Chirurgia (2020) 115: 707-714
No. 6, November - December

http://dx.doi.org/10.21614/chirurgia.115.6.707

Effectiveness of Terlipressin on Modulation of Portal Vein Pressure after Hepatic Resections in Non-Cirrhotic Patients.
A Systematic Review and Meta-Analysis of Randomised Controlled Trials

Paschalis Gavriilidis[1,2*], Keith J Roberts[1], Nicola de'Angelis[3], Riccardo Memeo[4], Madhava Pai[2], Salomone Di Saverio[5], Alan Askari[6], Robert P Sutcliffe[1]

[1]Department of Hepato-Pancreato-Biliary and Liver Transplant surgery,
Queen Elizabeth University Hospitals Birmingham NHS Foundation Trust, United Kingdom
[2]Department of Hepatopanceaticobiliary Surgery, Imperial College Healthcare NHS Trust, Hammersmith Hospital, London, United Kingdom
[3]Department of Digestive Surgery, University Hospital Henri Mondor (AP-HP), University of Paris Est, Créteil, France
[4]Department of Hepato-Pancreato-Biliary Surgery, Miulli Hospital, Acquaviva delle Fonti, Bari, Italy
[5]Department of Surgery, University of Insubria, Insubria, Italy
[6]Department of Upper Gastro-Intestinal Surgery, Luton and Dunstable University Hospitals NHS Trust, Luton, United Kingdom

*Corresponding author:
Paschalis Gavriilidis PhD
Queen Elizabeth University Hospitals
Birmingham NHS Foundation Trust,
B15 2TH, United Kingdom
E-mail: pgavrielidis@yahoo.com

Received: 23.10.2020
Accepted: 07.12.2020

Rezumat

Eficacitatea terlipresinei în modularea tensiunii venoase portale după rezecții hepatice la pacienți non-cirotici.
Bilanț sistematic și metaanaliză a unor teste clinice randomizate controlate

Context-Obiective: S-au raportat cazuri de efecte nefaste ale hipertensiunii venoase portale post-hepatectomie asupra parenchimului hepatic, de insuficiență hepatică post-hepatectomie şi de mortalitate sporită sub 90 de zile postoperator. Terlipresina este utilizată pe scară largă pentru atenuarea efectelor hipertensiunii portale. Studiile clinice randomizate (SCR) au demonstrat că rezultatele utilizării terlipresinei pentru modularea hipertensiunii venoase portale post-hepatectomie sunt încurajatoare. Obiectivul prezentului studiu este evaluarea eficacității modulării farmacologice a hipertensiunii venoase portale post-hepatectomie după hepatectomii majore.
Metode: S-a efectuat cercetare sistematică a literaturii de specialitate în baze de date electronice conform PRISMA. Metaanaliza s-a efectuat pe modele cu efecte stabilite şi aleatorii.
Rezultate: S-au selectat trei studii clinice controlate randomizate (SCR) comparative, cu administrare de terlipresină şi placebo, efectuate pe 284 dintr-un mix de 60 de studii, Pacienții din

cohorta tratată cu placebo erau semnificativ mai tineri, cu 5 ani, comparativ cu cei din cohorta tratată cu terlipresină. Totuşi, cohorta tratată cu terlipresină a prezentat spitalizare substanțial mai scurtă la terapie intensivă (ATI), comparativ cu cohorta tratată cu placebo.
Concluzii: Prima metaanaliză a demonstrat că pacienții din cohorta tratată cu terlipresină, deşi semnificativ mai în vârstă, cu 5 ani, au prezentat o durată substanțial mai scurtă a spitalizării la ATI, comparativ cu cohorta tratată cu placebo. În plus, deşi nesemnificativ statistic, doar 6% din pacienții tratați cu terlipresină au necesitat suport inotrop, comparativ cu 16,4% din cohorta tratată cu placebo.

Cuvinte cheie: tensiune venoasă portală, terlipresină, rezecție hepatică majoră, hepatectomie majoră, studii clinice controlate randomizate

Abstract
Background-Objectives: It has been reported, that high posthepatectomy portal vein pressure (PVP) has deleterious effect on the liver parenchyma and causes posthepatectomy liver failure (PHLF) and increased 90-day mortality. Terlipressin, is widely used to mitigate the effects of portal hyper-tension. Randomised clinical trials (RCTs) demonstrated encouraging results of use of terlipressin for modulation of increased posthepatectomy PVP. The aim of the present study was to evaluate the effectiveness of the pharmacological modulation of the increased post-hepatectomy PVP after major hepatectomy.
Methods: Systematic literature searches of electronic databases in accordance with PRISMA was conducted. Meta-analysis was conducted using both fixed- and random-effects models.
Results: Three randomised controlled trials (RCTs) comparing terlipressin versus placebo including 284 patients of pooled 60 studies were selected. Placebo cohort patients were significantly younger by 5 years compared to terlipressin cohort. However, the terlipressin cohort demonstrated significantly shorter intensive care unit (ICU) stay compared to placebo cohort.
Conclusions: The first meta-analysis demonstrated that terlipressin cohort patients although significantly older by 5 years had significantly shorter ICU stay compared to placebo cohort. Furthermore, though statistically nonsignificant only 6% of terlipressin patients needed inotropic support compared to 16.4% of placebo cohort.

Key words: portal vein pressure, terlipressin, major liver resection, major hepatectomy, randomised controlled trials

Introduction

The deleterious effect of the acute portal hypertension first identified in the "small for size syndrome" after living donor liver transplantation (LDLT) (1). It is reported that maintaining PVP < 15 mmHg is a crucial factor for successful LDLT using small grafts (2). Ligation of splenic artery and portocaval shunt were successfully used to reduce the portal venous pressure after small for size LDLT syndrome (3,4).

Furthermore, it has been reported that increased PVP might be contributed crucially in the development of ascites and PHLF after major hepatectomy. High intravascular shear stress associated with acute portal hyperperfusion together with compensatory decrease in hepatic arterial flow (hepatic arterial buffer response) were considered contributors of the above complications after major hepatic resections (5,6).

In 2013, first Allard et al reported that posthepatectomy PVP can be used as an

independent predictive factor for PHLF and 90-day mortality after major hepatectomy and recommended intraoperative modulation if the PVP is greater than 20 mmHg (7). Recently, three RCTs investigated the effectiveness of terlipressin for the management of increased PVP after major hepatic resections (8-10).

The aim of the present study was to investigate the evolution of evidence over time in studies investigating the role of terlipressin for management of increased PVP after major hepatic resections.

Methods and Materials

This systematic review was conducted following the guidelines set out in the Preferred Reporting in Systematic Review & Meta-Analysis (PRISMA) checklist (11).

Literature Search

A systematic literature search of articles published from inception until March 2020 performed in Embase, MEDLINE (PubMed), Cochrane library, and Google Scholar databases using free text and MeSH terms (portal venous pressure, posthepatectomy liver failure, 90-day mortality, portal venous flow, terlipressin, placebo). A grey literature search on www.clinicaltrials.gov was also performed. References cited in the retrieved articles were manually checked for further analysis. Disagreements between authors were resolved through discussion.

Study, Selection, and Inclusion and Exclusion Criteria

RCTs comparing terlipressin versus placebo after liver resections were included in this study. Abstracts, case reports, cases series and editorials without original data were excluded.

Definitions

Major hepatectomy was defined any removal of at least three segments (12). Posthepatectomy liver failure was defined according (a) the International study group of liver surgery (ISGLS-18) (13), (b) the criteria peak of serum bilirubin greater than 120 μmol/L (14), (c) the "50-50 criteria" on postoperative day 5 (15), (d) Liver cancer Study group of Japan (LCSGJ) (16).

Statistical Analysis

Cochrane's criteria were used to assess the methodological quality of all included RCTs. Two authors PG and RS stratified the risk of bias as low, unclear and high according to Cochrane criteria. Any discrepancies resolved by consensus (17).

The Review Manager 5.3 software (Cochrane Collaboration, Oxford, England) was used to conduct the statistical analysis. Heterogeneity was assessed using the I^2 test, and cut-off values of 25%, 50%, and 75% were considered of low, moderate, and high heterogeneity, respectively (18). In cases of I^2 value less than 25% fixed-effects models were used.

The odds ratios (ORs) with 95% confidence intervals were used to analyse dichotomous variables. For the outcomes considered, the reference categories were selected such that OR<1 favoured Terlipressin cohort.

Continuous variables were combined based on the mean difference (MD) and the standardised MD. The studies were then combined using the Mantel-Haenszel. For studies that did not report the means and variances of the 2 groups, these values were estimated from the median, range, and the size of sample, using the technique described by Hozo et al. where possible (19).

In all analyses, the point estimate was considered significant at $p<0.05$.

Sensitivity Analysis

In order to assess the impact of heterogeneity on the robustness of the conclusions the results of both secondary and primary outcomes were calculated using the random-effects and fixed-effect models.

Results

Search Strategy and Included Study Characteristics

Three studies from a pool of 60 studies including 142 in terlipressin cohort and 142 patients in placebo cohort were selected 8-10, (*Fig. 1, Table 1*). Terlipressin cohort included 29% cirrhotic patients of Child-Pugh A&B and placebo cohort 22% Child-Pugh A&B patients, respectively [OR=1.45(0.80, 2.64), p=0.22, I^2=6%], (*Table 2*).

Statistically Significant Results of the Meta-Analysis

Age

There was evidence that significantly younger patients by five years were included in the placebo cohort compared to terlipressin cohort (Mean difference (MD)= 4.84 (3.70, 5.94), p<001, I^2=0%), (*Table 2*).

Intraoperative Mean Arterial Pressure (MAP)

Intraoperative MAP was significantly lower in placebo cohort compared to terlipressin cohort (MD=4.51(1.72, 7.30), p=0.002, I^2=0%).

ICU Stay

Terlipressin cohort demonstrated significantly shorter ICU stay compared to placebo cohort [MD=-0.77 (-1.34, -0.19), p=0.009, I^2=60%] (*Table 2, Fig. 2*).

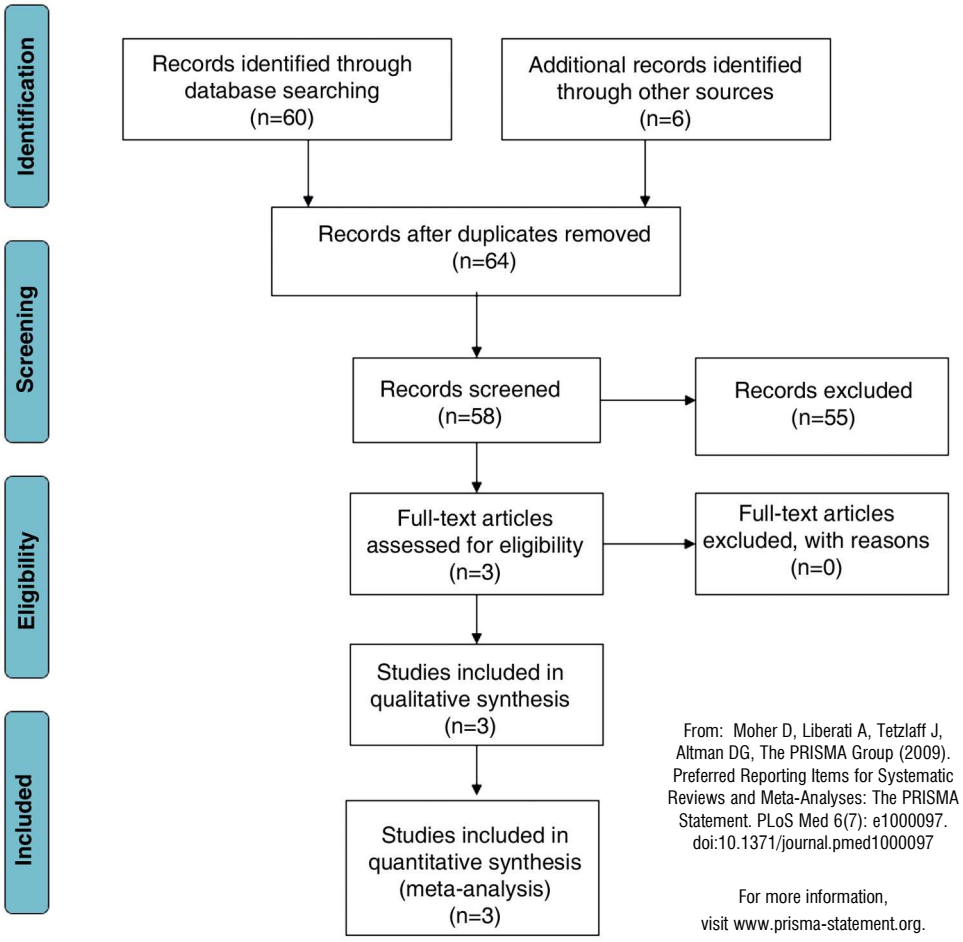

Figure 1. Diagram of the search strategy - PRISMA 2009 Flow Diagram

Table 1. Study characteristics of included RCTs

Author, country, year	Number of patients Tp vs Pl	Age Tp vs Pl	Gender male	Cirrhotic patients Tp vs Pl N(%)	Indications N (%)	Surgical intervention N (%)
Abbas, Egypt, 2018	42-42	55.86±9.5 51.59±12.7	30-25	19-12 Child A&B	NR	All Major resections
Mahdy, Egypt, 2019	25-25	58.7±5.9 55.5±8.4	10-12	NR	NR	R Hep/my: 6-5 L Hep/my: 7-9 Whipple's op: 12-11
Kohler, Switzerland, 2019	75-75	66±3.75 61±3.75	55-55	15-14 Child A&B	HCC:18-21 ICC:17-10 CRLM:21-21	All Major resections
Pooled estimates	142-142 284 total	MD=4.84 (3.70, 5.94) p<.001	OR=1.1 (0.67, 1.82) p=0.70	34(24) 26(18) p=0.22	NA	NA

HCC: hepatocellular carcinoma, CRLM: colorectal liver metastases, ICC: intrahepatic cholangiocarcinoma, R Hep/my: right hepatectomy, L Hep/my: left hepatectomy NR: nonreported, M: male, F: female, Tp: terlipressin, Pl: placebo, MD: mean difference, OR: odds ratio, NA: nonapplicable

Table 2. Outcome of interests

Outcome of Interest	Number of studies and patients (%;event/patients	Statistical method, estimated effect, 95% CI	p-value	I^2 (%)
Age	3,284	MD=4.84(3.70, 5.94)	<001	0
Male	3,284	OR=1.10(0.67, 1.82)	.70	0
Operative time	3,284	MD=0.09(-0.18, 0.36)	.51	17
Cirrhotic patients	2,234 (29;34/117) (22;26/117)	OR=1.45(0.80, 2.64)	.22	6
EBL	2, 234	MD=-114.63(-931, 702)	.78	91
HR Baseline	2, 134	MD=-2.31(-5.19, 0.57)	.12	0
HR intraoperative	2, 234	MD=-3.35(-8.13, 1.43)	.17	0
MAP Baseline	2, 234	MD=-2.79(-6.49, 0.92)	.14	0
MAP intraoperative	2, 234	MD=4.51(1.72, 7.30)	.002	0
CVP Baseline	2, 234	MD=0.60(-0.45, 1.65)	.26	0
CVP intraoperative	2, 234	MD=1.14(-0.02, 2.31)	.39	75
CI Baseline	2, 234	MD=-0.18(-0.52, 0.15)	.29	65
CI intraoperative	2, 234	MD=-0.03(-0.20, 0.14)	.78	66
SVV Baseline	2, 234	MD=-1.15(-2.30, 0.01)	.05	0
SVV intraoperative	2, 234	MD=0.05(-0.68, 0.78)	.89	0
TB Preop	2, 234	MD=-1.96(-4.91,1.00)	.19	0
TB POD 1	2, 234	MD=-2.52(-7.22, 2.19)	.72	19
ASAT Preop	2, 234	MD=-0.87(-5.64, 3.90)	.79	0
ASAT POD 1	2, 234	MD=6.53(-41.11, 54.19)	.60	0
ALAT Preop	2, 234	MD=2.21(-6.08, 10.50)	.69	0
INR Preop	2, 234	MD=-0.03(-0.07, 0.01)	.16	47
INR POD 1	2, 234	MD=-0.05(-1.34, -0.19)	.11	0
ICU stay	2, 234	MD=-0.77(-1.34, -0.19)	.009	60
Need of inotropic support	2, 134 (6;4/67) (16.4;11/67)	OR=0.32(0.10, 1.07)	.06	0

MD: mean difference, OR: odds ratio, CI: confidence intervals, EBL: estimated blood losses, HR: heart rate, MAP: mean arterial pressure, CVP: central venous pressure, CI: cardiac index, SVV: stroke volume variation, TB: total bilirubin, ASAT: aspartate aminotransferase, ALAT: alanine aminotransferase, ICU: intensive care unit, red highlighted significant results

Statistically Nonsignificant results of the Meta-Analysis

There was evidence that fewer patients in terlipressin cohort (6%; 4/67 patients) needed inotropic support compared to placebo cohort (16.4% 11/67), [OR=0.32(0.10, 1.07), p=0.06, I^2=0%]. Of note, the result was marginally statistically nonsignificant.

There was evidence of nonsignificant differences in gender, number of cirrhotic patients, operative time, estimated blood losses, heart rate, MAP, central venous pressure, cardiac index, stroke volume variation, systemic vascular resistance, liver function and clotting profile tests between the two cohorts (*Table 2*).

Risk of Bias of Included RCTs

The overall quality of RCTs was moderate. None of them blinded the outcome assessors. Therefore, detection bias might have influenced the results (*Table 3*).

Discussion

The results of the first conducted meta-analysis of RCTs comparing terlipressin versus placebo following major hepatectomy mainly in non-cirrhotic livers demonstrated that although significantly older patients by five years were included in the terlipressin cohort the ICU stay was significantly shorter compared to placebo. Further analysis demonstrated that terlipressin did not affect adversely the haemodynamics parameters such as MAP, CVP, CI, SVV (*Table 2*). In addition, the need for inotropic support was lower in terlipressin cohort without to reach significant levels compared to placebo cohort (*Table 2*).

Another point that need to be stressed although the difference was statistically non-significant more cirrhotic patients were included in the terlipressin cohort (29%; 34/ 117) compared to placebo cohort (22%; 26/ 117) 9,10. Therefore, more cirrhotic patients and significantly older total sample are suggestive of selection bias against the terlipressin cohort; however it is demonstrated significantly shorter ICU stay.

The risk of bias analysis of RCTs demonstrated low risk in the domains of sequence generation and allocation concealment. None of the included RCTs blinded the outcome assessors. Therefore, detection bias might have influenced the results (*Table 3*).

Limitations

Up to authors best knowledge this the first meta-analysis. However, the results of the present study should be interpreted in the context of its limitations. The total sample of

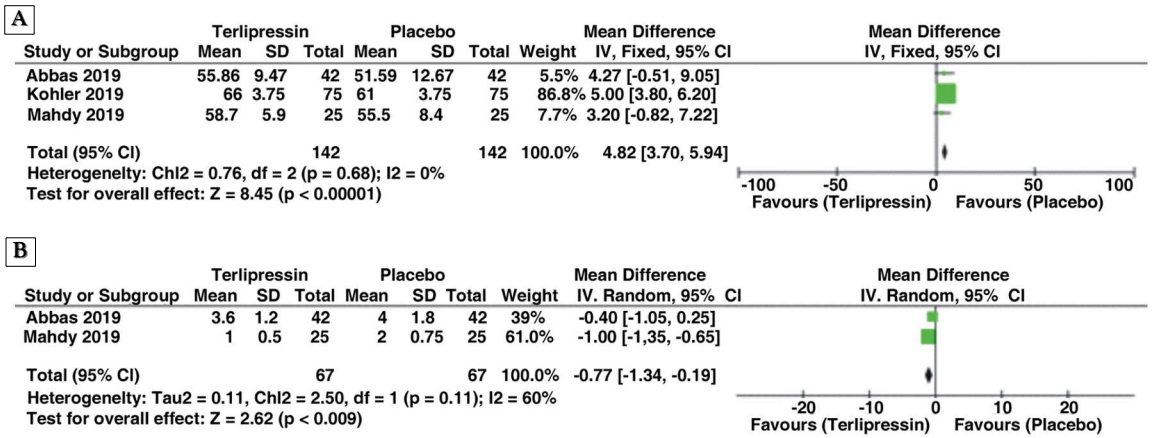

Figure 2. Forest plot depicting **(A)** Age, **(B)** ICU stay

Table 3. Risk of bias of RCTs

Author	Sequence generation	Allocation concealment	Incomplete Outcome data	Blinding of participants and personnel	Blinding of outcome assessors
Abbas	Low risk	Low risk	Low risk	Unclear risk	High risk
Kohler	Low risk	Low risk	Low risk	Unclear risk	High risk
Mahdy	Low risk	Low risk	Low risk	Unclear risk	High risk

the included RCTs were heterogenous and conducted in single centres. Therefore, national, institutional, selection and underpowered sample bias might have influenced the results.

Conclusions

Terlipressin demonstrated promising results by effectively modulated the increased PVP after major hepatic resections in non-cirrhotic patients. Although, significantly older patients by five years included in terlipressin cohort the ICU stay was significantly shorter compared to placebo cohort. Therefore, further investigation of terlipressin with multicentre RCT might shed further light on the topic.

Conflict of Interest

All named authors hereby declare that they have no conflict of interest to disclose.

Acknowledgements and Sources of Support:

None.

Ethical Approval

This study does not contain any studies with human participants or animals performed by any of the authors.

References

1. Clavien PA, Oberkofler CE, Raptis DA, Kuno Lehmann, Rickenbacher A, El-Badry AM. What is critical for liver surgery and partial liver transplantation: size or quality? Hepatology. 2010; 52(2):715-29.
2. Ogura Y, Hori T, El Moghazy WM, Yoshizawa A, Oike F, Mori A, Kaido T, et al. Portal pressure <15 mm Hg is a key for successful adult living donor liver transplantation utilizing smaller grafts than before. Liver Transpl. 2010;16(6):718-28.
3. Ito T, Kiuchi T, Yamamoto H, Oike F, Ogura Y, Fujimoto Y, Hirohashi K, et al. Changes in portal venous pressure in the early phase after living donor liver transplantation: pathogenesis and clinical implications. Transplantation. 2003; 75(8):1313-7.
4. Boillot O, Delafosse B, Mechet I, Boucaud C, Pouyet M. Small-for-size partial liver graft in an adult recipient: a new transplant technique. Lancet. 2002;359(9304):406-7.
5. Morsiani E, Aleotti A, Ricci D. Haemodynamic and ultrastructural observations on the rat liver after two-thirds partial hepatectomy. J Anat. 1998;192(Pt 4):507-15.
6. Eipel C, Abshagen K, Vollmar B. Regulation of hepatic blood flow: the hepatic arterial buffer response revisited. World J Gastroenterol. 2010;16(48):6046-57.
7. Allard MA, Adam R, Bucur PO, Termos S, Cunha SA, Bismuth H, et al. Posthepatectomy portal vein pressure predicts liver failure and mortality after liver resection on noncirrhotic liver. Ann Surg. 2013; 258(5):822-9; discussion 829-30.
8. Mahdy MM, Abbas MS, Kamel EZ, Mostafa MF, Herdan R, Hassan SA, et al. Effects of terlipressin during hepatobiliary surgery on systemic and splanchnic haemodynamics, renal function and blood loss: a double blind randomized clinical trial. BMC Anesthesiol. 2019;19(1):106.
9. Abbas MS, Mohamed KS, Ibraheim OA, Taha AM, Ibraheem TM, Fabel BA, et al. Effects of terlipressin infusion on blood loss and transfusion needs during liver resection: A randomised trial. Acta Anaesthesiol Scand. 2019;63(1):34-39. Epub 2018 Aug 5.
10. Kohler A, Perrodin S, De Gottardi A, Candinas D, Beldi G. Effectiveness of terlipressin for prevention of complications after major liver resection-A randomized placebo-controlled trial. HPB (Oxford). 2020;22(6):884-891. Epub 2019 Oct 31.
11. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7): e1000097.
12. Strasberg SM. Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. J Hepatobiliary Pancreat Surg. 2005;12(5):351-5.
13. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, et al. Posthepatectomy liver failure: a definition and grading by the international study group of liver surgery (ISGLS). Surgery. 2011;149(5):713-24.
14. Mullen JT, Ribero D, Reddy SK, Donadon M, Zorzi D, Gautam S, Abdalla EK, et al. Hepatic insufficiency and mortality in 1,059 non-cirrhotic patients undergoing major hepatectomy. J Am Coll Surg. 2007;204(5):854-62; discussion 862-4.
15. Balzan S, Belghiti J, Farges O, Ogata S, Sauvanet A, Delefosse D, et al. The "50-50 criteria" on postoperative day 5. An accurate predictor of liver failure and death after hepatectomy. Ann Surg.

2005;242(6):824-8, discussion 828-9.
16. Kudo M, Kitano M, Sakurai T, Nishida N. General rules for the clinical and pathological study of primary liver cancer nationwide follow-up survey and clinical practice guidelines: The outstanding achievements of the liver cancer study group of Japan. Dig Dis. 2015;33(6):765-70.
17. Higgins JPT, Greens S. (editors) Cochrane handbook for systematic reviews of interventions version 5.1 (update July 2019). The Cochrane Collaboration 2011. www.cochrane.handbook.org
18. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.
19. Hozo SP, Diulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5:13.