Novel Benchmark Values for Open Major Anatomic Liver Resection in Non-cirrhotic Patients

A Multicentric Study of 44 International Expert Centers

Richard X. Sousa Da Silva, MD, Eva Breuer, MD,* Sadhana Shankar, MD,† Shoji Kawakatsu, MD, PhD,‡ Wacław Hołówko, MD, PhD,§ João Santos Coelho, MD,‖ Heithem Jeddou, MD,¶ Teiichi Sugiura, MD, PhD,# Mohammed Ghallab, MD, PhD,** Doris Da Silva, MD,†† Genki Watanabe, MD, PhD,‡‡ Florin Botea, MD, PhD,§§ Nozomu Sakai, MD, PhD,‖‖ Pietro Addeo, MD, PhD,¶¶ Stylianos Tzedakis, MD,## Fabian Bartsch, MD,*** Kaja Balcer, MD,††† Chetana Lim, MD, PhD,‡‡‡ Fabien Werey, MD,§§§ Victor Lopez-Lopez, MD,‖‖‖ Luciana Peralta Montero, MD,¶¶¶ Rodrigo Sanchez Claria, MD,¶¶¶ Jennifer Leiting, MD,### Neeta Vachharajani, MD,**** Eve Hopping, MD,†††† Orlando J. M. Torres, MD, PhD,‡‡‡‡ Satoshi Hirano, MD, PhD,§§§§ Daan Andel, MD,‖‖‖‖ Jeroen Hagendoorn, MD, PhD,‖‖‖‖ Alicja Psica, MD,¶¶¶¶ Matteo Ravaioli, MD,#### Keun Soon Ahn, MD, PhD,***** Tim Reese, MD,††††† Leonardo A. Montes, MD,‡‡‡‡‡ Ganesh Gunasekaran, MD,§§§§§ Cándido Alcázar, MD, PhD,‖‖‖‖‖ Jin Hong Lim, MD, PhD,¶¶¶¶¶ Muhammad Haroon, MD,##### Qian Lu, MD,****** Antonio Castaldi, MD,†††††† Tatsuya Orimo, MD,‡‡‡‡‡‡ Beat Moeckli, MD, PhD,§§§§§§ Teresa Abadía, MD,‖‖‖‖‖‖ Luis Ruffolo, MD,¶¶¶¶¶¶ Josefina Dib Hasan, MD,###### Francesca Ratti, MD,******* Emmanuele F. Kauffmann, MD,††††††† Roeland F. de Wilde, MD, PhD,‡‡‡‡‡‡‡ Wojciech G. Polak, MD, PhD,‡‡‡‡‡‡‡ Ugo Boggi, MD,††††††† Luca Aldrighetti, MD,******* Lucas McCormack, MD,###### Roberto Hernandez-Alejandro, MD,¶¶¶¶¶¶ Alejandro Serrablo, MD, PhD,‖‖‖‖‖‖ Christian Toso, MD, PhD,§§§§§§ Akinobu Taketomi, MD,‡‡‡‡‡‡ Jean Gugenheim, MD,†††††† Jiahong Dong, MD, PhD,****** Faisal Hanif, MD,##### Joon Seong Park, MD, PhD,¶¶¶¶¶ José M. Ramia, MD, PhD,‖‖‖‖‖ Myron Schwartz, MD,§§§§§ Diego Ramisch, MD,‡‡‡‡‡ Michelle L. De Oliveira, MD, PhD,* Karl J. Oldhafer, MD,††††† Koo Jeong Kang, MD, PhD,***** Matteo Cescon, MD, PhD,#### Peter Lodge, MD,¶¶¶¶ Inne H. M. Borel Rinkes, MD, PhD,‖‖‖‖ Takehiro Noji, MD, PhD,§§§§ John-Edwin Thomson, MD,†††† Su Kah Goh, MD, PhD,†††† William C. Chapman, MD,**** Sean P. Cleary, MD,### Juan Pekolj, MD, PhD,¶¶¶ Jean-Marc Regimbeau, MD, PhD,§§§ Olivier Scatton, MD, PhD,‡‡‡ Stéphanie Truant, MD, PhD,††† Hauke Lang, MD,*** David Fuks, MD, PhD,## Philippe Bachellier, MD, PhD,¶¶ Masayuki Ohtsuka, MD, PhD,‖‖ Irinel Popescu, MD,§§ Kiyoshi Hasegawa, MD, PhD,‡‡ Mickaël Lesurtel, MD, PhD,†† René Adam, MD, PhD,** Daniel Cherqui, MD, PhD,** Katsuhiko Uesaka, MD, PhD,# Karim Boudjema, MD, PhD,¶ Hugo Pinto-Marques, MD, PhD,‖ Michał Grąt, MD, PhD,§ Henrik Petrowsky, MD,* Tomoki Ebata, MD, PhD,‡ Andreas Prachalias, MD, PhD,† Ricardo Robles-Campos, MD, PhD,‖‖‖✉ and Pierre-Alain Clavien, MD, PhD**

From the *Swiss HPB and Transplant Center Zurich, Department of Surgery and Transplantation, University Hospital Zurich, Zurich, Switzerland; †Department of Hepatobiliary and Pancreatic Surgery, King's College Hospital, London, UK; ‡Division of Surgical Oncology, Nagoya University Graduate School of Medicine, Nagoya, Japan; §Department of General, Transplant and Liver Surgery, Medical University Warsaw, Warsaw, Poland; ‖Hepato-Biliary-Pancreatic and Transplantation Centre, Curry Cabral Hospital, Centro Hospitalar Universitário de Lisboa Central, Lisbon, Portugal; ¶Department of Hepatobiliary and Digestive Surgery, Rennes University Hospital, Rennes, France; #Division of Hepato-Biliary-Pancreatic Surgery, Shizuoka Cancer Center Hospital, Shizuoka, Japan; **Paul Brousse Hospital, AP-HP, University Paris-Saclay, Villejuif, France; ††Department of HPB Surgery and Liver Transplantation, AP-HP Beaujon Hospital, University of Paris Cité, Clichy, France; ‡‡Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo,

Objective: This study aims at establishing benchmark values for best achievable outcomes following open major anatomic hepatectomy for liver tumors of all dignities.

Background: Outcomes after open major hepatectomies vary widely lacking reference values for comparisons among centers, indications, types of resections, and minimally invasive procedures.

Methods: A standard benchmark methodology was used covering consecutive patients, who underwent open major anatomic hepatectomy from 44 high-volume liver centers from 5 continents over a 5-year period (2016–2020). Benchmark cases were low-risk non-cirrhotic patients without significant comorbidities treated in high-volume centers (≥ 30 major liver resections/year). Benchmark values were set at the 75th percentile of median values of all centers. Minimum follow-up period was 1 year in each patient.

Results: Of 8044 patients, 2908 (36%) qualified as benchmark (low-risk) cases. Benchmark cutoffs for all indications include R0 resection $\geq 78\%$; liver failure (grade B/C) $\leq 10\%$; bile leak (grade B/C) $\leq 18\%$; complications $\geq$ grade 3 and CCI® $\leq 46\%$ and ≤ 9 at 3 months, respectively. Benchmark values differed significantly between malignant and benign conditions so that reference values must be adjusted accordingly. Extended right hepatectomy (H1, 4-8 or H4-8) disclosed a higher cutoff for liver failure, while extended left (H1-5,8 or H2-5,8) were associated with higher cutoffs for bile leaks, but had superior oncologic outcomes, when compared to formal left hepatectomy (H1-4 or H2-4). The minimal follow-up for a conclusive outcome evaluation following open anatomic major resection must be 3 months.

Conclusion: These new benchmark cutoffs for open major hepatectomy provide a powerful tool to convincingly evaluate other approaches including parenchymal-sparing procedures, laparoscopic/robotic approaches, and alternative treatments, such as ablation therapy, irradiation, or novel chemotherapy regimens.

Keywords: benchmarks, CCI®, complications, formal and extended hepatectomy, liver resection, malignant and benign tumors, open major hepatectomy, outcomes

(*Ann Surg* 2023;278:748–755)

Liver resection is the only chance of cure in many patients with benign and malignant tumors. The type of resections, often related to the presence of underlying liver diseases, and surgical approaches via open or minimally invasive surgery have dramatically evolved over the recent 2 decades. There is currently a trend to favor parenchyma-sparing hepatectomies and laparoscopic or robotic approaches. As such, reliable studies on open procedures, particularly on anatomic resections, are needed to enable conclusive comparisons and propose sound recommendations covering both safety of the procedures and long-term oncologic data in the presence of malignant diseases.

Most of the available studies evaluating postoperative morbidity and oncologic outcomes have focused on one surgical approach for specific indications and are typically from a single-institution or multicenter study including heterogeneous and small patient populations. As a result, there is a need to provide reference values for several outcome parameters, which can be used for conclusive comparisons. The recently developed benchmark methodology,[1] endorsed as a standard outcome metric in a recent jury-based consensus conference,[2] may serve the purpose of establishing reference value for major hepatectomies. Benchmark values covering living donor hepatectomies,[3] liver transplantation (LT),[4,5] redo-LT,[6] resection and LT for perihilar cholangiocarcinoma (PHC),[7,8] and Associating Liver Partition with Portal vein ligation for Staged hepatectomy (ALPPS)[9] are already available.

In this study, we aim at establishing reference values for anatomic open major hepatectomies, as this remains a standard procedure in many centers. Available benchmark values for formal anatomic resections may serve for baseline comparisons

Tokyo, Japan; §§Department of Surgery and Transplantation, Fundeni Clinical Institute, Bucharest, Romania; ||||Department of General Surgery, Chiba University, Graduate School of Medicine, Chiba, Japan; ¶¶Hepato-Pancreato-Biliary Surgery and Liver Transplantation, University Hospital, Strasbourg University, Strasbourg, France; ##Department of Hepatobiliary, Digestive and Endocrine Surgery, Cochin Hospital, Paris Cité University, Paris, France; ***Department of General, Visceral and Transplantation Surgery, University Hospital of Mainz, Mainz, Germany; †††Department of Digestive Surgery and Transplantation, CHU Lille, University Lille, Lille, France; ‡‡‡Department of Digestive, Hepato-Biliary and Pancreatic Surgery and Liver Transplantation, AP-HP Pitié-Salpêtrière, Sorbonne Université, Centre de Recherche de Saint-Antoine, Paris, France; §§§Department of Oncology and Digestive Surgery, CHU Amiens-Picardie, Amiens, France; ||||||Clinic and University Virgen de la Arrixaca Hospital, IMIB, Murcia, Spain; ¶¶¶Hepato-Pancreato-Biliary Surgery Section and Liver Transplant Unit, General Surgery Department, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; ###Division of Hepatobiliary and Pancreas Surgery, Mayo Clinic, Rochester, MN; ****Department of Surgery, Section of Abdominal Organ Transplant, Washington University School of Medicine, St Louis, MO; ††††Hepatobiliary Unit, Department of Surgery, Royal Adelaide Hospital, Adelaide & Hepatobiliary Unit, Department of Surgery, Flinders Medical Centre, Adelaide, Australia; ‡‡‡‡Department of Gastrointestinal Surgery, Hepatopancreatobiliary Unit, Presidente Dutra Hospital, São Luiz, Brazil; §§§§Department of Gastroenterological Surgery II, Hokkaido University Graduate School of Medicine, Hokkaido, Japan; ||||||||Department of Surgical Oncology, University Medical Center Utrecht Cancer Center, Utrecht, The Netherlands; ¶¶¶¶Department of Transplantation and Hepatobiliary Surgery, Leeds Teaching Hospitals NHS Trust, Leeds, UK; ####Hepato-biliary surgery and Transplant Unit, IRCCS, Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; *****Division of Hepatobiliary-Pancreatic Surgery, Department of Surgery, School of Medicine, Keimyung University, Dongsan Hospital, Daegu, Republic of Korea; †††††Department of Surgery, Division of Hepatobiliary and Pancreatic Surgery, Asklepios Hospital Barmbek, Semmelweis University of Medicine, Asklepios Campus Hamburg, Hamburg, Germany; ‡‡‡‡‡General Surgery Department Liver, Pancreas and Intestinal Transplant Unit, Favaloro Foundation University Hospital, Buenos Aires, Argentina; §§§§§Department of Surgery, Division of HPB Service, Icahn School of Medicine at Mount Sinai, New York, NY; ||||||||||Department of Surgery, HPB and Transplant Unit, General Universitary Hospital Alicante and Health and Biomedical Research Institute of Alicante, Alicante, Spain; ¶¶¶¶¶Department of Surgery, Division of HBP Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; #####Department of HPB and Liver Transplant, Bahria International Hospital Orchard, Lahore, Pakistan; ******Hepatopancreatobiliary Center, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China; ††††††Department of Digestive Surgery and Liver Transplant Unit, University Côte d'Azur, CHU de Nice, Nice, France; ‡‡‡‡‡‡Department of Gastroenterological Surgery I, Hokkaido University Graduate School of Medicine, Hokkaido, Japan; §§§§§§Division of Abdominal and Transplantation Surgery, University Hospitals of Geneva, Geneva, Switzerland; ||||||||||||HPB Surgical Division, Miguel Servet University Hospital, Zaragoza, Spain; ¶¶¶¶¶¶Department of HPB and Transplant Surgery, University of Rochester, Rochester, NY; ######Transplant Unit, Hospital Aleman de Buenos Aires, Buenos Aires, Argentina; *******Division of Hepatobiliary Surgery, IRCCS San Raffaele Hospital, Vita-Salute University, Milan, Italy; †††††††Division of General and Transplant Surgery, University of Pisa, Pisa, Italy; and ‡‡‡‡‡‡‡Department of Surgery, Division of HPB and Transplant Surgery, Erasmus MC University Medical Center, Rotterdam, Netherlands.

✉ rirocam@um.es.

The authors report no conflicts of interest.

This study is supported by the LGID (Liver and Gastrointestinal Disease) Foundation and the Yvonne Jacob Foundation.

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.annalsofsurgery.com.

ISSN: 0003-4932/23/27805-0748

DOI: 10.1097/SLA.0000000000006012

to many other approaches. For this purpose, we used the well-established benchmark method based on high-volume centers (reference centers) and low-risk cases (benchmark patients). A prerequisite is also the participation of centers from all around the globe holding a prospective database covering a long postoperative course, thereby allowing a worldwide representation.

The eventual goal is to provide robust evidence for optimal decision making to patients, health care providers and the society on treatment options based on the best achievable outcomes. This allows all centers to compare their respective results with these reference values to optimize their treatment strategy. Such ongoing self-assessment should be closely integrated into the development of new surgical and alternative treatment approaches. Some centers are also selecting their cases to be presented at mortality and morbidity conferences based on values outside of the benchmark references.

METHODS

Study Design

To generate robust reference values in patients subjected to formal and extended left- or right-sided hepatectomies for any indication, a well-established benchmark methodology was used.[10] Consequently, included centers were both designated as high-volume centers performing at least 30 major liver resections ($\geq$3 liver segments) per year and had already published in the area of liver surgery while maintaining a patient database providing a follow-up of at least 1 year in each patient. Data were collected from a cohort of low-risk patients meeting the prespecified criteria for benchmark patients (Supplemental Digital Content Table 1, http://links.lww.com/SLA/E742). To test the respective benchmark values, an additional cohort of higher-risk patients ($\geq$ ASA III, BMI $\geq$ 35 kg/m^2, multimorbidity, or cirrhosis) from the same study centers was used. The anonymized data were collected and stored in an encrypted online data registry (http://www.benchmarks4hepatectomy.org). The completeness of the data was verified by both principal investigators (R.X.S.D.S. and E.B.). Ethics approval was obtained from the Cantonal Ethics Committees of Zurich and Geneva (BASEC No. 2022-01381) for the main study site and from each respective center.

Study Population

Adult patients who underwent major open left or right formal or extended hepatectomy (H2-4/H2-5,8 or H5-8/H4-8)[11] with curative intent for any indication or for living donation (LDLT) during the study period ranging from January 1, 2016, to December 31, 2020, were included. Criteria for benchmark cases were a body mass index (BMI) $\leq$ 35 kg/m^2 and an American Society of Anesthesiologists (ASA) score $\leq$ 2, no significant comorbidities such as active cardiac disease including myocardial infarction $\leq$ 6 months before surgery, advanced chronic renal failure, significant obstructive pulmonary disease, poly-medicated or insulin-treated diabetes mellitus, or intake of anticoagulants (Supplemental Digital Content Table 1, http://links.lww.com/SLA/E742).[12–15] Cases of central resections, previous segmentectomy, or more extensive liver resections were excluded, whereas patients with a history of wedge resections that occurred more than 6 months ago were included (Supplemental Digital Content Table 1, http://links.lww.com/SLA/E742).

Outcome Metrics

The clinically most important outcome variables were analyzed, and benchmark cutoffs for each variable were calculated. Metrics for outcomes can be divided into 2 main groups, covering a) peri-/postoperative morbidity and mortality and b) oncological outcome. The former includes the duration of surgery, blood loss, 3-month mortality, and severity of complications measured by the Clavien–Dindo score[16,17] as well as the overall burden of complications assessed by the Comprehensive Complication Index (CCI®).[18,19] The oncological outcome is reflected by tumor-free resection margins and survival. These reference benchmark values reflect the desirable threshold for best achievable outcomes in open major anatomic liver resection following the current global standard of care.

Statistical Analysis

Benchmark cutoffs were set at either the 75th or 25th percentile of all median values across centers indicating poor and good outcomes, respectively. Survival benchmarks were calculated from the 50th percentile to attenuate the extreme effects of heavy-tailed distribution on expected survival rates. All statistical tests were 2-sided, with a P value <0.05 regarded as statistically significant. Statistics were performed using R Statistical Software (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics

Forty-four benchmark centers reported 8044 open major anatomic liver resections during the 5-year study period, of which 2908 (36%) were benchmark cases. Centers were spread worldwide across North America (n = 4), South America (n = 4), Europe (n = 25), Asia (n = 10), and Oceania (n = 1). Most procedures were formal right hepatectomy (H5-8)[11] (n = 1476, 52%), followed by formal left hepatectomy (H2-4)[11] (n = 792, 28%), extended right hepatectomy (H4-8)[11] (n = 378, 13%), and finally extended left hepatectomy (H2-5,8)[11] (n = 203, 7%) (Supplemental Digital Content Table 2, http://links.lww.com/SLA/E742). Segment 1 resection was completed in nearly one-third of cases, with a wide variation among procedures ranging from 20% of all formal right hepatectomies up to 64% of all extended left hepatectomies. Surgeries were performed predominantly for primary (n = 1390, 48%) or secondary (n = 1058, 36%) malignant liver tumors, whereas one-sixth of cases (n = 460, 16%) of resections were performed for benign conditions. Among malignancies, the most frequent indication was colorectal liver metastases (CRLM, n = 867, 35%) followed by perihilar cholangiocarcinoma (PHC, n = 610, 25%), hepatocellular carcinoma (HCC, n = 371, 15%), and intrahepatic cholangiocarcinoma (IHC, n = 368, 15%). Various rare entities accounted for 8% of all malignancies (n = 232), including neuroendocrine tumors (n = 42, 2%). Among resections for nonmalignant liver tumors, living liver donation (n = 95, 21%), echinococcosis (n = 61, 13%), and hemangioma (n = 53, 12%), were the most frequent indications, followed by adenoma, biliary cysts, and biliary cystadenoma with 7% each (Supplemental Digital Content Table 2, http://links.lww.com/SLA/E742).

Benchmark Values

For all open major hepatectomies, benchmark values showed relevant perioperative morbidity with an overall complication rate $\leq$ 58% and a severe (Clavien–Dindo grade $\geq$3a) complication rate of $\leq$ 46% (Table 1). The overall burden, though, was low, with benchmark values for CCI® $\leq$ 9 along with a low 3-month mortality of less than 6%. Reference values for clinically relevant liver failure[20] and bile leak[21] rate were $\leq$10% and $\leq$18%, while the actual 1- and actuarial 2-year overall survival for the entire cohort were $\geq$ 82% and $\geq$72%, respectively (Table 1). For malignant tumors, the R0 to be

TABLE 1. Benchmark Values Stratified for Benign and Malignant Indications

	Unit	All cases	Benign	Malignant
Operation time	min	≤ 370	≤ 339	≤ 353
Blood loss	mL	≤ 700	≤ 500	≤ 785
Intensive care unit stay	d	≤ 2	≤ 2	≤ 2
Hospital stay	d	≤ 12	≤ 10	≤ 13
Postoperative morbidity at 3 mo				
Any complication	%	≤ 57.6	≤ 52.9	≤ 60.1
Clavien–Dindo grade ≥3a	%	≤ 45.5	≤ 50.0	≤ 50.0
CCI®	%	≤ 8.7	≤ 8.7	≤ 20.1
Relaparotomy rate	%	≤ 7.2	≤ 2.6	≤ 8.9
Readmission rate	%	≤ 16.3	≤ 12.5	≤ 16.6
3-mo postoperative mortality	%	≤ 5.7	≤ 0.0	≤ 6.5
Liver failure – ISGLS Grade B/C	%	≤ 10.2	≤ 2.3	≤ 12.5
Bile leak – Grade B/C	%	≤ 17.5	≤ 11.8	≤ 18.9
Oncological outcomes				
R0*	%	—	—	≥ 77.8
Resection margin*	mm	—	—	≥ 1.5
Survival rates†				
Overall survival 1 y	%	≥ 88.4	100	≥ 85.9
Overall survival 2 y	%	≥ 78.4	100	≥ 75.3
Disease-free 1 y*	%	—	—	≥ 62.2
Disease-free 2 y*	%	—	—	≥ 47.7

The benchmark (75th percentile) for malignant indications are consistently worse than for benign lesion, not only in overall survival but also for postoperative morbidity and mortality.

*Calculated for malignant cases only.

†Survival benchmarks refer to the 50th percentile.

CCI® indicates Comprehensive Complication Index; ISGLS, International Study Group of Liver Surgery

achieved was ≥ 78% and a distance to the tumor resection margin of ≥ 1.5 mm. When comparing benchmark values stratified for tumor entities, patients with malignant tumors displayed consistently worse outcome parameters, not only regarding survival (eg, 2-year survival benchmark: ≥ 67% vs ≥ 100%), but as well in nononcological outcome parameters, such as CCI® (benchmark: ≤ 20.1 vs ≤ 8.7), relaparotomy rate (benchmark: ≤9% vs ≤ 2.6%), rates of clinically relevant posthepatectomy liver failure (benchmark for ISGLS B/C: ≤ 12.5% vs 2.3%), or bile leak rate (benchmark: 24% vs 17%) (Supplemental Digital Content Table 3, http://links.lww.com/SLA/E742). Expectedly, benchmark values for overall and disease-free survival varied widely among malignant entities (Table 2). In addition, the extent of resection affects benchmark values for survival differently for each malignant entity, for example, PHC shows cutoff values for 1-year disease-free survival (DFS) of ≥ 90% for extended resections versus ≥ 80% for formal resections. In contrast, for HCC, extended resections correlate with lower cutoff values for 1-year DFS than formal resections (≥ 50% vs ≥ 68%) (Table 2).

Anatomic Side and Extent of Major Hepatectomies

Benchmark values between left- and right-sided anatomic major hepatectomies were significantly different, as well as between formal and extended resections. Right-sided procedures demonstrated overall higher cutoffs for peri- and postoperative morbidity, such as complication rates (benchmark: ≤ 63% vs 54%) or liver failure of any grade (benchmark: 24% vs 11%) (Supplemental Digital Content Table 3, http://links.lww.com/SLA/E742). The only exception was found for biliary leaks (benchmark: ≤ 21% vs ≤ 26%) as well as for R0 resection rates (benchmark: ≥ 77% vs ≥ 75%), favoring right-sided resections. This contrasting risk distribution for liver failure rates – worse in right-sided – and bile leak rate – worse in left-sided – were more pronounced within extended hepatectomies (Supplemental Digital Content Table 3, http://links.lww.com/SLA/E742).

Although extended hepatectomies are naturally associated with impaired survival independent of sidedness [hazard ratio (HR) 1.08, 95% confidence interval (CI) 1.02–1.14, $P = 0.008$], our benchmark cohort demonstrates diverging results in the longer term. Although left formal hepatectomies displayed worsening survival rates compared to a right-sided equivalent resection over time (2-year survival of 76% vs 78%; HR 1.16, 95% CI 0.97–1.38, ns), the opposite was true for extended hepatectomies (2-year survival of 73% vs 66%; HR 0.84, 95% CI 0.62–1.13 ns) in favor of left-sided extended hepatectomies, although this difference was not statistically significant (Supplemental Digital Content Figure 1B, http://links.lww.com/SLA/E742) and was not applicable to Asian centers (Supplemental Digital Content Figure 1A, http://links.lww.com/SLA/E742).

The improved survival performance of extended over formal left resection remained unexplained and surprising in the presence of a higher percentage of malignant tumors (93% vs 76%, $P < 0.001$) and worse benchmark cutoffs regarding R0 (≥ 59% vs ≥ 73%) and resection margins (≥3 vs ≥1 mm) (see Supplemental Digital Content Table 2, http://links.lww.com/SLA/E742).

Comparison to Higher-risk Cohorts

To assess the robustness of the newly identified benchmark values, we analyzed "nonbenchmark" patients with liver cirrhosis, severe obesity (BMI ≥ 35 kg/m^2), and metabolic or cardiovascular disease qualifying as ≥ ASA III treated in all benchmark centers of this study (Supplemental Digital Content table 4, http://links.lww.com/SLA/E742). Most of the defined outcome parameters were distinctly worse in these high-risk populations (Supplemental Digital Content Table 5, http://links.lww.com/SLA/E742). Of note, the overall liver failure rates in cirrhotic patients were with 25.2% well above the benchmark value of ≤ 17.2%, as well as the hospital stay of 15 days (benchmark ≤ 12 days). In addition, patients with metabolic/cardiovascular comorbidities or severe obesity displayed worse 3-month mortality of 7.4% and 8.0% (benchmark ≤ 5.7%) and after a 1-year follow-up, only 79.1% and 82.3% were still alive

TABLE 2. Survival Benchmarks According Type of Disease and Resection Extent

		CRLM		PHC		HCC		IHC	
	All cases	Formal	Extended	Formal	Extended	Formal	Extended	Formal	Extended
Overall survival, %									
1 y	≥ 88.4	≥ 96.1	≥ 92.9	≥ 90.9	≥ 88.1	≥ 84.0	100	100	≥ 72.5
2 y	≥ 78.4	≥ 83.9	≥ 75.0	≥ 76.1	≥ 71.9	≥ 80.0	≥ 66.7	≥ 80.0	≥ 62.5
Disease-free survival, %									
1 y	≥ 62.2	≥ 58.1	≥ 62.5	≥ 80.0	≥ 90.3	≥ 68.4	≥ 50.0	≥ 66.7	≥ 62.5
2 y	≥ 47.7	≥ 37.7	≥ 62.5	≥ 56.1	≥ 66.7	≥ 58.1	≥ 33.3	≥ 50.0	≥ 62.5

The benchmark cutoffs for the 50th percentile presented for overall and disease-free survival vary widely between different malignant entities and the extent of resection. CRLM colorectal liver metastasis; PHC, perihilar cholangiocarcinoma; HCC, hepatocellular carcinoma; IHC, intrahepatic cholangiocarcinoma.

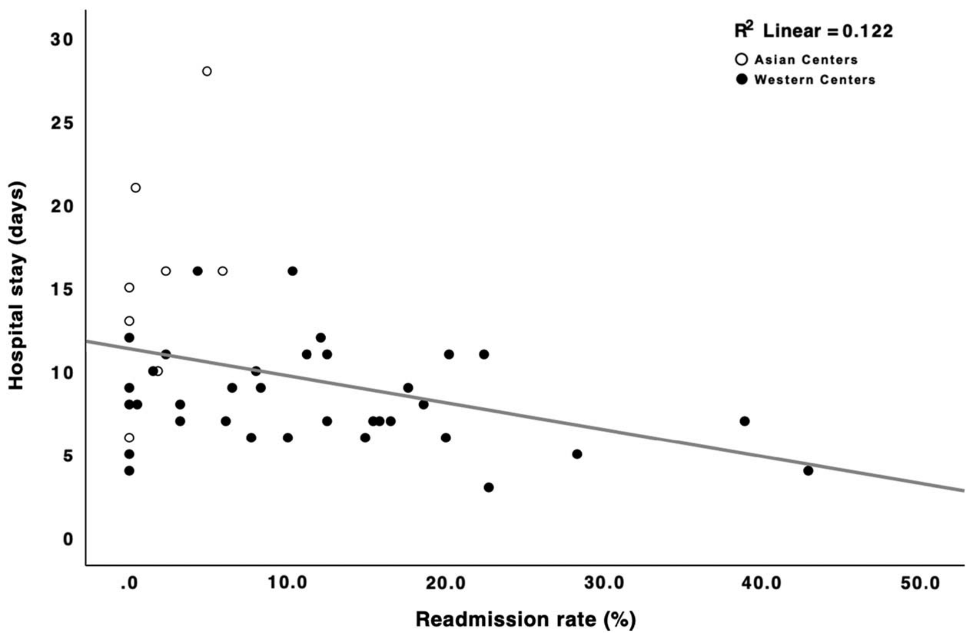

FIGURE 1. Correlation between readmission rate and length of hospital stay among centers. Centers with short median length of hospital stay have significantly higher readmission rates. One center was excluded due to missing data.

(benchmark ≥ 82.3). When comparing existing data from a low-risk cohort resected for PHC,[7] most complication parameters are outside of the benchmark cutoffs (Supplemental Digital Content Table 5, http://links.lww.com/SLA/E742). This comparable group of patients with resectable PHC underperforms our current cohort not only in survival but also in most other measured outcome parameters. This underscores the expected poor prognosis of PHC and heterogeneity of different tumor entities, not only on oncological outcomes and survival but also on perioperative morbidity and mortality.

Geographic Variations Among Asian vs Non-Asian Centers

Although previous benchmark studies on major hepatectomies showed better outcome results in Asian centers,[7,22] our data could confirm this observation only partially. The 3-month mortality was indeed significantly lower in Asian (653 patients) compared to non-Asian centers (2255 patients) with 0.5% and 3.8%, respectively ($P < 0.001$), but this effect did not translate into a better long-term overall survival (HR 1.07, 95% CI 0.88–1.28, $P = 0.511$). Disease-free survival was better in Asian centers (HR 1.30, 95% CI 1.12–1.51, $P < 0.001$), however, not reflected by higher R0-resection rates (83% vs 86%, $P = 0.506$), lower tumor stages, or larger tumor margins (3 vs 3 mm, $P = 0.191$). The operation time in Asian centers was significantly longer (590 vs 240 minutes, $P < 0.001$) than in non-Asian centers, with lower overall (18% vs 46%, $P = 0.006$) and severe ≥ 3a complication rates (17% vs 39%, $P = 0.034$). However, there was no difference in total blood loss, bile leaks, or rates of liver failure, but a significantly higher rate of segment 1 resection (57.3% vs 25.1%, $P < 0.001$) and portal vein resection (14.5% vs 9.7%, $P < 0.001$). The proportion of centers with a long hospital stay was higher in Asian countries. The length of hospital stay, however, inversely correlated with readmission rates (Fig. 1). The lower complication rates in Asian vs non-Asian centers (Supplemental Digital Content Table 6, http://links.lww.com/SLA/E742) did not translate in better long-term survivals. Of note, Asian centers performed significantly less extended hepatectomies (14.7% vs 23.2%, $P > 0.001$) and more left hepatectomies (45.7% vs 31.8%, $P < 0.001$) (Supplemental Digital Content Figure 1, http://links.lww.com/SLA/E742). In addition, we found higher median future liver remnant volumes for formal (52.1% vs 43%, $P < 0.001$) and extended (41.8% vs 34.2%, $P < 0.001$) hepatectomies in Asian centers. Survival differences were reduced when accounting for these co-factors in our analyses.

Center volume and the proportion of benchmarks cases (Fig. 2) did not show a correlation with outcome parameters. Only an increased number of low-risk benchmark cases was associated with lower 2-year survival (Pearson $R = 0.30$, $P = 0.054$), an effect amplified in extended left hepatectomies at 2-year posthepatectomy (Pearson $R = 0.51$, $P = 0.027$). Experience with robotic and/or laparoscopic cases did not affect outcome parameters.

DISCUSSION

This large multicentric international study provides benchmark thresholds for open major anatomic hepatectomies, which may newly serve as reference values for best achievable outcome. Although the current literature mostly reports on the oncologic results for specific tumor entities,[23,24] types of resections,[25,26] or surgical approaches,[27,28] this inaugural study focuses on both perioperative and long-term morbidity and oncologic outcome further stratified for tumor entity and the extent of resection. The availability of such reference values for standard open hepatectomy appears particularly valuable at a time of outbreak of novel minimally invasive approaches.

The study also enables a few key findings: First, we found a clear performance gap between benign and malignant indications beyond long-term patient survival rates, possibly related to underlying liver disease and undetected confounders, since this population appeared otherwise homogeneous.[29] Second, the extent of resection negatively impacted on postoperative morbidity and mortality. Contrarily to other benchmark studies[7] including one on LDLT presented at the 2023 Bordeaux ESA meeting,[22] we failed to identify any difference in morbidity, mortality, and long-term survival among regions, this after adjusting for procedures and baseline characteristics including tumor entity and comorbidities.

While patients with malignant tumors expectedly suffered from poorer long-term results, their outcome proved worse also for

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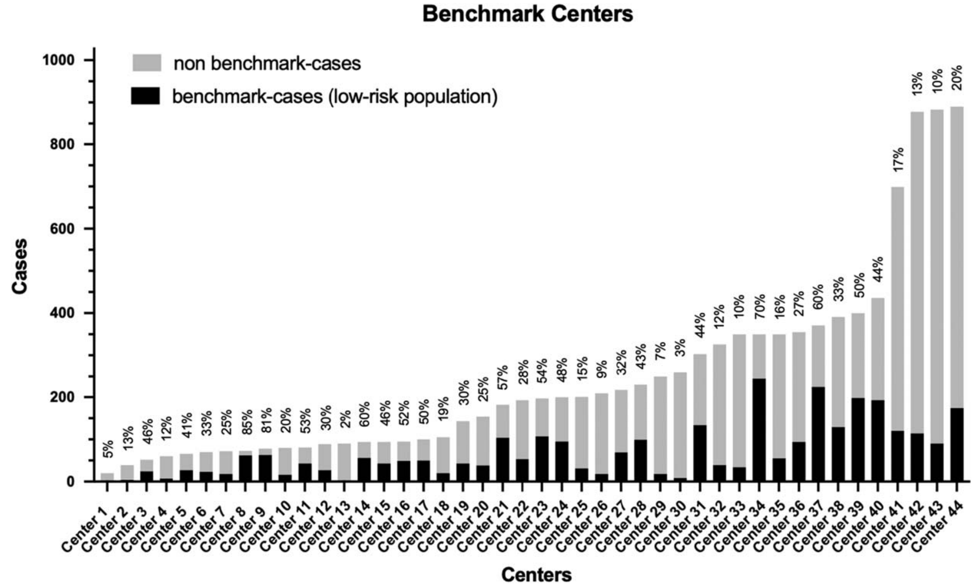

FIGURE 2. Case mix per center and center case volume. The total height of the bars represents all open major anatomic resections performed, whereas the black bars indicate the benchmark cases. The percentage given corresponds to the proportion of benchmark cases.

surgery-related benchmark values such as intraoperative blood loss, bile-leak rates, and 3-month mortality, best featured by a higher CCI®. This could be partially explained by the higher ASA score[30] and by the use of neo-adjuvant treatment[31,32] (eg, chemotherapy or interventional chemoembolization) in one-third of patients, as reflected by poorer liver function at baseline. Older age may also be a factor as our patients with malignant tumors were on average 16 years older than those with benign disorders. In addition, other factors not considered in the benchmark selection, such as a history of hepatitis[33] or presence of nonalcoholic liver disease,[34] may also be involved. The need for preoperative biliary drainage was mostly due to malignant biliary obstruction, which may affect outcome such as infectious complications.[35] Those factors were not included in the selection of benchmark cases. Patients with cancer are fragile even in the absence of clear clinical evidence, and logically prone to poorer outcome.

The study demonstrates a correlation between the extent of liver resection and outcome with worse benchmark cutoffs for extended anatomical resections, when compared to formal hemi-hepatectomies. The study also disclosed superior long-term survival rates in the extended left hepatectomy group (H2-5,8), when compared to formal left hemi-hepatectomies (H2-4) including all malignant indications. This underlines a benefit in these benchmark cases of wider resection to achieve proper oncologic clearance.

We also found poorer outcomes in most benchmark parameters for right-sided hepatectomies (H5-8 and H4-8), when compared to left-sided hepatectomies for both benign and malignant groups. This observation is possibly related to a smaller future liver remnant and associated posthepatectomy liver failure (PHLF). The site-specific differences in our benchmark cutoffs are presumably a result of 2 mechanisms: First, the more parenchyma is removed (H4-8 > H2-5,8 > H5-8 > H2-4), the higher the rate of PHLF. Second, the size of the resection area leading to a larger transection surface may explain the observed higher rates of bile leakage. Furthermore, if the resection line lies outside of a pure anatomical plane (ie, between segments 4 and 5,8), more biliary main branches are transected with enhanced risk of postoperative bile leaks.[36]

In contrast to previous benchmark studies on other complex procedures in abdominal surgery,[8,37] center-specific parameters such as case load and case mix, including proportion of benchmark cases, had no detectable impact on outcome parameters. We also failed to show a difference when stratifying by potential confounding factors, such as specific indications or preferred types of resection. These homogeneous results across centers and regions may possibly reflect the well-standardized surgical approach of formal hepatectomies, which, for example, is not the case for the surgical approach of PHC [7] and LDLT.[38]

A notorious advantage of these benchmark studies has been to identify the minimum follow-up needed to properly assess a procedure. For example, minimal clinically relevant follow-up for hepatectomy in living donors[3] and PHC[7] as well as distal pancreatectomy[39] is 3 months, while it is 6 months for LT in PHC[8] and prancreatico-duodenectomy,[12] and 1 year for LT.[4–6] Here, the minimal clinically relevant follow-up is 3 months for both malignant and benign tumors. The oncologic follow-up must of course be adjusted for the tumor entity and must be reported outside of the benchmark follow-up.

In contrast to other complex liver procedures such as PHC[7] or LDLT,[38] we did not identify better outcomes in Asian centers. After accounting for influential factors such as the proportion of extended hepatectomies or median future liver remnant, which were both significantly higher in Asian centers, no outcome difference could be detected. Again, this likewise relates to the highly standardized surgical approaches for the formal anatomic resection.

We tested the benchmark cohort with higher-risk group of patients (nonbenchmark cases) and found significantly worse outcomes in obese patients (BMI > 35 kg/m^2) as well as in those with cirrhosis, or significant major comorbidities. Risk factors, however, had varying detrimental effect on outcome. For example, cirrhosis increased mainly liver-related complications such as bleeding and liver failure, while surprisingly co-morbidities and BMI > 35 kg/m^2 led to a 2-fold increase in the 3-month mortality rates.

This study, which includes all tumor entities, shows poorer outcome parameters when compared to formal hepatectomies performed for living donor liver donation,[3] and consistently better benchmark cutoffs, than those identified in resection for PHC.[7] This further underlines the need for well-targeted benchmark studies to detect differences and propose clinically relevant benchmark values using the least biased methodology.[1,10] This study further suggests that benchmark values must be proposed according to the dignity of the lesions removed, and therefore, Table 1 should serve for clinically relevant benchmark values.

As in other benchmark studies, there are some inherent limitations. The heterogeneity in reported tumor entities leads to relevant constraints when analyzing subgroups of patients, particularly with rare conditions, such as neuroendocrine tumors. Second, benchmark studies can only be as good as the accuracy of the available data. Underreporting of adverse events and perioperative complications, especially lower-grade complications, cannot be fully avoided and might not be intentional but related to center-specific regulations and documentation policies (eg, differences in the digitalization process). The same is true regarding hospital stay and perioperative data collections (eg, median stay in the United States was 6 vs 16 days in Asian centers). Last, African centers are not represented in the current study.

In summary, with the rapid advent of minimally invasive approaches, particularly robotic surgery, the availability of reference values for open surgery are of paramount importance. This large international benchmark study following a standard methodology,[10] which has been used for many other conditions,[3–9,12,37,39] and recently endorsed in a jury-based consensus conference,[2] offers clinically relevant metrics for conclusive comparisons. Subsequent studies may target nonanatomic open resection to serve as references for increasingly popular parenchyma-sparing approaches. These benchmark values should also support decision making in the era of individualized treatment by setting an anchor for best achievable outcomes in patients requiring liver surgery.

REFERENCES

1. Staiger RD, Schwandt H, Puhan MA, et al. Improving surgical outcomes through benchmarking. *Br J Surg*. 2019;106:59.
2. Domenghino A, Clavien PA, Puhan M, et al. Outome4Medicine Consensus Conference – defining quality in surgery to improve patient care worldwide. *Nat Med*. 2023;29:811–822.
3. Rossler F, Sapisochin G, Song G, et al. Defining benchmarks for major liver surgery: a multicenter analysis of 5202 living liver donors. *Ann Surg*. 2016;264:492–500.
4. Muller X, Marcon F, Sapisochin G, et al. Defining benchmarks in liver transplantation: a multicenter outcome analysis determining best achievable results. *Ann Surg*. 2018;267:419–425.
5. Schlegel A, van Reeven M, Croome K, et al. A multicentre outcome analysis to define global benchmarks for donation after circulatory death liver transplantation. *J Hepatol*. 2022;76:371–382.
6. Abbassi F, Gero D, Muller X, et al. Novel benchmark values for redo liver transplantation: does the outcome justify the effort? *Ann Surg*. 2022;276:860–867.
7. Mueller M, Breuer E, Mizuno T, et al. Perihilar cholangiocarcinoma-novel benchmark values for surgical and oncological outcomes from 24 expert centers. *Ann Surg*. 2021;274:780–788.
8. Breuer E, Mueller M, Doyle MB, et al. Liver transplantation as a new standard of care in patients with perihilar cholangiocarcinoma? Results from an international benchmark study. *Ann Surg*. 2022;276:846–853.
9. Raptis DA, Linecker M, Kambakamba P, et al. Defining benchmark outcomes for ALPPS. *Ann Surg*. 2019;270:835–841.
10. Gero D, Muller X, Staiger RD, et al. How to establish benchmarks for surgical outcomes? A checklist based on an international expert Delphi consensus. *Ann Surg*. 2022;275:115–120.
11. Nagino M, DeMatteo R, Lang H, et al. Proposal of a new comprehensive notation for hepatectomy: the "New World" terminology. *Ann Surg*. 2021;274:1–3.
12. Sanchez-Velazquez P, Muller X, Malleo G, et al. Benchmarks in pancreatic surgery: a novel tool for unbiased outcome comparisons. *Ann Surg*. 2019;270:211–218.
13. Tran TB, Worhunsky DJ, Spain DA, et al. The significance of underlying cardiac comorbidity on major adverse cardiac events after major liver resection. *HPB (Oxford)*. 2016;18:742–747.
14. Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: the joint task force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur J Anaesthesiol*. 2014;31:517–573.
15. Fields AC, Divino CM. Surgical outcomes in patients with chronic obstructive pulmonary disease undergoing abdominal operations: an analysis of 331,425 patients. *Surgery*. 2016;159:1210–1216.
16. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–213.
17. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications five-year experience. *Ann Surg*. 2009;250:187–196.
18. Slankamenac K, Graf R, Barkun J, et al. The comprehensive complication index a novel continuous scale to measure surgical morbidity. *Ann Surg*. 2013;258:1–7.
19. Clavien PA, Vetter D, Staiger RD, et al. The Comprehensive Complication Index (CCI) added value and clinical perspectives 3 years "down the line". *Ann Surg*. 2017;265:1045–1050.
20. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery*. 2011;149:713–724.
21. Koch M, Garden OJ, Padbury R, et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. *Surgery*. 2011;149: 680–688.
22. Zhihao L, Rammohan A, Gunasekaran V, et al. Novel benchmark for adult-to-adult living-donor liver transplantation. Integrating eastern and western experiences. *Ann Surg*. 2023;278:798–806.
23. Mazzaferro V, Gorgen A, Roayaie S, et al. Liver resection and transplantation for intrahepatic cholangiocarcinoma. *J Hepatol*. 2020; 72:364–377.
24. Allaire M, Goumard C, Lim C, et al. New frontiers in liver resection for hepatocellular carcinoma. *JHEP Rep*. 2020;2:100134.
25. Deng G, Li H, Jia GQ, et al. Parenchymal-sparing versus extended hepatectomy for colorectal liver metastases: a systematic review and meta-analysis. *Cancer Med*. 2019;8:6165–6175.
26. Lee SY, Sadot E, Chou JF, et al. Central hepatectomy versus extended hepatectomy for liver malignancy: a matched cohort comparison. *HPB (Oxford)*. 2015;17:1025–1032.
27. Fretland AA, Dagenborg VJ, Bjornelv GMW, et al. Laparoscopic versus open resection for colorectal liver metastases: the OSLO-COMET randomized controlled trial. *Ann Surg*. 2018;267:199–207.
28. Pan Y, Xia S, Cai J, et al. Efficacy of laparoscopic hepatectomy versus open surgery for hepatocellular carcinoma with cirrhosis: a meta-analysis of case-matched studies. *Front Oncol*. 2021;11:652272.
29. Farges O, Malassagne B, Flejou JF, et al. Risk of major liver resection in patients with underlying chronic liver disease: a reappraisal. *Ann Surg*. 1999;229:210–215.
30. Longchamp G, Labgaa I, Demartines N, et al. Predictors of complications after liver surgery: a systematic review of the literature. *HPB (Oxford)*. 2021;23:645–655.
31. Field KM, Dow C, Michael M. Part I: liver function in oncology: biochemistry and beyond. *Lancet Oncol*. 2008;9:1092–1101.
32. Wang Y, Brodin E, Nishii K, et al. Impact of tumor-parenchyma biomechanics on liver metastatic progression: a multi-model approach. *Sci Rep*. 2021;11:1710.
33. Suhail M, Abdel-Hafiz H, Ali A, et al. Potential mechanisms of hepatitis B virus induced liver injury. *World J Gastroenterol*. 2014;20: 12462–12472.
34. Duan XY, Zhang L, Fan JG, et al. NAFLD leads to liver cancer: do we have sufficient evidence? *Cancer Letters*. 2014;345:230–234.
35. Guardado NV, Llorente K, Blondeau B. Evaluation and management of malignant biliary obstruction. *Surg Oncol Clin N Am*. 2021;30:491–503.
36. Lowe MC, D'Angelica MI. Anatomy of hepatic resectional surgery. *Surg Clin North Am*. 2016;96:183–195.
37. Gero D, Vannijvel M, Okkema S, et al. Defining global benchmarks in elective secondary bariatric surgery comprising conversional, revisional, and reversal procedures. *Ann Surg*. 2021;274:821–828.
38. Miller CM, Quintini C, Dhawan A, et al. The international liver transplantation society living donor liver transplant recipient guideline. *Transplantation*. 2017;101:938–944.
39. Muller PC, Breuer E, Nickel F, et al. Robotic distal pancreatectomy, a novel standard of care? Benchmark values for surgical outcomes from 16 International Expert Centers. *Ann Surg*. 2022;278:253–259.

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DISCUSSANT

Laurence Chiche (Bordeaux, France)

I would like to thank the ESA for the privilege of being the first discussant of this paper, and the authors for this huge work, considering a data collection of more than 8000 patients, including almost 3000 benchmark cases, taken from the databases of 44 centers all over the world, in different languages, from different software programs. Congratulations, as the topic is important. It aims to establish the best available outcomes of major open hepatectomies, in terms of short- and long-term results.

However, I have several concerns and questions: First, you defined the benchmark cases as including all hepatectomies in non-cirrhotic livers. Nevertheless, one of the main factors influencing the morbi-mortality is the quality of these non-cirrhotic livers. I'm sure you agree that it is very different to perform hepatectomies in cholestatic, drained, or steatotic livers, chemotherapy-induced parenchyma, or strictly normal livers. Don't you think stratification is mandatory?

Second, as I said, the number of centers is impressive, and I have experience in many aspects of such collective work: the operative time, the length of hospital stay, the way of counting blood loss, and even the way of reporting morbidity. All these factors are dependent on the center, the quality of the database, and the country. Don't you think that this heterogeneity can alter the results? Why didn't you include less centers, but with more verified and comparable items?

Third, you showed an important discrepancy between the 44 centers, from 2% to 70% BM cases, and with no effect of the center volume on results. Considering that you included complex procedures, such as extended hepatectomies, I would appreciate a comment on this. It is not very understandable.

Fourth, you said that you tested the Benchmark cohort with the high-risk group in cirrhosis or obese patients. Isn't it obvious? I do not understand how this comparison assesses the robustness of your study.

Finally, concerning the results, you gave survival benchmark according to the disease (some surprisingly high: HCC 100% at 1 year). Are they interpretable considering the heterogeneity of the tumors and their management?

Response From Richard X Sousa Da Silva (Zurich, Switzerland)

Thank you, Professor Chiche, for your challenging questions. Regarding your first question on whether stratification for the quality of the liver parenchyma is mandatory, the presence of underlying liver diseases clearly impact outcome. However, we only excluded cirrhotic livers, which are typically identified before surgery. We kept the other changes in the parenchyma, which are usually unknown or poorly known before surgery, since the benchmarking method focuses on real-world data to remain clinically relevant and applicable.

Your second question relates to the risk of including too many centers, causing variability in data collection. The methodology of current benchmark studies includes as many large centers that hold a prospective database and having published in the area. In fact, we avoided restricting ourselves to too few expert centers to, again, provide "real-world" benchmark cutoffs.

Third, you challenge the proportions of benchmark cases among centers ranging from 2% to 70%. While the rationale behind this discrepancy is not always clear, some large public or referral hospitals must treat high proportions of complex cases, and other may select more optimal cases. We would like to underline that the identification of benchmark cutoffs is not affected by such variability, obviating the need for a multivariate or complex statistical analysis. This is one of the most attractive aspects of the methodology. The results of open major anatomic liver resections is not superior in centers operating mostly on challenging cases, in contrast to many other procedures, such as pancreatectomy, LT, or esophagectomy. We speculated that this might be due to the standardization of these anatomic procedures.

Fourth, we routinely test benchmark values in higher-risk groups to secure some discrimination in outcomes. Failing to show this would question the relevance of the benchmark cutoffs.

Finally, we fully agree that the survival rates relate to the respective tumor entities, and the data is presented as such. The survival benchmark values, however, refer to the procedures, rather than the individual tumor stage, and thus, cannot be used for survival analyses and the management of individual patients. These reference values can only be used for comparisons among the types of hepatectomies, acknowledging heterogeneity among the individual tumors.

Antonio Pinna (Weston, United States)

I have one question regarding the methodology of the study. Why did you not include living donors in the study? Probably, they are the real benchmark for major liver resection.

Response From Richard X Sousa Da Silva (Zurich, Switzerland)

Thank you, Professor Pinna, for your question. We agree, and in fact, 95 cases of living donor hepatectomies were included.

Olivier Farges (Clichy, France)

First, you said that you excluded two-third of the population based on severe morbidity. Was this definition globally standardized? Second, you showed that the single outcome measurements were different according to geographical location. Let's say that you were to change the distribution of the centers tomorrow to include more centers in Asia; you would end up with textbook outcomes, which would differ from the ones you presented today. So, what should we do with this?

Response From Richard X Sousa Da Silva (Zurich, Switzerland)

Thank you, Professor Farges, for your questions. First, the definition of comorbidities was highly standardized. Once we received the data, we filtered and graded each comorbidity. Second, while including all large centers would of course be ideal, we included a solid number of centers from 5 continents offering robust – real-world – international benchmark thresholds.

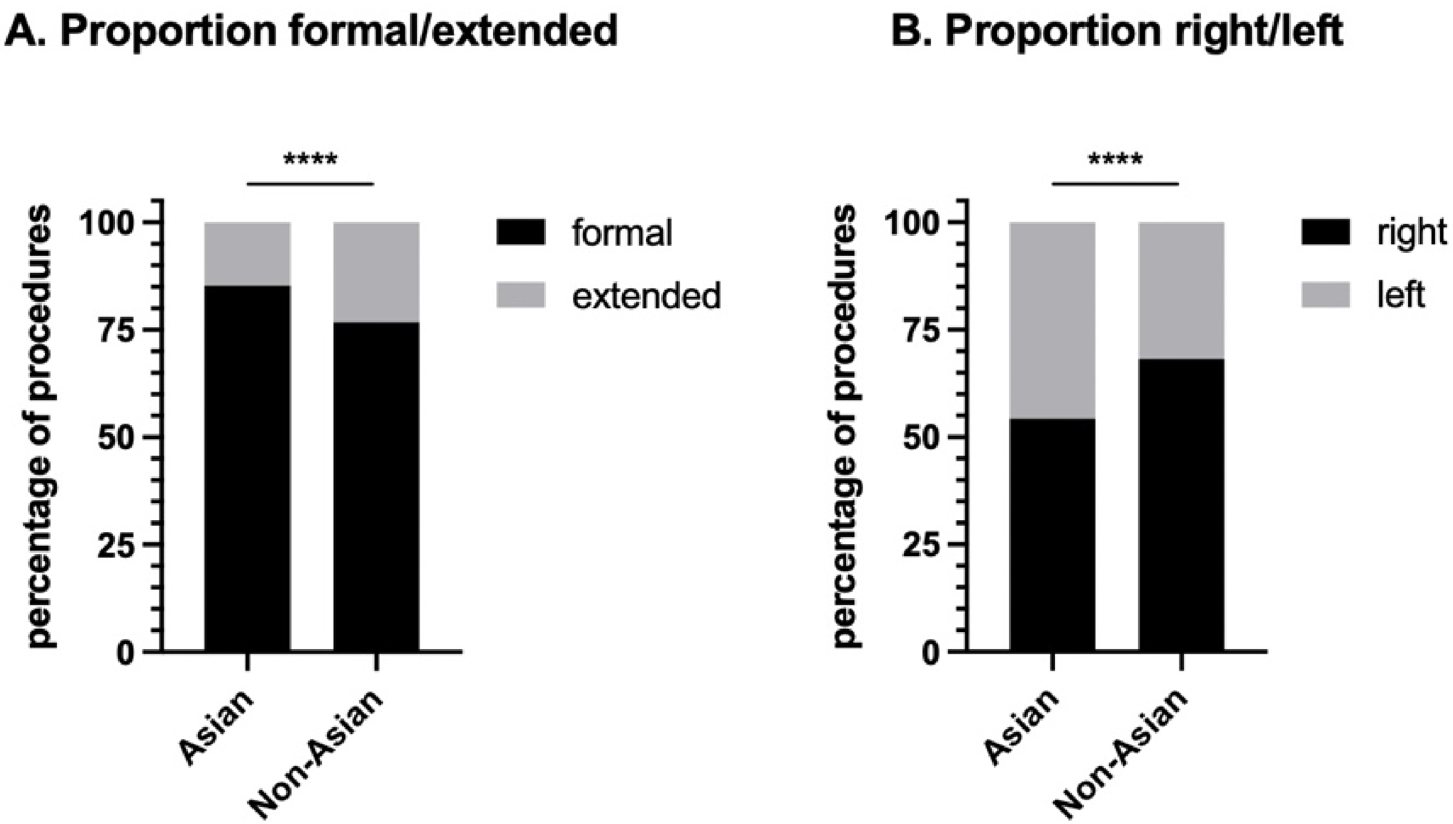
Christiane Bruns (Cologne, Germany)

In your benchmark analysis, did you include any kind of procedures of liver augmentation, such as two-stage hepatectomies, or portal vein ligations and ALPPS?

Response From Richard X Sousa Da Silva (Zurich, Switzerland)

Thank you, Professor Bruns, for this legitimate question. We excluded all two-stage procedures, as those are distinct operations. However, we included frequently performed portal vein embolization, which was performed in about a quarter of cases, and more frequently, in Asia.

Supplementary Figure 1: Differences Asian vs non-Asian Centers



Supplementary Figure 1. Main differences in the overall population of Asian vs. non-Asian centers. (**A**) Significantly less extended procedures performed in Asian centers compared to non-Asian centers (p<0.001). (**B**) Significantly fewer right hepatectomies performed in Asian centers (p<0.001).

Supplementary Table 1: Inclusion and Exclusion Criteria for the Low-Risk Cohort Treated in High-Volume Centers

Inclusion criteria	
	Age ≥ 18 years
	Any liver tumor (malignant/benign) and living-donors
	Underwent open major anatomic liver resection, i.e. formal or extended right/left hepatectomy, with curative intent
	± Concomitant bile duct, artery or portal vein resection
	± Cirrhotic liver (as non-benchmark control)
	No significant co-morbidities (see exclusion criteria bellow)
Benchmark criteria	
	Age from 18 to 70 years
	No distant lymph node metastasis
	No previous major hepatectomy (Note: small wedge resections older than 6 months are allowed)
	No previous central resection
	No major comorbidities as defined by the exclusion criteria
Medical exclusion criteria	
	ASA ≥ 3
	BMI ≥ 35 kg/m2
	Cardiac disease: (Note: arterial hypertension is not considered)
	Congestive heart failure (CHF) onset or exacerbation in 30 days prior to surgery
	History of angina pectoris within 1 month of surgery
	Myocardial infarct within 6 months prior to surgery
	History of percutaneous coronary intervention or cardiac surgery
	Atrial fibrillation
	Chronic renal failure MDRD ≥ Stage 3: GRF <60ml/min per 1.73m^2 or creatinine > 1.8 mg/dl or 160 µmol/l
	Chronic obstructive pulmonary disease with FEV1<80%
	Use of anticoagulants: (Note: patients under Aspirin 100mg should not been excluded)
	NOACs
	Vitamin K antagonist
	Clopidogrel
	Diabetes mellitus ≥ 2 oral antidiabetic drugs or insulin

Supplementary Table 1. Inclusion/exclusion criteria and definition of low-risk benchmark patients.

Supplementary Table 2: Characteristics Among Benchmark Patients

Patient Characteristics	Unit	All Cases	Benign	Malignant	Formal Left Hx	Extended Left Hx	Formal Right Hx	Extended Right Hx
Female sex	n (%)	1316 (47.1)	299 (66.4)	1016 (43.4)	351 (46.2)	103 (53.9)	667 (46.8)	170 (46.7)
Age (years)	median (IQR)	62 (IQR 51 - 70)	48 (IQR 35 - 60)	64 (IQR 55 - 71)	63 (IQR 51 - 71)	61 (IQR 51 - 70)	62 (IQR 51 - 70)	62 (IQR 52 - 69)
BMI (kg/m^2)	median (IQR)	24.2 (IQR 21.6 - 26.9)	24.0 (IQR 21.8 - 26.8)	24.2 (21.6 - 27.0)	24.2 (21.6 - 26.8)	23.3 (IQR 20.6 - 26.2)	24.4 (IQR 21.9 - 27.3)	23.8 (IQR 21.5 - 26.5)
ASA grade I	n (%)	739 (26.9)	232 (53.0)	507 (21.9)	229 (30.3)	56 (30.3)	369 (26.5)	76 (21.3)
ASA grade II	n (%)	2012 (73.1)	206 (47.0)	1805 (78.1)	527 (69.7)	129 (69.7)	1026 (73.5)	280 (78.7)
Surgery-related Characteristics								
Pringle Maneuver	n (%)	1675 (57.6)	293 (63.7)	1382 (56.5)	456 (57.6)	154 (75.9)	793 (53.7)	246 (65.1)
Concomittant resection segment I	n (%)	941 (32.4)	90 (19.6)	851 (34.8)	335 (42.3)	130 (64.0)	292 (19.8)	177 (46.8)
Previous cholecystectomy	n (%)	290 (10.0)	53 (11.5)	237 (9.7)	78 (9.8)	20 (9.9)	148 (10.0)	39 (10.3)
Previous wedge resection	n (%)	132 (4.5)	2 (0.4)	130 (5.3)	27 (3.4)	4 (2.0)	82 (5.6)	14 (3.7)
Calculated FLV (%)	median (IQR)	43.7 (IQR 35.3 - 56.2)	44.1 (IQR 35 - 61.4)	43.7 (35.6 - 55)	66.1 (IQR 60.1 - 71.7)	42.5 (IQR 36.1 - 48.2)	41.9 (IQR 35.2 - 49.3)	34.3 (IQR 29.1 - 40.5)
Tumor Characteristics								
Malignant tumors	n (%)	2448 (84.2)	-	2448 (100.0)	614 (77.5)	188 (92.6)	1231 (83.4)	357 (94.4)
Benign tumors	n (%)	460 (15.8)	460 (100.0)	-	178 (22.5)	15 (7.4)	245 (16.6)	21 (5.6)
CRLM	n (%)	867 (29.8)	-	867 (35.4)	154 (19.5)	27 (13.3)	555 (37.6)	105 (27.8)
PHC	n (%)	610 (21.0)	-	610 (24.9)	188 (23.8)	88 (43.3)	209 (14.2)	120 (31.7)
HCC	n (%)	371 (12.8)	-	371 (15.2)	76 (9.6)	20 (9.9)	209 (14.2)	50 (13.2)
IHC	n (%)	368 (12.7)	-	368 (15.1)	139 (17.6)	42 (20.7)	124 (8.4)	57 (15.1)
NET	n (%)	42 (1.4)	-	42 (1.7)	7 (0.9)	4 (2.0)	25 (1.7)	5 (1.3)
Other malignant tumor	n (%)	190 (6.5)	-	190 (7.7)	50 (6.2)	7 (3.4)	109 (7.4)	20 (5.3)
Echinococcosis	n (%)	61 (2.1)	61 (13.3)	-	15 (1.9)	5 (2.5)	37 (2.5)	4 (1.1)
Hemangioma	n (%)	53 (1.8)	53 (11.5)	-	10 (1.3)	1 (0.5)	39 (2.6)	3 (0.8)
Adenoma	n (%)	34 (1.2)	34 (7.4)	-	11 (1.4)	0 (0.0)	2 (0.1)	0 (0.0)
Biliary cyst	n (%)	34 (1.2)	34 (7.4)	-	18 (2.3)	1 (0.5)	13 (0.9)	2 (0.5)
Biliary cystadenoma	n (%)	32 (1.1)	32 (6.9)	-	23 (2.9)	1 (0.5)	7 (0.5)	1 (0.3)
FNH	n (%)	22 (0.8)	22 (4.8)	-	7 (0.9)	2 (1.0)	11 (0.7)	2 (0.5)
ADPLD / polycystosis	n (%)	22 (0.8)	22 (4.8)	-	16 (2.0)	0 (0.0)	6 (0.4)	0 (0.0)
Biliary stenosis	n (%)	14 (0.5)	14 (3.0)	-	3 (0.4)	3 (1.5)	7 (0.5)	1 (0.3)
Other benign tumor	n (%)	188 (6.5)	188 (40.9)	-	75 (9.5)	2 (1.0)	123 (8.3)	8 (2.1)

Supplementary Table 2. Patient, surgery-related and tumor characteristics among all benchmark patients. Stratification further divides cases for lesion entity and the extent of resection.

Supplementary Table 3: Stratified Benchmark Values

	Unit	All Cases	Tumor dignity		Left Sided Hx			Right Sided Hx			
			Benign	**Malignant**	**All left**	**Formal**	**Extended**	**All left**	**Formal**	**Extended**	**Non-BM**
Operation time	min	≤370	≤339	≤353	≤362	≤348	≤510	≤360	≤342	≤405	≤386
Blood loss	ml	≤700	≤500	≤785	≤600	≤596	≤1150	≤800	≤800	≤962	≤825
Intensive care unit stay	days	≤2	≤2	≤2	≤2	≤2	≤2.5	≤2	≤2	≤3	≤3
Hospital stay	days	≤12	≤10	≤13	≤12	≤13.5	≤23.5	≤12	≤11	≤17	≤17
Postoperative morbidity at 3 months											
Any complication	%	≤57.6	≤52.9	≤60.1	≤53.8	≤47.1	≤78.9	≤62.5	≤57.1	≤81.8	≤66.7
Clavien-Dindo Grade ≥ 3a	%	≤45.5	≤50.0	≤50.0	≤52.2	≤46.4	≤75.0	≤53.3	≤50.0	≤66.7	≤55.6
CCI®		≤8.7	≤8.7	≤20.1	≤8.7	≤0.0	≤27.3	≤20.9	≤9.6	≤29.2	≤23.4
Relaparotomy rate	%	≤7.2	≤2.6	≤8.9	≤10.2	≤9.6	≤15.1	≤8.5	≤5.7	≤14.3	≤7.1
Readmission rate	%	≤16.3	≤12.5	≤16.6	≤12.2	≤8.9	≤23.2	≤18.8	≤16	≤32.1	≤18.2
3-month postoperative mortality	%	≤5.7	≤0.0	≤6.5	≤4.0	≤1.8	≤9.1	≤5.5	≤3.6	≤11.7	≤8.1
Liver failure											
All ISGLS grades	%	≤17.2	≤6.3	≤19.4	≤11.2	≤8.9	≤27.8	≤23.6	≤22.0	≤35.1	≤20.0
ISGLS Grade B/C	%	≤10.2	≤2.3	≤12.5	≤7.1	≤4.4	≤20.0	≤13.2	≤9.8	≤25.8	≤11.8
Bile leak											
All grades	%	≤21.6	≤17.2	≤24.0	≤25.6	≤17.8	≤50.0	≤21.0	≤18.9	≤35.6	≤16.7
Grade B/C	%	≤17.5	≤11.8	≤18.9	≤18.4	≤14.6	≤48.2	≤18.2	≤14.5	≤35.6	≤16.7
Oncological outcomes											
R0 resection margin rate	%	≥78.3	-	≥77.8	≥74.6	≥73.3	≥58.5	≥77.2	≥83.2	≥63.9	≥73.6
Distance tumor resection margin	mm	≥1.5	-	≥1.5	≥3.0	≥3.0	≥1.0	≥4.0	≥3.5	≥2.0	≥1.0
Overall survival rate*											
1 yr	%	≥88.4	100	≥85.9	≥91.6	≥93.0	≥86.6	≥87.5	≥88.9	≥91.0	≥85.7
2 yr	%	≥78.4	100	≥75.3	≥82.8	≥85.1	≥83.3	≥79.5	≥82.7	≥80.0	≥72.9
Disease-free survival rate*											
1 yr	%	≥83.0	-	≥62.2	≥66.7	≥66.7	≥72.9	≥63.9	≥65.1	≥63.5	≥74.0
2 yr	%	≥62.7	-	≥47.7	≥52.0	≥50.0	≥58.3	≥49.8	≥49.0	≥50.0	≥51.0

Supplementary Table 3**. Benchmark values stratified for tumor entity and type of resection.** Benchmark values for all cases, benign vs malignant cases only, followed by stratification for side and resection extent. As a comparison the high-risk non-benchmark patients. *Survival benchmarks refer to the 50th percentile.

Supplementary Table 4: **Basic Patient Characteristics** *(part one of two)*

Patient characteristics	Unit	Benchmark patients (n=2908)	High-risk cohort (n=705)	p	Missing
Age (years)	median (IQR)	62 (51 – 70)	66 (58 – 72)	<0.001	0.0%
Female gender	n (%)	1316 (45.3)	210 (29.8)	<0.001	4.1%
BMI (kg/m^2)	median (IQR)	24.2 (21.6 – 26.9)	25 (22.2 – 29.0)	<0.001	7.8%
Anticoagulation	n (%)			<0.001	11.0%
None		2541 (97.3)	488 (80.8)		
Acetylsalicylic acid		66 (2.5)	69 (11.4)		
NOACs		0 (0.0)	25 (4.2)		
Vitamin K antagonists		0 (0.0)	14 (2.3)		
Other		4 (0.2)	8 (1.3)		
Previous wedge resection	n (%)	132 (4.5)	49 (7.0)	0.008	0.0%
Weightloss	n (%)	422 (14.5)	97 (13.8)	0.609	0.0%
Fibrosis	n (%)			<0.001	30.7%
F0		1680 (80.5)	281 (67.7)		
F1		230 (11.0)	59 (14.2)		
F2		140 (6.7)	51 (12.3)		
F3		38 (1.8)	24 (5.8)		
Cirrhosis	n (%)	0 (0.0)	173 (24.5)	<0.001	0.0%
Preoperative					
Endoscopic confirmation with biopsy	n (%)	385 (13.2)	132 (18.7)	<0.001	0.0%
Ipsilateral PV involvement	n (%)	151 (25.1)	33 (33.3)	0.086	80.6%
Ipsilateral HA involvement	n (%)	85 (14.1)	14 (14.1)	1.000	80.6%
Portal vein embolization	n (%)	737 (25.3)	199 (28.2)	0.117	0.0%
Hepatic vein embolization	n (%)	44 (1.5)	9 (1.3)	0.639	0.0%
Future liver remnant (%)	median (IQR)	43.7 (35.3 – 56.2)	47 (38 – 56.8)	0.093	58.2%
Preoperative biliary drainage	n (%)			0.007	21.3%
None		1727 (76.2)	455 (78.9)		
Endoscopic biliary stenting (EBS)		271 (12.0)	41 (7.1)		
Endoscopic naso-biliary drainage (ENBD)		147 (6.5)	45 (7.8)		
PTCD		120 (5.3)	36 (6.2)		
Preoperative cholangitis	n (%)	202 (6.9)	50 (7.1)	0.892	0.0%
Antibiotic treatment if cholangitis	n (%)	194 (96.0)	47 (94.0)	0.527	0.0%
General tumor characteristics					
Malignant tumor	n (%)	2448 (84.2)	661 (93.8)	<0.001	0.0%
Preoperative therapy	n (%)				
Chemotherapy		809 (33.1)	163 (24.7)	<0.001	14.1%
Radiotherapy		39 (1.6)	15 (2.3)	0.237	14.1%
Local treatment				<0.001	63.5%
None		903 (88.6)	229 (76.8)		
Thermal ablation (RFA or MWA)		33 (3.2)	11 (3.7)		
TARE		25 (2.5)	12 (4.0)		
TACE		50 (4.9)	42 (14.1)		
Other (e.g. Nano-Knife, HAI pump)		8 (0.8)	4 (1.4)		
Preoperative laboratory values	median (IQR)				
Bilirubin (mg/dl)		0.5 (0.3 - 0.82)	0.6 (30.4 - 0.9)	0.061	8.6%
INR		1.01 (0.98 – 1.09)	1.03 (1.00 – 1.11)	0.129	13.5%
Quick (%)		97 (87 – 101)	93 (81 – 100)	<0.001	32.4%
CEA (μg/L)		2.80 (1.56 – 7.60)	3.40 (1.80 – 13.00)	0.007	37.8%
AFP (μg/L)		3.37 (2.18 – 6.00)	5.45 (3.00 – 42.65)	0.888	60.1%
CA 19-9 (kU/L)		24 (8.81 – 110.0)	28 (10.6 – 385)	0.024	40.4%
Surgery					
Pringle maneuvre	n (%)	1675 (57.6)	365 (51.8)	0.005	0.0%
Total time of pringle, if done	median (IQR)	35 (22 – 54)	30 (19 – 50)	0.634	8.8%
PV-resection	n (%)	314 (10.8)	126 (17.9)	<0.001	0.0%
HA-resection	n (%)	120 (4.1)	67 (9.5)	<0.001	0.0%
Hepaticojejunostomy	n (%)	812 (27.9)	207 (29.4)	0.446	0.0%
Fresh frozen section	n (%)	472 (78.5)	63 (63.6)	0.001	80.6%
Intraoperative bloodloss (ml)	median (IQR)	500 (250 – 906)	695 (316 – 1200)	0.047	33.2%
EC substitution	n (%)	446 (15.3)	152 (21.6)	<0.001	0.0%
FFP substitution	n (%)	186 (6.4)	75 (10.6)	<0.001	0.0%
Operative time (minutes)	median (IQR)	300 (240 – 406)	316 (240 – 462)	<0.001	10.8%
Postoperative course					
Postoperative laboratory values	median (IQR)				
AST peak (U/l)		360 (216 – 607)	383 (231 – 685)	0.233	11.6%
ALT peak (U/l)		341 (199 – 569)	341 (191 – 614)	0.137	17.9%
Bilirubin (mg/dl) peak		1.42 (0.82 – 2.44)	1.7 (1 – 2.9)	0.030	8.9%
INR peak		1.4 (1.2 – 1.6)	1.4 (1.3 – 1.7)	0.046	16.2%
Quick (%) peak		60 (48 – 71)	56 (44 – 67)	<0.001	34.8%
ICU stay (days)	median (IQR)	1 (1 – 2)	1 (0 – 3)	0.075	5.9%
Hospital stay (days)	median (IQR)	10 (7 – 18)	12 (7 – 22)	<0.001	3.0%

Supplementary Table 4: **Basic Patient Characteristics** *(part two of two)*

Complications	**Unit**	**Benchmark patients** (n=2908)	**High-risk cohort** (n=705)	p	Missing
Any complication	n (%)	1350 (46.4)	343 (48.7)	0.287	0.0%
Complication > grade 3a	n (%)	1107 (38.1)	260 (36.9)	0.560	0.0%
CCI®	median (IQR)	0 (0 – 26.2)	0 (0 – 26.2)	0.244	0.0%
CCI® of all ≥ grade II	median (IQR)	29.6 (20.9 – 42.4)	29.6 (20.9 – 45.4)	0.027	58.4%
Bile leak	n (%)			0.089	11.0%
Grade A		94 (3.6)	14 (2.3)		
Grade B		288 (11.0)	78 (12.9)		
Grade C		57 (2.2)	7 (1.2)		
Liver failure	n (%)			0.150	25.6%
Grade A		110 (5.0)	36 (7.3)		
Grade B		138 (6.3)	31 (6.3)		
Grade C		65 (3.0)	19 (3.8)		
Delayed gastric emptying	n (%)	139 (4.8)	23 (3.3)	0.081	0.0%
PV-thrombosis	n (%)	52 (1.8)	12 (1.7)	0.877	0.0%
Relaparotomy	n (%)	157 (5.4)	29 (4.1)	0.166	0.0%
Postoperative hemorrhage	n (%)	85 (2.9)	11 (1.6)	0.044	0.0%
EC substitution	n (%)	295 (10.1)	84 (11.9)	0.169	0.0%
Readmission	n (%)	259 (8.9)	81 (11.5)	0.035	0.0%
Days to readmission	median (IQR)	26 (15 – 50)	32 (18 – 95)	0.002	2.9%
Recurrence	n (%)			0.917	27.9%
No recurrence		897 (43.8)	248 (44.4)		
Distant recurrence		553 (27.0)	153 (27.4)		
Locoregional recurrence		597 (29.2)	158 (28.3)		
Survival					
90-day mortality	n (%)	88 (3.0)	38 (5.4)	0.002	0.0%
				0.002	15.1%
1-year overall survival (%)		88.0	82.5		
2-year overall survival (%)		78.5	71.9		
				0.567	
1-year disease-free survival (%)		65.4	66.4		
2-year disease-free survival (%)		48.9	47.8		

Supplementary Table 4**. Characteristics of all benchmark patients and a comparative high-risk group from the same high-volume centers.** The high-risk group includes patients fulfilling the medical exclusion criteria and/or having proven cirrhosis.

Supplementary Table 5: Outcome Benchmarks After Major Anatomic Hepatectomies

	Benchmark		Non-benchmark, high-risk populations (medians)			PHC Benchmark cohort[7]	
	Benchmark values	**median**	**Comorbidities**	**Cirrhosis**	**BMI**	**Benchmark values**	**median**
Operation time (min)	**≤370**	280	320	349	300	**≤480**	437*
Blood loss (mL)	**≤700**	498	674	900*	600	**≤1100**	800*
Intensive care unit stay (d)	**≤2**	1	2	1	2*	**≤2**	1
Hospital stay (d)	**≤12**	9	13*	15*	9	**≤19**	17*
Morbidity at 3 months							
Any complication (%)	**≤57.6**	44.6	45.2	52	50	**≤87**	80.5*
Clavien-Dindo Grade ≥ 3a (%)	**≤45.5**	36.6	36.8	30.6	40	**≤70**	58.1*
CCI®	**≤8.7**	0	0	0	4.4	**≤30.5**	28.9*
Re-laparotomy rate (%)	**≤7.2**	3.2	4	3.5	6	**≤19**	9*
Readmission rate (%)	**≤16.3**	7.9	9.9	16.8*	12.0	**≤31**	11.5
3-month mortality (%)	**≤5.7**	1.2	7.4*	3.5	8*	**≤13**	7*
Liver failure							
ISGLS Grade B/C (%)	**≤10.2**	5.2	11.9*	11.9*	3	**≤16/≤10**	17.9*
Bile leak							
Grade B/C (%)	**≤17.5**	11.4	14.9	13.6	13	-	-
Oncological outcomes							
R0 (%) #	**≥77.8**	83.2	86.1	83.3	77.1*	**≥56.7**	70.9
Resection margin (mm) #	**≥1.5**	3	3	6	3	-	-
Survival rates**							
Overall survival 1 yr (%)	≥88.4	-	79.1*	85*	82.3*	**≥77.5**	85.1*
Overall survival 2 yr (%)	≥78.4	-	67.7*	73.8*	77.3*	**≥61.5**	73.6*
Disease-free 1 yr (%) #	≥62.2	-	67.5	63.4	80.3	**≥33.3**	72
Disease-free 2 yr (%) #	≥47.7	-	49.9	45.7*	54.5	**≥7.9**	52.9

Supplementary Table 5**. Benchmark values of our benchmark cohort compared to non-benchmark patients and previous benchmarks and medians from resected perihilar cholangiocarcinoma patients**[7]**.** The benchmark cases from this study include benign and malignant lesions and all resection extents (H234, H23458, H5678, and H45678). Median values with * are outside the current benchmark values for outcome parameters. # Calculated for malignant cases only. **Survival benchmarks refer to the 50th percentile.

Supplementary Table 6: Benchmark Values Stratified for Region

		Western Centers (n=35)	Asian Centers (n=8)
	Unit	**Benchmark**	**Benchmark**
Operation time	min	≤322	≤660
Blood loss	ml	≤620	≤850
Intensive care unit stay	days	≤2	≤1.8
Hospital stay	days	≤11	≤18.5
Postoperative morbidity at 3 months			
Any complication	%	≤60.3	≤38.6
Clavien-Dindo Grade ≥ 3a	%	≤49.4	≤37.8
CCI®		≤20.9	≤0
Relaparotomy rate	%	≤8.0	≤2.8
Readmission rate	%	≤17.9	≤5.4
3-month postoperative mortality	%	≤6.3	≤0
Hepatectomy specific			
Liver failure, ISGLS Grade B/C	%	≤11.8	≤4.2
Bile leak, Grade B/C	%	≤17.4	≤20.8
Oncological outcomes			
R0 resection margin rate #	%	≥76.4	≥78.1
Distance tumor resection margin #	mm	≥2.0	≥1
Overall survival rate *			
1 yr	%	≥82.1 (≥86.7)	≥83.9 (≥90.7)
2 yr	%	≥72.4 (≥78.4)	≥67.7 (≥85.1)
Disease-free survival rate *			
1 yr #	%	≥55.6 (61.5)	≥50.5 (≥70.9)
2 yr #	%	≥36.7 (≥45.8)	≥41.8 (≥50.9)

Supplementary Table 6. Benchmark values stratified for region. The benchmark for malignant indications are consistently worse than for benign lesion, not only in overall survival, but also for postoperative morbidity and mortality. #Calculated for malignant cases only. *Survival benchmarks refer to the 50th percentile. One Asian center was excluded due to missing data.