

Retrospective Cohort Study

Risk factors for acute kidney injury after partial hepatectomy

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Abstract**AIM**

To identify risk factors for the occurrence of acute kidney injury (AKI) in the postoperative period of partial hepatectomies.

METHODS

Retrospective analysis of 446 consecutive resections in 405 patients, analyzing clinical characteristics, pre-operative laboratory data, intraoperative data, and postoperative laboratory data and clinical evolution. Adopting the International Club of Ascites criteria for the definition of AKI, potential predictors of AKI by logistic regression were identified.

RESULTS

Of the total 446 partial liver resections, postoperative AKI occurred in 80 cases (17.9%). Identified predictors of AKI were: Non-dialytic chronic kidney injury (CKI), biliary obstruction, the Model for End-Stage Liver Disease (MELD) score, the extent of hepatic resection, the occurrence of intraoperative hemodynamic instability, post-hepatectomy haemorrhage, and postoperative sepsis.

CONCLUSION

The MELD score, the presence of non-dialytic CKI

and biliary obstruction in the preoperative period, and perioperative hemodynamics instability, bleeding, and sepsis are risk factors for the occurrence of AKI in patients that underwent partial hepatectomy.

Key words: Kidney injury; Hepatectomy; Postoperative; Liver; Resection

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Core tip: Acute kidney injury (AKI) is a serious complication after partial hepatectomy. This research aims to identify risk factors for the occurrence of AKI in the postoperative period of partial hepatectomies. The Model for End-Stage Liver Disease score, the presence of non-dialytic chronic kidney injury and biliary obstruction in the preoperative period, and perioperative hemodynamics instability, bleeding, and sepsis are risk factors for the occurrence of AKI in patients that underwent partial hepatectomy.

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INTRODUCTION

Despite of the limited data regarding the occurrence of acute kidney injury (AKI) after partial hepatectomy, the reported incidence ranges from 0.9% to 15.1%^[1-4]. A comprehensive analysis of the scarce data^[5] is also hampered by the lack of consensus in the exact definition of AKI after liver resection.

Candidates for liver resections often present with multiple potential risk factors regarding postoperative AKI, such as excessive bleeding during the hepatectomy, and the occurrence of post-hepatectomy liver failure (PLF)^[2,3,5-7]. Eventually, patients can have a combination of insults, that can be aggravated by distributive circulatory derangements by sepsis^[2,3,5-8] or exposure to nephrotoxic drugs^[9].

The hemodynamic changes in patients after major liver resections, mainly in patients with underlying chronic liver injury, may simulate those of patients with acute liver failure or cirrhosis^[10]. Thus, the current criteria suggested by the International Club of Ascites (ICA) for definition of AKI would be the most appropriate criteria for these patients^[11], since urine output measurement and static serum creatinine (sCr) levels are not included in ICA criteria.

Assuming post-operative AKI as primary endpoint, the aim of the present report was to identify the risk factors for the occurrence of this serious complication after partial hepatectomies.

MATERIALS AND METHODS

This report is based on a historical cohort study of patients

who underwent partial hepatectomy from January 2008 to July 2016 at the Hepatobiliary Surgery Department of Cancer Hospital-UOPECCAN. Patients with evidence of dialytic chronic renal dialysis at the time of surgery, the need of emergency hepatectomy or patients who died at the intraoperative or immediate postoperative period (within the first 24 h after the procedure) were excluded. The study was approved by the Research Ethics Board at West Parana University (No. 1.665.135; July 2016), and the need for informed written consent was waived. The study was conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Preoperative data

The data collected included: Patient demographic data, preoperative use of nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme and inhibitors, the presence of comorbidities including: Non-dialytic chronic kidney disease (CKI), defined as estimated glomerular filtration rate (eGFR) less than 60 mL/min per 1.73 m²^[12], liver cirrhosis with Model End- Liver Disease (MELD) score calculation^[13], biliary obstruction and prior exposure to chemotherapy.

Preoperative baseline laboratory tests values were obtained from the patient electronic charts in the previous 3 mo, and in patients with more than one value, the value closest to the hospital admission date were selected. Laboratory tests included: Serum dosages of urea, creatinine, sodium, potassium, bilirubin, and albumin, International Normalized Ratio value, serum platelet count and eGFR value calculation according to the formula^[14]:

$$eGFR: \text{mL/min per } 1.73 \text{ m}^2 = k \times 186 \times (sCr)^{-1.15} \times (\text{age})^{-0.203},$$

$$K = 1 \text{ (if male) or } 0.72 \text{ (if female)}$$

Intraoperative and surgical data

The surgical and anesthetic covariates recorded were: Open or laparoscopic resection, extent of liver resection (major hepatectomy was defined as resection of at least three Couinaud liver segments), resection modalities according to Brisbane nomenclature^[15], type of vascular clamping of the liver (intermittent Pringle maneuver^[16], continuous Pringle maneuver^[17] or total vascular exclusion^[18]), segment I resection, two-stage resection^[19], associated extrahepatic resection, complex vascular reconstruction (portal vein, hepatic artery or hepatic veins, with or without prothesis), regional lymphadenectomy (hepatic pedicle lymph nodes^[20]), intraoperative transfusions of red blood cells, and intraoperative hemodynamic instability, defined as a sustained systolic blood pressure less than 90 mmHg or more than 40 mmHg below the patient's usual systolic blood pressure during 30 min.

Postoperative data and complications

Similarly to the preoperative laboratory blood tests, we retrieved its values in the postoperative period, including the most altered values in the first 30 postoperative days.

Postoperative complications the first 30 postoperative

Table 1 Postoperative overall complications and acute kidney injury staging according to International Club of Ascites^[11], risk, injury, failure, loss, end-stage^[27] and Acute Kidney Injury Network^[28] criteria (n = 446) n (%)

Overall complications	113 (25.3)
Overall complications (Clavien-Dindo classification)	
I	46 (10.3)
II	25 (5.6)
III a/b	18 (4.0)
IV a/b	7 (1.6)
V (death)	17 (3.8)
AKI (ICA)	80 (17.9)
I	26 (5.8)
II	21 (4.7)
III	33 (7.4)
AKI (RIFLE)	70 (15.7)
Risk	16 (3.6)
Injury	21 (4.7)
Failure	33 (7.4)
AKI (AKIN)	80 (17.9)
I	26 (5.8)
II	21 (4.7)
III	32 (7.2)
HRS	11 (2.5)
RRT (hemodialyses)	9 (2.0)

AKI: Acute kidney injury; ICA: International Club of Ascites; RIFLE: Risk, injury, failure, loss, end-stage; AKIN: Acute Kidney Injury Network; HRS: Hepatorenal syndrome; RRT: Renal replacement therapy.

days recorded were: Post-hepatectomy haemorrhage (PHH)^[21], post-hepatectomy liver failure (PHLF)^[22], biliary fistula^[23], postoperative ascites, wound infection^[24], pulmonary complications, including pulmonary infection^[25], acute respiratory distress syndrome and acute lung injury^[26], cardiovascular complications, including coronary insufficiency, cardiac arrhythmias, peripheral thrombosis, thromboembolism, and stroke^[5].

The occurrence and staging of AKI were defined according to the ICA^[11] criteria, although the RIFLE^[27] and AKIN^[28] criteria were used for comparative purposes (Table 1). The use of aminoglycosides, renal replacement therapy (hemodialysis), the occurrence of hepatorenal syndrome (HRS)^[11] and hospitalization time in days were recorded. The overall complications were classified according to Clavien-Dindo classification for postoperative complications^[29].

Statistical analysis

To ensure the stability of our multivariate model, the sample size of the study was determined based on the results of a historical cohort not published in our Hepatobiliary Surgery Department, with an incidence of ARF after partial hepatectomies fixed at 18%, ensuring the adequate number of events per variable^[30]. Categorical variables were expressed in absolute numbers and percentages were compared by the χ^2 test or Fisher's exact test when indicated. Continuous variables were expressed as absolute and mean \pm SD, and the comparison by the Student's *t*-test or non-parametric Mann-Whitney test after checking the normality assumptions by the Shapiro-

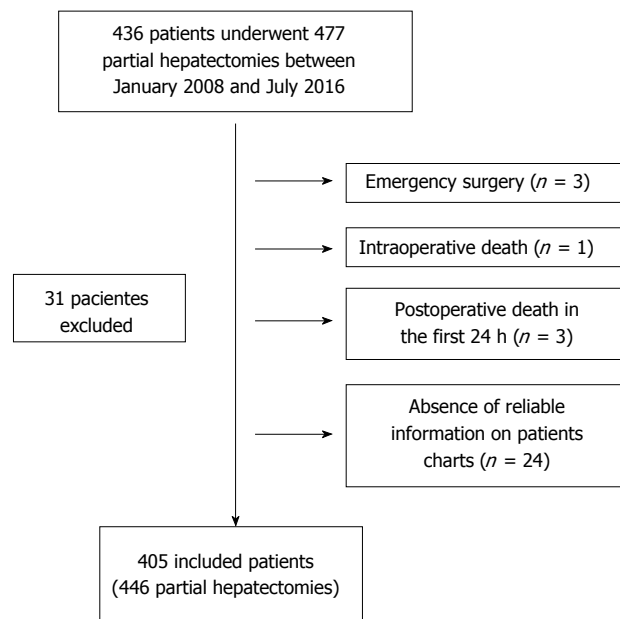


Figure 1 Flow chart outlining the included and excluded patients in the study.

Wilk test. The variables selected in the univariate model ($P < 0.05$) were tested in the multiple logistic regression model to identify independent binary predictors on the occurrence of postoperative AKI. The results of the model were expressed by means of the odds ratio, together with the corresponding 95% CIs and the *p* values of the Wald test. A value of $P < 0.05$ (two-tailed) was considered significant. Statistical calculations were made with the software GPower 3.0.10 and SPSS 16.0 package for Windows.

RESULTS

During the period from January 2008 to July 2016, 436 patients underwent liver resection surgery, of which 31 patients were excluded, with 405 included patients in the study for the final analysis (Figure 1).

Of the total of included patients, 271 underwent minor partial hepatectomies (60.7%) and 175 patients (39.3%) underwent major resections, and the most common resection modalities according to Brisbane nomenclature^[14] were bisegmentectomy in 105 patients, segmentectomy in 103 patients, right hepatectomy in 85 patients, non-anatomical resections in 63 patients and left hepatectomy in 45 patients. The segment I were resected in 31 patients.

The most common indications for partial hepatectomy in patients with malignant tumors were colorectal cancer metastases 183 patients (41%) and hepatocellular carcinoma in 75 patients (16.8%), and patients with benign tumors were hepatic adenoma in 35 patients (7.8%) and hepatic hemangioma in 15 patients (3.4%).

Table 2 shows the clinical data of the patients prior the 466 partial hepatectomies according to the occurrence of AKI. It is observed that in the AKI group the prevalence

Table 2 Preoperative patient characteristics according to the occurrence of postoperative acute kidney injury in 466 partial hepatectomies *n* (%)

	No AKI (<i>n</i> = 366)	AKI (<i>n</i> = 80)	<i>P</i>
Gender, male	180 (49.2)	43 (53.8)	0.269
Age (years), mean (SD)	54.6 (16.57)	57.4 (16.10)	0.842
ACE inhibitors	19 (5.2)	10 (12.5)	0.210
NSAIDs	26 (7.1)	10 (12.5)	0.082
Non-dialytic CKI	1 (0.27)	8 (10.0)	< 0.001
Diabetes mellitus	44 (12.0)	14 (17.5)	0.121
Systemic arterial hypertension	70 (19.1)	15 (18.8)	0.467
Preoperative chemotherapy	85 (23.2)	24 (30.0)	0.402
Cirrhosis	23 (6.3)	10 (12.5)	0.042
MELD score, mean (SD)	7.67 (1.15)	8.05 (1.05)	0.020
Biliary obstruction	6 (1.6)	13 (16.2)	< 0.001
Baseline laboratory tests			
Serum urea (mg/dL), mean ± SD	31.45 ± 10.71	35.63 ± 23.77	0.021
Serum creatinine (mg/dL), mean ± SD	0.90 ± 0.71	0.98 ± 0.62	0.229
eGFR (mL/min per square meter), mean ± SD	98.38 ± 51.32	89.86 ± 35.46	0.944
Sodium (mEq/L), mean ± SD	135.67 ± 3.25	134.25 ± 3.00	0.350
Potassium (mEq/L), mean ± SD	4.44 ± 0.63	4.34 ± 0.75	0.697
INR, mean ± SD	1.13 ± 0.45	1.14 ± 0.20	0.912
Bilirubin (mg/dL), mean ± SD	1.63 ± 3.05	2.84 ± 3.95	0.002
Albumin (g/dL), mean ± SD	3.61 ± 0.87	3.41 ± 0.92	0.505
Platelets (mm ³), mean ± SD	211869.55 ± 103744.67	215522.81 ± 115186.57	0.129

AKI: Acute kidney injury; ACE: Angiotensin conversion enzyme; NSAIDs: Non-steroidal anti-inflammatory drugs; CKI: Chronic kidney injury; MELD: Model for End-Stage Liver Disease; INR: International normalized ratio.

Table 3 Intraoperative characteristics of the 446 liver resections according to the occurrence of postoperative acute kidney injury *n* (%)

	No AKI (<i>n</i> = 366)	AKI (<i>n</i> = 80)	<i>P</i>
Surgical approach			0.071
Open	343 (93.7)	79 (98.8)	
Laparoscopic	23 (6.3)	1 (1.2)	
Extent of resection			0.002
Major resection	128 (35.2)	45 (56.2)	
Minor resection	238 (64.8)	35 (43.8)	
Tumoral histology			0.134
Benign	70 (19.1)	6 (7.5)	
Malignant	296 (80.9)	74 (92.5)	
Segment I resection	23 (6.3)	8 (10.0)	0.098
Two-stage hepatectomy	26 (7.1)	6 (7.5)	0.439
Intermittent Pringle maneuver (15' \ 5')	124 (33.9)	31 (38.8)	0.438
Continuous Pringle maneuver	26 (7.1)	10 (12.5)	0.254
Total vascular exclusion	6 (1.6)	2 (2.5)	0.212
Complex vascular reconstruction	6 (1.6)	1 (1.2)	0.634
Regional lymphadenectomy	86 (23.5)	25 (31.2)	0.155
Associated extrahepatic resection	27 (7.4)	10 (12.5)	0.103
Intraoperative instability	26 (7.1)	25 (31.2)	< 0.001
Red blood cell transfusion	31 (8.5)	23 (28.8)	< 0.001

AKI: Acute kidney injury.

of non-dialytic CKI and cirrhosis were higher, as well as higher MELD scores and biliary obstruction prior to partial hepatectomy. Regarding preoperative laboratory tests, the AKI group had higher bilirubin levels than non-AKI group, 2.84 ± 3.95 mg/dL vs 1.63 ± 3.05 mg/dL, respectively.

Overall and renal postoperative complications rates are shown in Table 1. A total of 113 patients (25.3%) presented some type of complication, and according to

the Dindo-Clavien scale, the complications grade I were the most common, occurring in 46 patients (10.3%). According to ICA criteria, AKI occurred in 80 patients (17.9%), as well as by the AKIN criteria. A slight difference in the incidence of AKI was observed according to RIFLE criteria (15.7%).

Regarding surgical and intraoperative information, patients with AKI underwent more extensive surgical procedures (major hepatectomies), and especially, had significantly higher rates of hemodynamic instability and red blood cell transfusion during liver resections than non-AKI patients, 31.2% vs 7.1% and 28.8% vs 8.5%, respectively, with $P < 0.001$ for both variables (Table 3).

According to the postoperative laboratory tests (Table 4), patients with AKI had significantly higher levels of urea and creatinine after surgery, with a significant lower eGFR, 53.73 ± 34.38 mL/min per square meter vs 83.24 ± 60.04 mL/min per square meter ($P < 0.001$).

In the postoperative evolution, patients with AKI had higher rates of IHPH (25%), PHH (11.2%), sepsis (16.2%) and longer hospital stay (12.20 ± 9.41 d) (Table 4). According to the univariate model (Table 5), six covariates were statistically more frequent in the AKI group and the six were confirmed in the multiple logistic regression model as predictors: MELD score, the presence of biliary obstruction and non-dialytic CKI in the preoperative period, intraoperative hemodynamic instability, and finally PHH and sepsis in the postoperative period.

DISCUSSION

This study aimed to identify the main risk factors for AKI in the postoperative period of partial hepatectomies.

Table 4 Postoperative laboratory tests values and complications after 466 partial hepatectomies according to the occurrence of postoperative acute kidney injury *n* (%)

	No AKI (<i>n</i> = 366)	AKI (<i>n</i> = 80)	<i>P</i>
Laboratory tests			
Serum urea (mg/dL), mean ± SD	47.61 ± 49.36	82.19 ± 77.45	< 0.001
Serum creatinine (mg/dL), mean ± SD	1.29 ± 1.16	2.29 ± 2.21	< 0.001
eGFR (ml/min/m ²), mean ± SD	83.24 ± 60.04	53.73 ± 34.38	< 0.001
Sodium (mEq/L), mean ± SD	132.88 ± 4.27	132.29 ± 5.55	0.385
Potassium (mEq/L), mean ± SD	4.86 ± 0.81	5.16 ± 0.94	0.013
INR, mean ± SD	1.82 ± 2.46	2.08 ± 1.161	0.438
Bilirubin (mg/dL), mean ± SD	3.46 ± 4.54	4.54 ± 6.84	0.001
Albumin (g/dL), mean ± SD	2.58 ± 0.62	2.36 ± 0.59	0.069
Platelets (mm ³), mean ± SD	144101.93 ± 120446.829	132906.89 ± 113193.18	0.518
Aminoglycosides	7 (1.9)	3 (3.8)	0.341
PHLF	7 (1.9)	21 (26.3)	< 0.001
A	4 (1.1)	3 (3.8)	
B	3 (0.8)	10 (12.5)	
C	0 (0)	8 (10.0)	
PHH	1 (0.3)	9 (11.3)	< 0.001
A	0 (0)	2 (2.5)	
B	0 (0)	4 (5.0)	
C	1 (0.3)	3 (3.8)	
Biliary fistula	25 (6.8)	10 (12.5)	0.086
A	15 (4.1)	6 (7.5)	
B	7 (1.9)	3 (3.8)	
C	3 (0.8)	1 (1.2)	
Postoperative ascites	58 (15.9)	23 (28.8)	0.059
Wound infection	13 (3.6)	7 (8.8)	0.062
Pulmonary complications	15 (4.1)	6 (7.5)	0.177
Cardiovascular complications	7 (1.9)	2 (2.5)	0.501
Sepsis	2 (0.5)	13 (16.2)	< 0.001
Hospital stay (d), mean ± SD	6.68 ± 3.65	12.20 ± 9.41	0.008

AKI: Acute kidney injury; eGFR: Estimated glomerular filtration rate; PHLF: Post-hepatectomy liver failure; PHH: Post-hepatectomy haemorrhage.

Table 5 Univariate and logistic regression analyses of risk factors for acute kidney injury

Univariate analyses	Multiple logistic regression				
	<i>P</i>	OR	95%CI	<i>P</i>	
Extent of resection	0.002	2.249	1.217	4.156	0.010
Biliary obstruction	< 0.001	10.240	3.094	33.891	< 0.001
Hemodynamics instability	< 0.001	5.244	1.337	20.568	0.017
Red blood cell transfusion	< 0.001				0.244
Cirrhosis	0.042				0.241
MELD score	0.020	4.342	1.347	15.654	0.046
Sepsis	< 0.001	11.609	3.185	39.911	< 0.001
Posthepatectomy haemorrhage	< 0.001	12.652	7.769	53.612	< 0.001
CKI	< 0.001	8.975	1.533	44.675	0.022

AKI: Acute kidney injury; OR: Odds ratio; MELD: Model for End-Stage Liver Disease; CKI: Chronic kidney injury.

There is a certain disparity of the available criteria for postoperative AKI definition in these situations, thus, we adopted the current criteria suggested by the ICA^[11] for definition of AKI in cirrhotic patients. In patients eligible for partial hepatectomy with underlying liver diseases or who underwent major liver resections, often the both, the ICA criteria^[11] do not include unreal measurements for these patients, such as static sCr measurements and urine output.

The incidence of AKI in the present study according to ICA and AKIN criteria was 17.9%, and according to RIFLE criteria was 15.7%. These AKI incidence were higher than other publications on the subject^[1-5]. The

AKIN and RIFLE criteria were applied for comparison, and this slight underestimation of AKI by RIFLE criteria can be probably explained by the fact that the ICA and AKIN criteria consider as stage I AKI a small increase of 0.3 mg/dL in sCr.

Including AKI, the overall complication rate in this study was 25.3%, and the mortality rate was 3.8%, that is comparable to the results of two large retrospective studies evaluating morbidity and mortality of partial hepatectomies^[31,32].

The present study did not neglect the analysis of the two main AKI risk factors after partial hepatectomies, which would be perioperative bleeding and PHLF^[6]. Peri-

operative haemorrhage with renal hypoperfusion^[6], with or without the deleterious effects of blood transfusion^[3], was a strong predictor of postoperative AKI in this study, reflected by intraoperative hemodynamic instability and posthepatectomy haemorrhage. An increased renal susceptibility to the perioperative renal ischemia^[22-25], such as in CKI, was a predictor in the authors' series.

Additionally, it is expected that major resections may have larger blood losses during operation and higher incidence of PHLF as well, it was corroborated by the significant influence of major resections on AKI occurrence, according to our logistic regression model. In a recent report of a large series of liver resections for hepatocellular carcinoma, major liver resection was a predictor for postoperative AKI^[4].

For prevention of intraoperative bleeding, there are intraoperative maneuvers that may be crucial, such as vascular control of the liver^[2] and LCVP anesthesia^[1,33,34], preventing the back bleeding from hepatic veins. The Pringle maneuver (intermittent^[16] or continuous^[17]) is routinely applied in liver resections at the authors' Department, thus there was no difference between the groups, and LCVP anesthesia parameters were not evaluated.

Second factor relates to the occurrence of PLF with its distributive circulatory changes, which is a major cause of death after hepatic resection, and eventually can progress to HRS^[11]. Similar to the results from a previous report^[4], the MELD score^[13], a usefully and extensively validated tool for predicting liver failure progression, was a predictor of postoperative AKI, and the most important, it can be applied in the preoperative period.

The presence of biliary obstruction was an independent predictor of postoperative AKI according to the authors' results, and the mechanism by which bilirubin may be toxic to the kidneys seems to be inflammatory as well as obstructive^[35], and hemodynamic changes may also play a role in biliary cast nephropathy^[36]. In addition to the aforementioned effects, patients who are candidates for surgery in the presence of biliary obstruction with congestive cholestasis in the liver^[37,38] may undergo major hepatic resections, with consequent decrease in the volume of a functionally deficient liver parenchyma, predisposing for PHLF.

Eventually, patients can have combinations of renal insults that can be aggravated by sepsis^[2,3,5,6], which was an independent predictor in the authors' analysis. The septicemia and its hemodynamic and systemic repercussions may eventually coexist with liver failure, often being the final event of PHLF^[5].

The shortcomings of the current study, besides its retrospective nature, were the non-inclusion of anesthetic maneuvers among covariates, such as LCVP anesthesia, and the non-inclusion of hepatic steatosis, since it is a determinant of the functional quality of the parenchyma^[39,40]. As mentioned, the retrospective nature of the study did not allow the authors to include non-standardized non-reliable data.

In order to reduce the incidence of postoperative AKI after partial hepatectomy, a careful patient selection and preoperative resection planning are mandatory, specially

in the case of predisposing CKI, biliary obstruction and underlying cirrhosis, in which MELD score calculation can be extremely worthwhile^[41-43]. Measures for preventing sustained intraoperative hypotension and postoperative bleeding must be undertaken, as well as prevention and prompt treatment of sepsis. In the case of high risk patients for postoperative AKI, the nephrologist must be promptly involved in multidisciplinary discussions.

COMMENTS

Background

Acute kidney injury (AKI) is a serious complication after partial hepatectomy, however, there are limited published data regarding this subject, in addition, there is no consensus about the definition of AKI in these patients.

Research frontiers

The present study did not neglect the analysis of the two main AKI risk factors after partial hepatectomies, which would be perioperative bleeding, with or without the deleterious effects of blood transfusion, and post-hepatectomy liver failure.

Innovations and breakthroughs

The hemodynamic changes in patients after major liver resections may simulate those of patients with acute liver failure or cirrhosis. Thus, the current criteria suggested by the International Club of Ascites (ICA) for definition of AKI would be the most appropriate criteria for these patients.

Applications

In order to reduce the incidence of postoperative AKI after partial hepatectomy, a careful patient selection and preoperative resection planning are mandatory, specially in the case of predisposing CKI, biliary obstruction and underlying cirrhosis, in which Model for End-Stage Liver Disease score calculation can be extremely worthwhile.

Terminology

Candidates for liver resections often present with multiple potential risk factors regarding postoperative AKI, such as excessive bleeding during the hepatectomy, and the occurrence of post-hepatectomy liver failure (PLF). The current criteria suggested by the ICA for definition of AKI would be the most appropriate criteria for these patients. For prevention of intraoperative bleeding, there are intraoperative maneuvers that may be crucial, such as vascular control of the liver and low central venous pressure anesthesia. Second factor relates to the occurrence of PLF with its distributive circulatory changes, that eventually can progress to hepatorenal syndrome.

Peer-review

This paper was retrospectively analyzed the clinical data, and found some risk factors of acute kidney injury. The material was rich, the result was reasonable, and the discussion did have some valuable information.

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