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ORIGINAL ARTICLE

Metabolic Disorders, Non-Alcoholic Fatty Liver Disease and Major Liver Resection: An Underestimated Perioperative Risk

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Abstract
Introduction Despite increasing evidence of an association of metabolic syndrome and liver degeneration, little is known about the results of major hepatic resection in patients with metabolic disorders. Following the observation of some unexplained perioperative deaths following uncomplicated right hepatectomy in patients presenting metabolic disorders, we analyzed the perioperative mortality in such population.
Material and Methods A retrospective analysis of immediate outcome was performed of patients undergoing right hepatectomy and affected by two or more metabolic disorders (diabetes mellitus, hypertension, dyslipidemia, obesity/overweight) without any other known cause of liver disease from January 2001 to May 2010.
Results Among 151 patients undergoing right hepatectomy, 30 patients presented two or more metabolic disorders. Perioperative mortality in this group reached 30 % (nine patients). In patients presenting MS (≥3 disorders), mortality reached 54 %. Univariate analysis identified four criteria associated with poor prognosis: MS, perioperative bleeding ≥1,000 mL, middle hepatic vein resection and primary hepatic malignancy. At multivariate analysis, middle hepatic vein resection and underlying primary hepatic malignancy resulted as being related to mortality.
Conclusions Patients presenting with multiple metabolic disorders should be carefully evaluated before major liver resection, especially when the procedure is planned for hepatocellular carcinoma and when a middle hepatic vein resection is required.

Key Words Liver resection · NAFLD · Metabolic syndrome · Middle hepatic vein

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Introduction

The metabolic syndrome (MS) is defined as the association of at least three metabolic disorders among central obesity/increased waist circumference, dyslipidemia (including hypertriglyceridemia or decreased high-density lipoprotein cholesterolemia), arterial hypertension, and diabetes mellitus.[1–3] With rising incidence in Western countries [4], this syndrome is also known to be related with a reduced life-expectancy [5] and non-alcoholic fatty liver disease (NAFLD).[6–11] Currently, NAFLD includes a spectrum of histological liver alterations ranging from steatosis to NASH [12] and end-stage cirrhosis [6, 12] without any other documented etiology, and might predispose to the development of primary liver cancer, with [13] or without [14] fibrosis. NAFLD may also rise in patients presenting with individual components of the MS including diabetes mellitus (DM) [15, 16], hypertriglyceridemia [17], and obesity.[7, 18, 19]

As NAFLD is a histopathological diagnosis [20], accuracy of liver biopsy seems inadequate to assure a preoperative diagnosis: histopathological alterations are heterogeneously spread in the liver parenchyma [21] and interpretation is extremely operator-dependent (including steatosis).[22] In contrast, MS criteria are easily collected and reliable.

In agreement with the literature, we found the mortality of major liver resection to vary considerably (from 0 to 20 %), depending on several factors including blood transfusion [23] and cirrhosis.[24] Recently, following the observation of some unexpected deaths in otherwise apparently healthy patients with metabolic disorders undergoing liver resections, we hypothesized that the association of metabolic disorders may be a major surgical risk factor in such patients.

In order to confirm this hypothesis, a retrospective analysis of perioperative outcomes in patients with two or more metabolic syndrome criteria and without other known cause of acute or chronic liver affection was carried out. All patients underwent the same surgical procedure (right hepatectomy—RH) using a standardized approach with well established operative risk according to the underlying liver disease (except MS-related NAFLD). The present study reports this analysis of several preoperative, operative and pathology criteria with respect to perioperative mortality.

Material and Methods

In the Service de Chirurgie Hépatobiliaire of Antoine Béclère Hospital, a University Tertiary hepatobiliary surgical center, a retrospective analysis from January 2001 to May 2010 was performed of all consecutive patients undergoing RH and concomitantly presenting at least two metabolic criteria (in accordance with a previous contribution).[14] Metabolic disorders included overweight or obesity [intended as body mass index (BMI)>25 kg/m^2], DM (defined as fasting plasma glucose>5.5 mmol/L), arterial hypertension (defined as blood pressure>130/85 mmHg), and dyslipidemia (including triglycerides≥1.7 mmol/l and/or high-density lipoprotein cholesterol<1 mmol/L in males or<1.3 mmol/L in females).

RH is arbitrarily intended as the resection of Couinaud's liver segments V to VIII. Open and laparoscopic techniques are reported in previous contribution.[25] When required, RH was combined with other smaller left hemiliver wedge resections and/or middle hepatic vein (MHV) resection.

All patients presenting with acute or chronic liver disease associated with any of the following conditions were excluded from the analysis: hepatitis B and C virus infection (defined as positive serological tests), autoimmune liver diseases (confirmed with serum autoantibodies), alcohol abuse (alcoholic consumption>40 g/day), or genetic hemochromatosis (positive genetic testing or hepatic iron index>1.9).

Perioperative mortality (defined as mortality related to surgery) of patients undergoing RH, regardless of etiology and/or the presence of metabolic disorders, was also evaluated.

Data collected in the studied population included:

- Preoperative data, including age, gender, BMI (in kilograms per square meter), American Society of Anesthesiology (ASA) score, DM, arterial hypertension, dyslipidemia, coronary disease, renal failure (defined as creatinine clearance<50 ml/min), tobacco consumption (packs per year), alcohol consumption (grams per day), and preoperative treatment. Serum concentrations of total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma glutamyl transferase, creatinine, prothrombin time and factor V were measured preoperatively and postoperatively (on days3, 5 and 7, and later when required);
- Intraoperative management, including type of procedure, setting (elective/emergency), MHV resection, amount of bleeding (in millimeter), pedicular clamping and its duration, hepatic vascular exclusion, procedure duration, associated procedures (including atypical left liver resections);
- Perioperative outcome, including postoperative complications [as classified by Clavien–Dindo [26] Clavien–Dindo classification: Grade I: any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiologic interventions (except physiotherapy, antiemetics, antipyretics, diuretics, electrolytes); Grade II: requiring pharmacological treatment with drugs other than such allowed for grade I complications; Grade III: requiring surgical, endoscopic or radiological intervention; Grade IV: life-threatening complication requiring IC/ICU management; Grade V: death], early and late hepatocellular insufficiency (defined as synchronous prothrombin time <50 % and serum total bilirubin>50 μmol/l before and after postoperative day5, respectively [27]), hospital stay, ICU stay, postoperative day of death, cause of death;
- Histopathological examination of liver tumor(s) and adjacent parenchyma was performed on paraffin-tissue sections stained with hematoxylin–eosin, Masson's trichrome, and reticulin staining. Collected data included histology of liver tumor(s), which were grouped as follows: primary malignancies [including hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma] secondary malignancies (liver metastases) and benign tumors. The term steatosis was used when the percentage of involved hepatocytes exceeded 5 %; steatosis was evaluated as absent (<5 %), mild (5 to 33 %), moderate (33 to 66 %), or severe (>66 %). Depending on morphology, steatosis was defined as macrovesicular, microvesicular, or mixed. Fibrosis was staged according to Kleiner [20]: no fibrosis (stage 0), zone 3 or perisinusoidal and portal fibrosis (stage 1), perisinusoidal and portal fibrosis without bridging (stage 2), bridging fibrosis

(stage 3), and cirrhosis (stage 4). Lobular inflammation with polynuclear or lymphocyte infiltration was noted. Size of resection (gr.) was recorded.

Several variables (*Preoperative criteria*: age, ASA grade, MS criteria including type and number, chemotherapy; *Intraoperative criteria*: MHV resection, bleeding; *Anatomo-pathological criteria*: lesion diagnosis, adjacent liver parenchyma macro- or microvesicular steatosis) were selected according to established or theoretical clinical importance and compared with respect to perioperative mortality.

For clarity, we will refer to Metabolic Disorders Association (MDA) when considering the whole series of selected patients (including patients with two metabolic disorders), whereas the term MS will be used to define patients with three or more metabolic disorders.

Statistical Analysis

The mean, standard deviation (SD) and range was calculated for continuous variables (age, bleeding, BMI, operative time). Univariate analysis using the Pearson's Chi-square or Fisher's exact test (where appropriate) was performed. Continuous variables were collapsed into subcategories and dealt with as dichotomous variables to enable incorporation into the logistic regression model. Factors whose univariate test had a p value of <0.05 were considered candidates for multivariate analysis. Such a p value was set to avoid "overfitting" the multivariate model by including too many variables from a small dataset examined in the present study. Multiple logistic regression analysis with forward stepwise variable selection was performed to examine independent predictors of perioperative mortality. Odds ratios (OR) and 95 % confidence intervals (CI) were calculated. A p value of 0.05 was considered statistically significant, and OR with CI were calculated. All statistical analyses were performed with PASW (SPSS) 18.0 (SPSS Inc, Chicago, IL).

Results

From January 2001 to May 2010, four surgeons performed 769 hepatectomies at our institution with an overall mortality of 3.5 % (27patients). In particular 151 (20 %) RHs were recorded with an overall perioperative mortality of 8.6 % (Table 1). Thirty (20 %) out of 151 patients presented isolated MDA without another known cause of liver disease, represent the studied population.

Patients were male in 21 cases (70 %) with a mean age was 66.2 years (SD 9.6, range 48–83 years) and the mean BMI 26.6 kg/m^2 (SD 4.35, range 17.3-38.6 kg/m^2). Two patients of ASA grade I, 20 of ASA grade II, and eight of ASA grade III were recorded. None of the patients suffered from renal or liver impairment, or known cirrhosis (preoperatively, prothrombine time: SD 8.1 ranges 73–100 %; total bilirubin: SD 9.2 ranges 2–51 μmol/L; creatininemia: SD 21 ranges 67–153 μmol/L). Patients suffered from arterial hypertension, overweight/obesity, dyslipidemia, and DM/hyperglycemia in 24 (80 %), 21 (70 %), 17 (57 %) and 12 cases (40 %), respectively. Preoperative chemotherapy was given in nine patients (30 %) affected by secondary malignancies. Ten patients (33 %) had preoperative right portal branch embolization (achieved for potential resection of MHV), in one case after right hepatic artery chemoembolization (4 %). In all cases, preoperative liver CT scanning showed hepatic remnant to be ≥25 % of total liver volume.

All the procedures were accomplished in an elective setting, with a laparoscopic approach in three cases (one conversion). For oncological reasons, in seven cases (23 %),

Table 1 Sex, presence of liver cirrhosis, surgical indications and mortality in patients undergoing right hepatectomy with respect of metabolic disorders

		Patients undergoing RH overall	Patients undergoing RH with less than 2 metabolic disorders (or presenting other causes of liver disorder)	Patients undergoing RH with 2 or more metabolic disorders[a]	Patients undergoing RH with 3 or more metabolic disorders[a]
Total no. [%][b]		151 [100][b]	121 [80][b]	30 [20][b]	13 [9][b]
Male gender no. [%]		86 [57]	65 [54]	21 [70]	10 [77]
Liver cirrhosis no. [%]		22 [15]	20 [17]	2 [7]	2 [15]
Indication no.	Primary lesion [%]	39 [26]	29 [24]	10 [33]	5 [38]
	Secondary lesion [%]	76 [50]	59 [49]	17 [57]	7 [54]
	Benign lesion [%]	36 [24]	33 [27]	3 [10]	1 [8]
Mortality no. [%]		13 [9]	4 [3]	9 [30]	7 [54]

RH right hepatectomy

[a] Without any other cause of underlying liver disorders

[b] Percentage among patients undergoing RH

RH was associated with resection of the MHV without segment IV resection. No hepatic vascular exclusion was performed, while intermittent pedicular clamping (Pringle maneuver) was performed in 21 cases (70 %), with a mean clamping time of 27 min (SD 8.1, range 10–53 min). Mean operative blood loss was 897 mL (SD 775.3, range 100–3,000 mL). A "wedge" resection of the left liver and resection of segment I were additionally performed in 10 and one patients respectively. Associated procedures involving right hemicolectomy and biliary confluence resection (followed by Roux-en-Y hepaticojejunostomy) were performed in three and one patient respectively. None of the associated procedures caused specific intra- or postoperative complications. Overall, mean operative time was 343 min (SD 110, range 180–620 min).

Tumor histology showed metastasis from colorectal adenocarcinoma in 16 patients (54 %), hepatocellular carcinoma in seven (23 %), intrahepatic cholangiocarcinoma in three (10 %), hepatic adenoma in two (7 %), renal carcinoma metastasis in one (3 %), and hemangioma in one (3 %). Mean specimen weight was 948 g (SD 380, range 555–2,075 g). Steatosis was absent in 10 patients, mild in 18 and moderate in 2. Abnormalities were not classified as chemotherapy-induced injuries to sinusoidal obstruction syndrome or steatohepatitis. Remnant liver parenchyma histology is reported in Table 2.

Perioperative outcome is reported in Table 3. The overall in-hospital mortality was 30 % (9/30), the 30 day postoperative mortality was 20 % (6/30). All nine deceased patients had developed hepatic failure with jaundice at postoperative days3 to 8, followed by renal failure, then hemodynamic instability, requiring ICU management with inotropic support. The patients died at a 6-to-53-day-interval (mean 26 days) from surgery. The case by case analysis revealed no sepsis, no bleeding, no pulmonary embolism or other obvious medical events explaining these deaths. Overall morbidity was 60 %, with a non-lethal morbidity (Clavien–Dindo grades I to IV) rate of 30 %. Fifteen patients (50 %) required ITU care. A comparison of the mortality of patients undergoing RH and concomitantly presenting less than two, two, and three or more metabolic disorders (MS) is reported in Table 4.

The results of univariate analysis of predictive criteria are shown in Table 5. Four criteria associated with perioperative mortality were identified as follows: the presence of three or more metabolic disorders, intraoperative bleeding exceeding 1,000 mL, MHV resection, and primary malignancy at histology.

The results of multivariate analysis of predictive criteria are shown in Table 6. Two criteria independently associated with perioperative mortality were identified: the resection of the MHV and a primary malignancy at histology.

All four patients undergoing RH with MHV resection for primary malignancy died.

Discussion

During the last three decades, major liver resection mortality has progressively decreased from 8.6–14.7 % [28, 29], to 3.1–8.7 %.[30–33] Although consistent with current literature, the overall mortality rate of our RH series (8.6 %) is positioned in the upper part of the range in line with other French studies including Pol et al. (7 %) [33] and Belghiti et al. (8.7 %).[30] Moreover, our datum refers specifically to the overall mortality of RH regardless of histology of liver parenchyma (fibrosis, cirrhosis).

The perioperative mortality of RH in the presence of MDA is dramatically high (30 %) when compared with the overall mortality of RH performed at our environment during the same period and with recent literature.[30–33] Interestingly, patients with MDA represent 69 % (9/13) of RH

Table 2 Histology of liver parenchyma of patients presenting two or more metabolic disorders (Metabolic Disorder Association)

Histological alterations		Number of patients[a] [%]
Steatosis	Absent (<5 %)	10 [33]
	Mild (5–33 %)	18 [60]
	Moderate (33–66 %)	2 [7]
	Severe (>66 %)	0 [0]
Macrovesicular steatosis[b]		18 [60]
Microvesicular steatosis[b]		4 [13]
Inflammation		14 [47]
Fibrosis	Stage 0	19 [63]
	Stage 1	6 [20]
	Stage 2	2 [7]
	Stage 3	1 [3]
	Stage 4	2 [7]
No evident disease[c]		4 [13]

[a] Patients' total number=30

[b] In two cases, both macrovesicular and microvesicular steatosis were present

[c] Liver parenchyma did not show steatosis, fibrosis or inflammation

Table 3 Perioperative outcome of patients presenting two or more metabolic disorders (Metabolic Disorder Association)

Complication	Number of patients[a] [%]	Type of complication [number of patients]
Grade I	3 [10]	Ascitis [2]
		Early hepatocellular failure [1]
Grade II	1 [3]	Rectorrhagia [1]
Grade III	3 [10]	Biliary endoscopic stenting for stenosis or leakage [3]
Grade IV	2 [7]	Biliary leakage requiring thoracotomy and laparotomy [1]
		Septic state requiring laparotomy [1][b]
Grade V	9 [30]	Death [9]
Total complications	18 [60]	(see above)

[a]Patients' total number=30

[b]No evident etiology was found at laparotomy

mortality over the past decade at our institution. This RH mortality should have decreased from 8.6 % to 4.3 % or 3.3 % (Table 4) if patients with MS or MDA, respectively had been excluded from surgery.

Different from the vast majority of authors who include patients undergoing various liver resections [24, 27, 28, 30, 32, 34], we decided to include patients undergoing the same procedure (RH) and to select the patients on the basis of the metabolic disorders rather than NAFLD or steatosis.[14, 35, 36] The choice of RH reduces bias, and selecting patients on the basis of metabolic disorders presents several advantages and more accuracy. As NAFLD and MS are linked [6–11, 37], NAFLD remains a histopathological diagnosis [20], needing an invasive liver biopsy for certainty. But histology of liver biopsy is questionable for accurate diagnosis since its interpretation is extremely operator-dependent [22] and histopathological alterations are heterogeneously spread.[21] In contrast, MS criteria are easily collected from the patient's personal history, physical examination and routine preoperative work up. In our series, the association between NAFLD and two or more metabolic disorders [14] is confirmed, as [22] pathology showed histological NAFLD abnormalities in remnant liver of the vast majority of the patients (26 out of 30—87 %), which matches that reported between MS and NAFLD in the literature.[38] Although the size of the series, the lack of difference (p=0.655) in perioperative mortality between patients with and without NAFLD at pathology (31 vs. 25 % respectively) may lead us to believe that MDA may play a role in increasing perioperative mortality independently of NAFLD histological alterations (or in the presence of some undetected liver alterations).

We verified managements, cut-offs for future remnant liver after RH [39] and chemotherapy-induced liver parenchyma injuries, but no other preoperatively condition/complication other than metabolic disorders justified such an increase in perioperative mortality. Nonetheless, results of hepatectomy in patients presenting MS/NAFLD remain unclear. Only one article selected patients on the basis of MS criteria [14]; however, the extent of liver resection, the type of procedure and mortality/morbidity of surgery are not reported.[14] These criteria may be useful in understanding the underlying mechanism of liver failure and death, and, since metabolic disorders (including MS) are at present not considered as being inclusion/exclusion criteria, in improving patient selection before major hepatic resection.

But which factors play a determinant role in such a poor prognosis? Can they enable the identification of a category of patients with an even poorer surgical risk, to be excluded from major hepatic resection?

Although some of the analyzed preoperative criteria, DM (p=0.060) approached significance in univariate analysis, none of them significantly affected the prognosis. The datum concerning DM to some extent matches those of the literature [34, 40–42], which show higher perioperative mortality rates after liver resection of HCC and colorectal hepatic metastases in diabetic patients. The presence of one among the remaining three metabolic disorders other than DM (*overweight/obesity*, *dyslipidemia*, and *arterial hypertension*) did not significantly modify patients' perioperative survival. There is no unanimous opinion in recent literature concerning the role of overweight/obesity in modifying perioperative mortality following major hepatic resection

Table 4 Mortality of surgery with respect of the number of metabolic disorders

Patients' group	Mortality [no.]	p value
Patients with≥2 metabolic disorders undergoing RH (studied population)	30 % [9/30]	<0.001[a]
Rest of the patients undergoing RH	3.3 % [4/121]	
Patients with Metabolic syndrome (≥ 3 metabolic disorders)	53.8 % [7/13]	<0.001[b]
Patients with 2 metabolic disorders	11.8 % [2/17]	
Rest of the patients undergoing RH	3.3 % [4/121]	

[a]Chi square test

[b]Fisher's exact test

Table 5 Univariate analysis (one-way Fisher's exact test) of criteria predictive of perioperative mortality after right hepatectomy in patients presenting two or more metabolic disorders

Criteria				Deaths [Total patients]	Mortality %	OR (C.I. 95 %)	*p* value
Preoperative criteria	Age (years)	≤65		4 [14]	28.6	1.14 (0.24–5.46)	0.873
		>65		5 [16]	31.3		
	ASA class[a]	ASA ≤2		6 [20]	30.0	1.60 (0.29–8.86)	0.590
		ASA 3		3 [8]	37.5		
	Metabolic syndrome criteria	Hypertension	Yes	1 [6]	16.7	2.50(0.25–25.15)	0.437
			No	8 [24]	33.3		
		Diabetes Mellitus	Yes	3 [18]	16.7	5.0(0.93–26.79)	0.060
			No	6 [12]	50.0		
		Dyslipidemia	Yes	2 [13]	15.4	3.85 (0.64–23.05)	0.140
			No	7 [17]	41.2		
		BMI	≤25	3 [9]	33.3	0.80 (0.15–4.29)	0.794
			>25	6 [21]	28.6		
		2 criteria		2 [17]	11.8	8.75 (1.40–54.80)	0.020
		3 or more criteria		7 [13]	53.8		
	ChemoTP	Yes		1 [9]	11.1	4.92 (0.52–47.07)	0.166
		No		8 [21]	38.1		
Operative criteria	Middle hepatic vein resection	No		4 [23]	17.4	11.87 (1.67–84.52)	0.013
		Yes		5 [7]	71.4		
	Bleeding (ml)	<1,000 ml		3 [19]	15.8	6.4 (1.16–35.44)	0.034
		≥1,000 ml		6 [11]	54.5		
Pathology criteria	Surgical indication	Secondary malignancies		3 [17]	17.6	7.0 (1.19–41.36)	0.032
		Primary malignancies		6 [10]	60.0		
	Liver parenchyma	Macrovesicular steatosis	No	8 [26]	30.8	0.75 (0.07–8.36)	0.815
			Yes	1 [4]	25.0		
		Macrovesicular steatosis	No	1 [12]	8.3	8.8 (0.93–83.35)	0.058
			Yes	8 [18]	44.4		

[a] Two patients were classified ASA 1 and no patient ASA 4

[36, 43], and there are no data available concerning dyslipidemia or arterial hypertension. Interestingly, in our series, the association of multiple metabolic disorders implies a significant worsening of the prognosis. The increase in mortality from 3.3 % in the general population to 11.8 % with two metabolic disorders and to 53.8 % when three criteria are present seems to suggest a "cumulative" negative effect of MS criteria on the immediate prognosis. This data is not reported in the literature.

Among intraoperative criteria, *bleeding≥1,000 mL* was significantly related to mortality ($p=0.034$), whereas *operating time* and *pedicular clamping* were not (data not shown). This datum is consistent with the literature.[30, 33] Surprisingly, *MHV resection* resulted as significantly related to an increased mortality (71 %) at univariate analysis, and multivariate analysis confirmed the pivotal role of this factor in increasing the mortality of surgery. This result is even more interesting when compared to RH/right lobectomy (RH extended to the entire segment IV) performed on healthy liver, as in the case of adult living donor transplantation [44], where the resection of the MHV does not imply any increase in perioperative mortality.[45] Seemingly, patients affected by

Table 6 Multivariate analysis (logistic multiple regression) of criteria predictive of perioperative mortality after right hepatectomy in patients with metabolic disorder association (two or more metabolic disorders)

Criteria[§]	*p* value	Exp(B)	Lower 95 % CI	Upper 95 % CI
Middle Hepatic Vein Resection	0.038	23.86	1.19	476.96
Primitive malignancies	0.027	29.01	1.48	569.07

Forward stepwise method; dependent variable: perioperative mortality

Of the four variables resulted significantly related to perioperative mortality at univariate analysis, two (*presence of 3 or more metabolic disorders and bleeding*) were excluded by model metabolic disorders do not tolerate changes in venous outflow, which is in accordance with alterations microcirculation in liver [46] and in the kidney.[47]

Multivariate analysis also showed the histology of *primary malignancy* as being another variable to be independently correlated to a poor prognosis (60 % mortality). This is correlated with recent literature.[48] The recent finding that HCC in patients with MS often develops without liver fibrosis [14] seems to indicate that liver carcinogenesis in patients affected by MS differs from that from other etiologies. Also major liver resections are reported to have a better prognosis when performed for benign pathology than for malignancy [49], whereas few papers compare clearly the perioperative mortality of liver resections carried out for HCC and colorectal metastasis.[49] It is difficult to compare this finding with the literature: surprisingly, most of the papers analyze the results of surgery within a group of patients affected by the same cancerous disease, such as HCC [14] or colorectal metastasis [49], whereas the analysis of perioperative mortality with respect to the nature of the tumor is seldom performed. Our short series shows results after a highly accurate selection: analysis of perioperative mortality with respect of the procedure (RH) and the chronic metabolic disorder linked to a chronic liver disease (NAFLD).

The reason why the variables *MHV resection* and *primary malignancy* independently (and dramatically) increase the mortality of major hepatic resection in patients with multiple metabolic disorders is unclear. Theoretically, although preoperative evaluation excluded that FRL was greater than 25 %, it may be hypothesized that patients undergoing MHV resection finally had more liver parenchyma resected than the others, and the cause of liver failure ultimately is a small FRL. If we also admit that liver function in patients with MDA is reduced, it may be deduced that a 25 % FRL is a too low cut-off for patients with MDA undergoing right hepatectomy. Although it may be objected that MHV in all patients was resected because of direct tumor infiltration, and virtually no additional parenchyma has been resected, this represents a potential bias of the paper. Alternatively, it may be hypothesized that a reduction in venous outflow of remnant left liver may cause liver failure. Obviously, larger series are needed to explain the cause of such an increased mortality.

Interestingly, when we verified retrospectively, all the four patients undergoing RH with associated MHV resection for primary malignancy died of surgery. The presence of a *primary malignancy*, the need for an *MHV resection* or both these conditions theoretically contraindicates major liver resections according to our results, since a mortality of 60, 71, and 100 % respectively may be expected. The small sample size in the present study precludes any definitive conclusions and further, larger scale studies are necessary to clarify the issue. Considering these results, patients with metabolic disorders association and a malignancy requiring an extended right hepatectomy (segments 4–8) should be considered unresectable. Other therapeutic strategies should be preferred; chemotherapy, chemo-embolization, wedge and staged hepatic resection, radiofrequency ablation. In primary liver cancers (intrahepatic cholangiocarcinoma and hepatocellular carcinoma), liver transplantation is an option. Unfortunately, liver transplantation in patients presenting metabolic syndrome has been associated recently with poor outcomes.[37, 50, 51]

Difference in prognosis depending on the degree of steatosis did not reach statistical significance. *Macrovesicular steatosis* however approached statistical significance in the univariate analysis and may have a role to play in the perioperative prognosis. This datum is somewhat consistent with recent literature: some authors report steatosis to be associated with increased mortality, rising to 14 % [46] while others do not.[30, 32, 35] The heterogeneity of the series (microvesicular and macrovesicular steatosis, various etiologies of the steatosis, and performed procedures) [30, 32, 34, 35] and the “operator-dependent” histological interpretation [22] may discredit any conclusions.

Conclusion

Although our small and retrospective study, our results clearly need to be confirmed by larger studies. As we report a 30 % mortality rate, ethical concerns may compel to confine to retrospective analysis, as ethics compels us to report these honest but shocking results: patients presenting MS and undergoing RH are at increased risk of perioperative death. When planning the surgical strategy, it should be kept in mind that, if the indication for surgery is a *primary malignancy* or if a *MHV resection* is performed, in our experience mortality rises to 60 and 71 % respectively, and, when both these conditions are met, mortality is 100 %. The recent trend towards an increasing aggressiveness of liver surgery and the rising incidence of metabolic disorders in Western countries should lead us to improve patient selection and to reduce the mortality of surgery.

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