured to prevent multiple responses by the same individual and were removed after the survey was closed. The medical ethical committee of the Amsterdam UMC, location AMC, waived the need for informed consent of this study because no patients were involved.

Participants included liver surgeons and anesthesiologists who annually performed at least 10 liver resections. Incomplete responses were excluded. The total number of invited surgeons and anesthesiologists was unknown because of an overlap in the membership databases of the associations and the confidentiality requirements of these societies.

Members of the American Association of Anesthesiologists, Americas Hepato-Pancreato-Biliary Association, International Hepato-Pancreato and Biliary Association, European-African Hepato-Pancreato-Biliary Association, Australia-New Zealand Hepato-Pancreato-Biliary Association, Liver Intensive Care Group of Europe, European Guidelines Meeting on Laparoscopic Liver Surgery, Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, Japanese Society of Hepato-Biliary-Pancreatic Surgery, and several other national societies were invited to participate in this study and received up to 2 reminders. Data were collected anonymously with SurveyMonkey Platinum (SurveyMonkey Inc., San Mateo (CA), United States). Responders were given the option to include their information (e-mail address) separately to receive the study results.

### Data collection

Collected demographic information included type of specialty (surgeons: liver surgery, transplantation, hepatopancreatobiliary, or general; anesthesiologists: general, focus on liver resections, liver transplantation), type of hospital (academic or nonacademic), country, work experience, annual personal volume, and annual hospital volume of liver resections. Survey questions on opinions

were answered on a visual analog scale (range 0% [no influence] to 100% [major influence]; Fig. 1). Participant views on a possible relationship between analgesic modality and outcomes were answered on a 4-point scale (yes, maybe, no, don't know). The proportion of specialists who answered yes or maybe was dichotomized as positive for a potential relationship. Participant opinions regarding future improvements were queried using a 5-point Likert scale (no impact, minor impact, neutral, substantial impact, huge impact), and substantial and huge impact were dichotomized as positive.

### Definitions

A major liver resection was defined as a resection of  $\geq 3$  Couinaud segments.<sup>15</sup> Incomplete responses were defined as responses with  $\geq 25\%$  of answers missing (arbitrary cutoff). Liver resection was defined as any liver resection excluding transplantation. Low CVP was defined as  $< 5$  mm Hg. GDFT was defined as fluid therapy based on dynamic preload parameters (such as pulse pressure variation, systolic pressure variation, stroke volume variation, delta down, or stroke volume).

### Sample size

The aim of this study was to receive in total at least 740 responses, with 370 valid responses per specialty. Given a theoretical population size of  $\geq 10,000$ , a sample size of 370 respondents per specialty was calculated to be sufficient to estimate response percentages for any response category in the survey, with the 2-sided 95% confidence interval falling within the margin of error of 5%.<sup>16</sup>

### Statistical analysis

The database was crosschecked for entry errors. Results were analyzed using SPSS Version 22.0 (IBM Corporation, Armonk, NY), in consultation with a medical statistician. Categorical data were reported as numbers with percentages, normally distributed continuous data as means with standard deviation, and non-normally distributed continuous data as median with interquartile range (IQR). Differences were assessed using Fisher exact test for categorical variables. Continuous variables were assessed using the Mann-Whitney *U* test or Student's *t* test, as appropriate.

## Results

### Participants

Between December 2016 and April 2017, 1,200 completed surveys from 583 surgeons and 617 anesthesiologists were received. After removal of 181 incomplete responses and 106 responses from participants who performed fewer than 10 liver resections per year, a total of 913 surveys remained (495 surgeons and 418 anesthesiologists) from 66 different countries (Fig. 2). Participants had a median professional experience of 12 years (IQR: 6–20). Surgeons reported a median experience of 11 years after residency (IQR: 6–19), a median annual hospital volume of 70 liver resections (IQR: 39–140), and a median annual personal volume of 30 resections (IQR: 20–50) as the first or second surgeon (Table 1). Anesthesiologists reported a median experience of 14 years (IQR: 6–22) after residency, a median annual hospital volume of 104 liver resections (IQR: 60–200), and a median personal annual volume of 20 liver resections (IQR: 15–30) (Table 1).

### Perceived value

Surgeons perceive the influence of type of fluid therapy on the quality of the surgical field (1%–100% scale) as greater compared

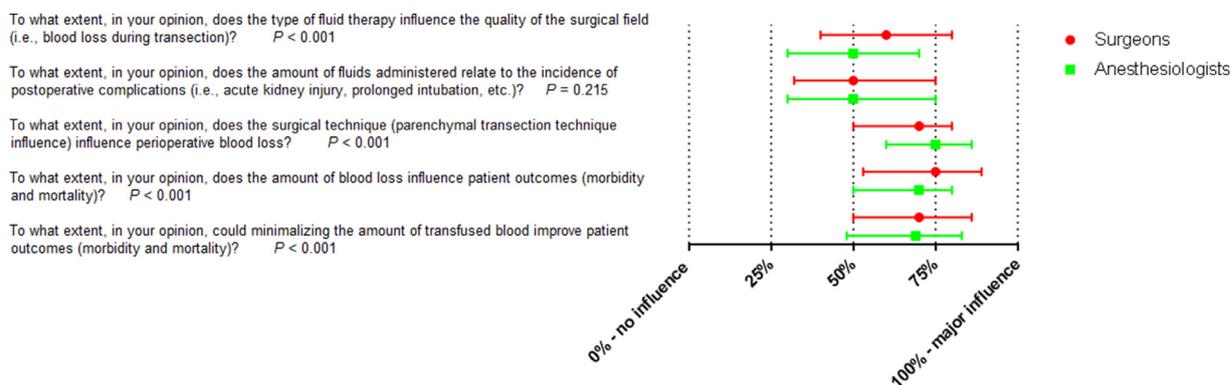


Fig. 1. Opinions on the influence of several strategies on outcomes on a visual analog scale.

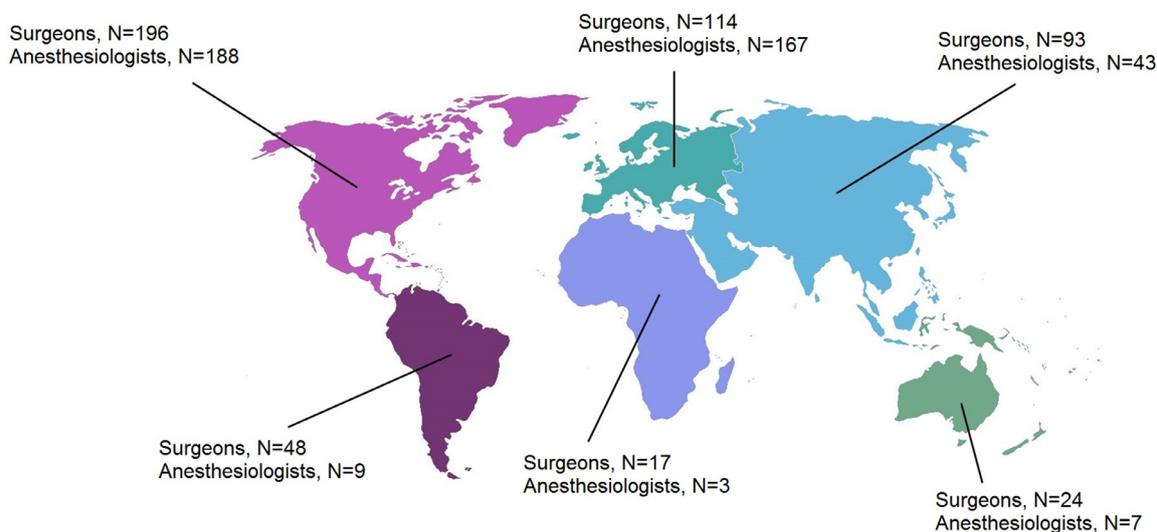


Fig. 2. Geographic representation of survey respondents.

**Table 1**  
Demographic characteristics of survey respondents stratified by specialization (N = 927).

	Surgeons (n = 495)	Anesthesiologists (n = 418)
Work experience, median (IQR), y	11 (6–19)	14 (6–22)
Annual hospital volume of liver resections, median (IQR), n	70 (39–140)	104 (60–200)
Annual personal volume of liver resections, median (IQR), n	30 (20–50)	20 (15–35)
Employed at academic hospital	421 (86%)	358 (86%)
Scope of practice, n (%)		
Hepatopancreatobiliary surgeon	304 (62%)	–
Oncologic surgeon	95 (19%)	–
General surgeon	33 (7%)	–
Transplantation surgeon	61 (12%)	–
Anesthesiologist with focus on liver surgery	–	72 (17%)
Anesthesiologist with focus on liver transplantation	–	159 (38%)
Anesthesiologist with other focus (not liver)	–	45 (11%)
General anesthesiologist	–	142 (34%)
Dedicated team for liver surgery, n (%)		
Yes, both liver surgeon + liver anesthesiologist	216 (44%)	236 (57%)
Yes, liver surgeon but no specific anesthesiologist	249 (49%)	135 (32%)
Yes, liver anesthesiologist but no liver surgeon	0	4 (1%)
No, there is no dedicated team	34 (7%)	43 (10%)

with anesthesiologists (median 60% [IQR: 40–80] vs 50% [30–70];  $P < .001$ ; Fig. 1). Also, surgeons feel that blood loss has a larger influence on patient outcomes (eg, morbidity and mortality) compared with anesthesiologists (median 75% [IQR: 53–89] vs 70% [50–80];  $P < .001$ ). Anesthesiologists perceive the influence of surgical technique on perioperative blood loss to be greater than

surgeons (median 75% [IQR: 60–86] vs 70 [50–80];  $P < .001$ ; Fig. 1).

#### Fluid management practices

The most common fluid management strategy in major open liver resections is low CVP, used by 66% ( $n = 599$ ) of participants,

**Table 2**  
Fluid management practices.

	Surgeons (n = 495)	Anesthesiologists (n = 418)	P
What type of fluid therapy is predominantly used during most of your open major liver resections?			<.001
Low CVP	382 (77%)	217 (52%)	
Goal-directed fluid therapy	64 (13%)	141 (33%)	
Normovolemia	27 (6%)	31 (7%)	
Don't know / no specific plan / other	18 (4%)	29 (7%)	
If this was a major laparoscopic resection, what would you use?			.001
Low CVP	314 (66%)	180 (45%)	
Goal-directed fluid therapy	81 (17%)	136 (34%)	
Normovolemia	43 (9%)	59 (15%)	
Don't know / no specific plan / other	40 (8%)	24 (6%)	
How do you use a low-CVP/restrictive fluid strategy?	—	356 (85%)	—
If yes, how do you achieve this?			
Restrictive fluid infusion	—	337 (95%)	
Patient position	—	145 (41%)	
Furosemide (Lasix)	—	47 (13%)	
Autotransfusion	—	50 (14%)	
Fasting	—	27 (8%)	
Epidural analgesia	—	10 (3%)	
Volatile anesthesia	—	5 (1%)	
Does your department have a general protocol for fluid management?			
No	—	230 (55%)	
Yes, a general protocol	—	99 (24%)	
Yes, a specific protocol for fluid therapy in liver surgery	—	84 (20%)	
How would you describe your postoperative fluid management (in the first 4 hours postoperatively)?			—
Goal-directed fluid therapy	—	181 (43%)	
Normovolemia	—	178 (43%)	
Fluid infusion on basis of diuresis	—	37 (9%)	
Infusion of standard amount of fluid (1–2 L) regardless of other parameters	—	16 (4%)	
In your hospital, what is the estimated percentage of patients with a significant increase in weight (>5% of preoperative body weight) in the first few days after liver resections? Median (IQR), proportion	30% (18–50)	—	

whereas GDFT is used by 22% ( $n=205$ ) and normovolemia by 6% ( $n=58$ ), with 5% ( $n=43$ ) answering “don't know/no specific plan/other” (Table 2). Fluid therapy preferences for major laparoscopic resections and major open resections were comparable.

Regarding the use of protocols for fluid therapy, 20% of the anesthesiologists have a specific protocol in their clinic for fluid therapy in liver surgery, 24% use a general protocol, and 55% have no protocol. In major laparoscopic resections the results were comparable (Table 2).

Questions about restrictive fluid therapy were only directed at anesthesiologists. Restrictive fluid therapy practices are used by 85% of anesthesiologists (Table 2). The most common methods to achieve this are the following: restricting fluid infusion, 95%; patient position, 41%; and nitroglycerin, 24%.

In the early postoperative phase (defined as the first 4 hours after surgery) 43% of anesthesiologists prefer to use GDFT, 43% use normovolemia, 9% resuscitate patients on the basis of diuresis, and 4% use a standard amount (eg, 1 or 2 L) regardless of other parameters.

#### Pain management practices

In open liver surgery, epidural analgesia is used by 49% of participants ( $n=450$ ), whereas 25% ( $n=227$ ) use patient-controlled analgesia (PCA) with opioids. Transversus abdominis plane (TAP) blocks are preferred by 62 (7%) of participants, whereas continuous wound infiltration is used by 5% ( $n=48$ ; Table 3).

In laparoscopic liver resections, 53% prefer PCA with opioids and 20% prefer epidural analgesia. Use of alternatives is comparable to open surgery; however, more TAP blocks are used in the laparoscopic procedure (Table 3).

Most participants assume that there is a relation between the choice of a perioperative analgesic technique and morbidity and

mortality (78% of surgeons vs 89% of anesthesiologists;  $P < .001$ ). Regarding the relationship between perioperative analgesic technique and cancer recurrence, fewer surgeons significantly expect a potential relationship compared with anesthesiologists (14% vs 52%;  $P < .001$ ) (Table 3).

#### Future improvements

Both surgeons and anesthesiologists mentioned minimally invasive approaches (ie, laparoscopic and robot-assisted surgery) and enhanced recovery protocols as the most important factors for future improvements (Table 4). Fluid therapy, blood transfusion strategies, and improvement of postoperative analgesia are also seen as potentially relevant for improvement of clinical outcomes (Table 4).

#### Discussion

This global and multidisciplinary study to assess perioperative practices in liver surgery detected considerable heterogeneity for both fluid and pain management practices. Future studies should focus on those topics on which no consensus exists. Low CVP is the preferred method for fluid therapy in liver surgery, but other strategies are also commonly applied. Epidural analgesia is the most preferred method for analgesia in open liver surgery, although good alternatives such as continuous wound infiltration and TAP blocks are now available.<sup>9,13,14</sup>

The large variation in practices described in this study is an interesting and possibly concerning finding because, in general, large interprovider variability is disadvantageous for patients.<sup>17,18</sup> Furthermore, in most institutions neither a specific nor a general protocol for fluid therapy is used because only 20% of anesthesiologists have a specific protocol for fluid therapy in liver surgery.

**Table 3**  
Pain management practices.

	Surgeons (n = 495)	Anesthesiologists (n = 418)	P
What method for pain management is predominantly used in your hospital in open major liver resections?			
Patient-controlled epidural analgesia	253 (54%)	197 (48%)	.816
Patient-controlled analgesia (with opioids)	129 (27%)	98 (23%)	
Continuous wound infiltration (CWI) or surgical site infiltrative catheters	26 (6%)	22 (5%)	
TAP block	28 (6%)	34 (8%)	
Spinal analgesia	12 (3%)	29 (7%)	
Other	23 (5%)	34 (8%)	
What method for pain management is, in your experience, the most effective (regarding analgesia, side effects, and patient satisfaction) in open major liver resections?			.119
Patient-controlled epidural analgesia	285 (62%)	280 (70%)	
Patient-controlled analgesia with opioids	98 (21%)	54 (14%)	
CWI/surgical site infiltrative catheters	27 (6%)	16 (4%)	
TAP block	26 (6%)	27 (7%)	
Spinal analgesia	18 (4%)	20 (5%)	
Other	3 (1%)	0	
If this would be a laparoscopic major liver resection, what would be your choice? ( $\geq 3$ Couinaud segments)			.970
Patient-controlled epidural analgesia	102 (23%)	81 (20%)	
Patient-controlled analgesia (with opioids)	284 (55%)	194 (48%)	
CWI/surgical site infiltrative catheters	25 (6%)	16 (4%)	
TAP block	48 (11%)	63 (16%)	
Spinal analgesia	14 (3%)	18 (5%)	
Other	14 (3%)	29 (7%)	
Do you think there is a relation between choice of perioperative analgesic technique and morbidity and mortality?			<.001
Yes	178 (39%)	204 (50%)	
Maybe	181 (39%)	159 (39%)	
No	71 (15%)	30 (7%)	
Don't know	31 (7%)	17 (4%)	
Do you think there is a relation between choice of perioperative analgesic technique and cancer recurrence?			<.001
Yes	14 (3%)	54 (13%)	
Maybe	49 (11%)	159 (39%)	
No	331 (72%)	111 (27%)	
Don't know	68 (15%)	86 (21%)	

**Table 4**  
Potential for future improvements in liver surgery.

	Surgeons (n = 495)	Anesthesiologists (n = 418)
Less invasive operative techniques (laparoscopy or robot-assisted surgery)	73%	81%
Enhanced recovery pathways	73%	78%
Fluid therapy	73%	70%
Blood transfusion (restrictive versus liberal)	69%	69%
Improvement of postoperative analgesia	66%	70%
Development of guidelines and strict guideline adherence	62%	59%
Physiotherapy	58%	54%
Nonsurgical ablative therapy (eg, RFA, stereotactic radiotherapy)	50%	65%
Ventilation techniques (eg, volume, pressure) during the operative period	32%	39%

Displayed as the proportion of specialists who rated the potential impact as substantial or huge on a 5-point Likert scale (no impact, minor impact, neutral, substantial impact, huge impact).  
RFA, radiofrequency ablation.

Protocols and evidence-based standardization could improve outcomes in this respect.

Low CVP, which is aimed at reducing blood loss during resection, has historically been advocated by liver surgeons.<sup>9,19</sup> The goal is to keep CVP less than 5 mm Hg, which is thought to result in decreased liver blood flow and a reduced blood-to-liver tissue ratio. It is a major challenge in liver surgery to maintain low venous pressure and simultaneously balance sufficient oxygenation of the liver and other end organs. Although several small nonrandomized studies did report a significant decrease in blood loss in the presence of low CVP, high-quality evidence for its beneficial effects is scarce.<sup>19,20</sup> Regarding methods to decrease CVP, patient position by means of reverse Trendelenburg (head-up tilt) can be an easy, effective, and reversible method to attain this.<sup>21</sup> It besides may offer liver surgeons good access to the hepatic veins.

In GDFT, cardiac output monitoring is used to guide fluid therapy. GDFT aims at optimizing perioperative tissue perfusion by keeping a patient normovolemic. Normovolemia is thought to prevent tissue hypoxia and fluid overload. This could provide the much needed benefit in this patient population at high risk for complications like renal failure, myocardial ischemia, and even stroke. In general, evidence supports GDFT,<sup>10,22</sup> but specifically in liver surgery high-quality evidence remains scarce.<sup>19,23,24</sup> Adequately designed, procedure-specific studies are therefore needed, with standardized protocols for GDFT. A recent randomized study in liver surgery was stopped prematurely because of the lack of any difference in outcomes with GDFT and no GDFT.<sup>25</sup> However, because GDFT was only applied after the parenchymal transection, the full potential of this strategy could have been missed in this study. Notably, the Enhanced Recovery After Surgery (ERAS)

guideline<sup>9</sup> states that goal-directed fluid therapy with maintenance of a low intraoperative central venous pressure induces faster recovery. This suggests a beneficial effect of combining GDFT and low CVP, although this combination is not standardized or particularly straightforward to put together in one protocol. This study found fluid therapy preferences for open and laparoscopic major liver surgery to be comparable. The differences between both approaches is caused by an expected larger amount of insensible perspiration (evaporation) in open surgery. The difference between open and laparoscopy might be small because, in general, insensible perspiration is expected to range between 0.5 mL/kg/h (in awake patients) and 1.0 mL/kg/h (in major abdominal surgery).<sup>26</sup>

Adequate postoperative analgesia, with as few side effects as possible, is important for optimal recovery. The present study confirms the popularity of epidural analgesia in open liver resections. The current ERAS guideline states that other analgesic methods could also be considered in liver surgery.<sup>9</sup> The impact of epidural analgesia on patients' hemodynamics is well known and may be of particular importance in liver surgery with its relatively large fluid shifts. Moreover, thoracic epidurals carry a 1 in 1,000 to 6,000 risk of neurologic complications (including epidural hematoma and abscess).<sup>27–29</sup> This risk may be increased in liver surgery because of the higher likelihood of intra- and postoperative onset coagulopathy.<sup>30</sup> Delayed catheter removal as a result of coagulation disorders will not contribute to fast recovery. In addition, epidural analgesia-induced hypotension may lead to increased fluid requirements in the surgical ward. In several studies the use of a higher volume of postoperative fluids has been associated with an increased morbidity.<sup>31,32</sup> Furthermore, epidural analgesia has been described as independent risk factor for acute kidney injury in patients undergoing major hepatectomy in the presence of low CVP.<sup>33</sup>

In several well-designed RCTs continuous wound infiltration, as part of a multimodal strategy, has been found to be a promising alternative to epidural analgesia in liver surgery.<sup>13,14</sup> This method has been suggested as a possible ideal alternative to epidural analgesia, providing the benefits of local analgesia but without the risk of major neurologic complications. In addition, the placement of wound catheters is not precluded by existing or expected coagulopathies.<sup>14</sup> A recent RCT using clinical recovery as primary endpoint found a shorter recovery time with continuous wound infiltration compared with epidural analgesia, whereas pain scores were comparable.<sup>13</sup> Both continuous wound infiltration and intrathecal opioids are mentioned in ERAS guidelines as good alternatives for epidural analgesia.<sup>9,14,34</sup> Interestingly, for laparoscopic liver surgery epidural analgesia was only used in 20% of patients with PCA and TAP blocks as potential alternatives, indicating the paucity of studies in this field. Although spinal analgesia is recommended often in ERAS protocols, such as for colorectal surgery,<sup>35</sup> its use in liver surgery is quite low (around 5%) according to our results.

A majority of anesthesiologists (52%) believe that the type of analgesia may be of influence in cancer recurrence, a belief shared by only a minority of surgeons (14%). If some anesthetic modalities would indeed influence tumor biology,<sup>36,37</sup> it would obviously be an important consideration in the choice of anesthetic method. Recent data have, however, somewhat downplayed the role of anesthesia in tumor biology.<sup>38</sup>

This study has several limitations. First, surveys are naturally at risk for selection bias and response bias, and perceived outcomes might differ from real clinical practice. Therefore the results of this study should be interpreted with these limitations in mind. The manuscript summarizes feelings and perceptions of individual providers who responded to the survey, which may or may not

reflect actual practice patterns; however, we sampled clinicians from many countries and backgrounds (eg, academic, private practice) in an attempt to capture actual practice patterns. Although most participants (73%) originated from the Western world (North America and Europe), we feel that an adequate sample has been assessed and that it is representative of liver surgery practices worldwide, because a large number of international professional organizations participated in the project. Second, the response rate to the survey cannot be calculated because the total number of surgeons and anesthesiologists that received the survey is unknown. However, the sample size is adequate based on our pre-defined sample size calculation. Third, a substantial number of responses had to be excluded because of a low number of procedures performed annually, especially those from anesthesiologists ( $n = 95$ ). Whereas liver surgery is increasingly centralized to include dedicated liver surgeons, this may not automatically hold true for anesthesiologists.

The main strength of this study is the worldwide representation of current practices and views on this topic. An adequate and comparable number of participants from surgery and anesthesiology participated, making this survey unique. Both surgeons and anesthesiologists expect improvements in clinical outcomes with further development of minimally invasive surgical techniques and enhanced recovery strategies. Interestingly, because no clear inter-continental differences exist, such studies could actually be international in design.

In conclusion, this study gives unique insight into current worldwide practices and views on fluid and pain management in liver surgery. There is large and consistent heterogeneity in current practices on both topics. Well-designed trials are needed on these key issues to standardize and improve care of patients undergoing liver surgery.

## Acknowledgments

The authors gratefully thank all participating liver surgeons and anesthesiologists as well as the leadership of the International Hepato-Pancreato-Biliary Association (IHPBA), American Society of Anesthesiologists (ASA), Americas Hepato-Pancreato-Biliary Association (A-HPBA), European-African Hepato-Pancreato-Biliary Association (E-AHPBA), Australia New-Zealand Hepato-Pancreato-Biliary Association (ANZ-HPBA), Liver Intensive Care Group of Europe (LICAGE), European Guidelines Meeting on Laparoscopic Liver Surgery (EGMLLS), Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS), Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS), and other participating national societies. Special thanks to Rob Padbury, Rene Adam, Monty Mythen, Philipp Lirk, Andre van Zundert, Indrek Rätsep, Sven Felsby, Goran Rondovic, Dorel Sandesc, Kári Hreinsson, Paraskevi Matsota, Nichola Bartlett, Satoshi Toyama, Elise Sarton, Sandra Gijtenbeek, Eva Gottfried, Natalie Zimmelman, Michelle Peters, Alison Shamwana, Ramani Moonesinghe, Tritan Shehu, and Benjamin Drenger for their help with the distribution of the survey. We thank Else Ouweneel, Marcel Dijkgraaf, and Sjors Klomp maker for their help with optimization of the survey content, sample size calculation and assistance with the statistical analysis.

## Appendix

Table A1 and A2

**Table A1**  
Fluid Management Practices Stratified by Region.

		Surgeons (n = 491)	Anesthesiologists (n = 417)
<b>What type of fluid therapy is predominantly used during most of your open major liver resections?</b>			
Low-CVP	North-America	158 (81%)	97 (52%)
	Europe	97 (85%)	93 (56%)
	Asia, Australia, South-America, Africa	125 (69%)	27 (44%)
Goal-directed fluid therapy	North-America	24 (12%)	65 (35%)
	Europe	11 (10%)	52 (31%)
	Asia, Australia, South-America, Africa	29 (16%)	24 (39%)
Normovolemia	North-America	11 (6%)	15 (8%)
	Europe	4 (4%)	9 (5%)
	Asia, Australia, South-America, Africa	11 (6%)	6 (10%)
Don't know / no specific plan / other	North-America	1 (2%)	6 (3%)
	Europe	2 (2%)	6 (4%)
	Asia, Australia, South-America, Africa	14 (8%)	2 (3%)

**Table A2**  
Pain Management Practices Stratified by Region.

		Surgeons (n = 454)	Anesthesiologists (n = 398)
<b>What method for pain management is, in your experience, the most effective (regarding analgesia, side effects and patient satisfaction) in open major liver resections?</b>			
(Patient-controlled) epidural analgesia	North-America	107 (59%)	135 (74%)
	Europe	68 (62%)	106 (68%)
	Asia, Australia, South-America, Africa	107 (66%)	38 (64%)
Patient-controlled analgesia (with for example morphine)	North-America	40 (22%)	19 (10%)
	Europe	27 (25%)	28 (18%)
	Asia, Australia, South-America, Africa	31 (19%)	7 (12%)
Continuous wound infiltration (CWI) / surgical site infiltrative catheters	North-America	7 (4%)	3 (2%)
	Europe	11 (10%)	10 (6%)
	Asia, Australia, South-America, Africa	9 (6%)	3 (5%)
Transversus abdominis plane (TAP) block	North-America	22 (12%)	19 (10%)
	Europe	1 (1%)	6 (4%)
	Asia, Australia, South-America, Africa	3 (2%)	4 (7%)
Spinal analgesia	North-America	5 (3%)	7 (4%)
	Europe	2 (2%)	6 (4%)
	Asia, Australia, South-America, Africa	11 (7%)	7 (12%)

## References

- Dimick JB, Cowan Jr JA, Knol JA, Upchurch Jr GR. Hepatic resection in the United States: indications, outcomes, and hospital procedural volumes from a nationally representative database. *Arch Surg.* 2003;138:185–191.
- Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. *Ann Surg.* 2002;236:397–406 discussion 406–7.
- Poon RT, Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK, et al. Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1222 consecutive patients from a prospective database. *Ann Surg.* 2004;240:698–708 discussion 708–10.
- Wei AC, Tung-Ping Poon R, Fan ST, Wong J. Risk factors for perioperative morbidity and mortality after extended hepatectomy for hepatocellular carcinoma. *Br J Surg.* 2003;90:33–41.
- Khuri SF, Daley J, Henderson W, Hur K, Gibbs JO, Barbour G, et al. Risk adjustment of the postoperative mortality rate for the comparative assessment of the quality of surgical care: results of the National Veterans Affairs Surgical Risk Study. *J Am Coll Surg.* 1997;185:315–327.
- Gurusamy KS, Kumar Y, Ramamoorthy R, Sharma D, Davidson BR. Vascular occlusion for elective liver resections. *Cochrane Database Syst Rev.* 2009.
- Moggia E, Rouse B, Simillis C, Li T, Vaughan J, Davidson BR, et al. Methods to decrease blood loss during liver resection: a network meta-analysis. *Cochrane Database Syst Rev.* 2016;10.
- Lortat-Jacob JL, Robert HG. [Well defined technic for right hepatectomy]. *Presse Med.* 1952;60:549–551.
- Melloul E, Hubner M, Scott M, Snowden C4,5, Prentis J4, Dejong CH, et al. Guidelines for perioperative care for liver surgery: Enhanced Recovery After Surgery (ERAS) Society recommendations. *World J Surg.* 2016;40:2425–2440.
- Pearse RM, Harrison DA, MacDonald N, Gillies MA3, Blunt M4, Ackland G, et al. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. *JAMA.* 2014;311:2181–2190.
- Ripolles J, Espinosa A, Martinez-Hurtado E, Abad-Gurumeta A, Casans-Francis R, Fernández-Pérez C, et al. [Intraoperative goal directed hemodynamic therapy in noncardiac surgery: a systematic review and meta-analysis]. *Rev Bras Anestesiol.* 2016;66:513–528.
- Revie EJ, McKeown DW, Wilson JA, Garden OJ, Wigmore SJ. Randomized clinical trial of local infiltration plus patient-controlled opiate analgesia vs. epidural analgesia following liver resection surgery. *HPB (Oxford).* 2012;14:611–618.
- Hughes MJ, Harrison EM, Peel NJ, Stutchfield B, McNally S, Beattie C, et al. Randomized clinical trial of perioperative nerve block and continuous local anaesthetic infiltration via wound catheter versus epidural analgesia in open liver resection (LIVER 2 trial). *Br J Surg.* 2015;102:1619–1628.
- Mungroop TH, Veelo DP, Busch OR, van Dieren S, van Gulik TM, Karsten TM, et al. Continuous wound infiltration versus epidural analgesia after hepato-pancreato-biliary surgery (POP-UP): a randomised controlled, open-label, non-inferiority trial. *Lancet Gastroenterol Hepatol.* 2016;1:105–113.
- Bismuth H. Revisiting liver anatomy and terminology of hepatectomies. *Ann Surg.* 2013;257:383–386.
- Bartlett JE, Kotrlík JW, Higgins CC. Organizational research: determining appropriate sample size in survey research. *Info Techn Learning Performance J.* 2001;19:43–50.
- Greenfield S, Nelson EC, Zubkoff M, Manning W, Rogers W, Kravitz RL, et al. Variations in resource utilization among medical specialties and systems of care. Results from the medical outcomes study. *JAMA.* 1992;267:1624–1630.
- McGlynn EA, Asch SM, Adams J, Keesey J, Hicks J, DeCristofaro A, et al. The quality of health care delivered to adults in the United States. *N Engl J Med.* 2003;348:2635–2645.

19. Jones RM, Moulton CE, Hardy KJ. Central venous pressure and its effect on blood loss during liver resection. *Br J Surg*. 1998;85:1058–1060.
20. Wang WD, Liang LJ, Huang XQ, Yin XY. Low central venous pressure reduces blood loss in hepatectomy. *World J Gastroenterol*. 2006;12:935–939.
21. Soonawalla ZF, Stratopoulos C, Stoneham M, Wilkinson D, Britton BJ, Friend PJ. Role of the reverse-Trendelenberg patient position in maintaining low-CVP anaesthesia during liver resections. *Langenbecks Arch Surg*. 2008;393:195–198.
22. Rollins KE, Lobo DN. Intraoperative goal-directed fluid therapy in elective major abdominal surgery: a meta-analysis of randomized controlled trials. *Ann Surg*. 2016;263:465–476.
23. Chen H, Merchant NB, Didolkar MS. Hepatic resection using intermittent vascular inflow occlusion and low central venous pressure anesthesia improves morbidity and mortality. *J Gastrointest Surg*. 2000;4:162–167.
24. Li Z, Sun YM, Wu FX, Yang LQ, Lu ZJ, Yu WF. Controlled low central venous pressure reduces blood loss and transfusion requirements in hepatectomy. *World J Gastroenterol*. 2014;20:303–309.
25. Correa-Gallego C, Tan KS, Arslan-Carlon V, Gonen M, Denis SC, Langdon-Embry L, et al. Goal-directed fluid therapy using stroke volume variation for resuscitation after low central venous pressure-assisted liver resection: a randomized clinical trial. *J Am Coll Surg*. 2015;221:591–601.
26. Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M. A rational approach to perioperative fluid management. *Anesthesiology*. 2008;109:723–740.
27. Moen V, Dahlgren N, Irestedt L. Severe neurological complications after central neuraxial blockades in Sweden 1990–1999. *Anesthesiology*. 2004;101:950–959.
28. Popping DM, Zahn PK, Van Aken HK, Dasch B, Boche R, Pogatzki-Zahn EM. Effectiveness and safety of postoperative pain management: a survey of 18 925 consecutive patients between 1998 and 2006 (2nd revision): a database analysis of prospectively raised data. *Br J Anaesth*. 2008;101:832–840.
29. Christie IW, McCabe S. Major complications of epidural analgesia after surgery: results of a six-year survey. *Anaesthesia*. 2007;62:335–341.
30. Tzimas P, Prout J, Papadopoulos G, et al. Epidural anaesthesia and analgesia for liver resection. *Anaesthesia*. 2013;68:628–635.
31. Muller S, Zalunardo MP, Hubner M, Clavien PA, Demartines NZurich Fast Track Study Group. A fast-track program reduces complications and length of hospital stay after open colonic surgery. *Gastroenterology*. 2009;136:842–847.
32. Brandstrup B, Tonnesen H, Beier-Holgersen R, Hjortsø E, Ørding H, Lindorff-Larsen K, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg*. 2003;238:641–648.
33. Kambakamba P, Slankamenac K, Tschuor C, Kron P, Wirsching A, Maurer K, et al. Epidural analgesia and perioperative kidney function after major liver resection. *Br J Surg*. 2015;102:805–812.
34. Kasivisvanathan R, Abbassi-Ghadi N, Prout J, Clevenger B, Fusai GK, Mallett SV. A prospective cohort study of intrathecal versus epidural analgesia for patients undergoing hepatic resection. *HPB (Oxford)*. 2014;16:768–775.
35. Helander EM, Webb MP, Bias M, Whang EE, Kaye AD, Urman RD. Use of regional anesthesia techniques: analysis of institutional Enhanced Recovery After Surgery protocols for colorectal surgery. *J Laparoendosc Adv Surg Tech A*. 2017;27:898–902.
36. Colvin LA, Fallon MT, Buggy DJ. Cancer biology, analgesics, and anaesthetics: is there a link? *Br J Anaesth*. 2012;109:140–143.
37. Divatia JV, Ambulkar R. Anesthesia and cancer recurrence: what is the evidence? *J Anaesthesiol Clin Pharmacol*. 2014;30:147–150.
38. Sekandarzad MW, van Zundert AAJ, Lirk PB, Doornebal CW, Hollmann MW. Perioperative anesthesia care and tumor progression. *Anesth Analg*. 2017;124:1697–1708.