ISSN: 2643-4466

Atallah et al. Int Arch Intern Med 2022, 6:039
DOI: 10.23937/2643-4466/1710039
Volume 6 | Issue 2
Open Access

International Archives of Internal Medicine

RESEARCH ARTICLE

Morbidity and Mortality in Patients Undergoing Surgery for Hepatocellular Carcinoma

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Abstract

Background: Liver resection for hepatocellular carcinoma in patients with normal or chronic liver disease remains a major therapeutic tool. Its indications keep expanding over the years nevertheless it is still burdened with a significant morbidity and mortality. The purpose of our study was to investigate the postoperative morbidity and mortality of the liver resection in patients with hepatocellular carcinoma on cirrhotic liver, chronic liver disease or normal liver and to identify its risk factors.

Methods: It was a unicentric, retrospective study, including 41 patients who had liver resection for hepatocellular carcinoma in the department of general surgery of Mongi Slim hospital between January 2007 and December 2017. We carried out a descriptive then an analytic study with as main outcomes the measure of postoperative morbidity and mortality.

Results: This study includes 41 patients whose median age was 61. The sex ratio (M/F) was 1.9. The main etiologies were viral dominated by hepatitis C virus (32%) followed by hepatitis B virus (29%). Eight patients have developed hepatocellular carcinoma on a normal liver. The most performed interventions were uni or bisegmental resection (37%) then non-anatomic resection (32%). Ten patients underwent a major hepatectomy. The mortality rate was 10%. Mortality factors were intraoperative blood loss (p = 0.013) as well as postoperative liver failure (p = 0.03). The overall morbidity rate was 41%. Multivariate analysis revealed that preoperative albumin (p = 0.008) and operative time (p = 0.015) significantly predict the occurence of morbidity.

Conclusion: Appropriate prevention together with a rigorous quantitative and qualitative hepatic evaluation as well as an improvement in the surgical technique and anesthetic management are key to limit the risks of postoperative complications.

Keywords

Hepatocellular carcinoma, Mortality, Morbidity

Introduction

Hepatocellular carcinoma is the most common primary liver cancer (70-85%) [1]. It represents the seventh cancer in terms of incidence in the world. With more than 781,000 deaths in 2018 [2] (or 8.2% of all cancer deaths), it ranks fourth among the causes of death from cancer in the world after lung, colorectal and gastric cancers.

In recent decades, its incidence has tended to decrease in developing countries and to increase in developed countries. The vast majority of HCC develop in a liver with cirrhosis, more rarely in a non-cirrhotic liver disease and exceptionally in a healthy liver.

Thanks to the establishment of vaccination programs against hepatitis B as well as treatment programs for hepatitis C, the incidence of HCC linked to viral liver disease tends to decline in favor of liver disease secondary to alcohol and non-alcoholic hepatic steatopathy [3].

Its prognosis remains poor, due to its often-late diagnosis due to its quiet clinical manifestations, causing a short median survival.

Its management is multidisciplinary. In the past, the only chances of survival in cirrhotics were possible thanks to liver transplantation, the indication of which

Citation: Atallah A, Talbi G, Ayadi F, Medhioub F, Wael F, et al. (2022) Morbidity and Mortality in Patients Undergoing Surgery for Hepatocellular Carcinoma. Int Arch Intern Med 6:039. doi.org/10.23937/2643-4466/1710039

Accepted: October 07, 2022: **Published:** October 09, 2022

nevertheless remains limited. Today, for patients who do not meet the Milan criteria [4] and faced with the shortage of grafts, surgical resection or percutaneous ablative treatment can be curative, thanks to the advance of knowledge, to better selection of candidates for liver resection as well as progress in perioperative management [5].

Despite the emergence of these new tools in the management of HCC, surgery remains the major and most effective therapeutic weapon [6], but nevertheless remains burdened with significant morbidity and mortality, particularly in cirrhotic. In fact, postoperative complications can reach 30 to 40% in the majority of series.

In Tunisia, hepatic resection for HCC has been performed for years, but no study has looked at the postoperative evolution of these interventions.

The aim of our work was to study the postoperative morbidity and mortality of hepatic resection in patients with HCC on liver of cirrhosis, chronic or healthy liver disease, to identify the risk factors with a view to ensure better management and better select candidates for such an intervention.

Methods

Study type and population

Our study was retrospective and analytical. This was carried out over a period of 11 years, between January 2007 and December 2017. We collected 41 consecutive patients who had surgical resection for hepatocellular carcinoma, on healthy or pathological liver, in the department of general surgery of the Mongi Slim University Hospital.

Patient selection

The inclusion criteria for our study were the following patients with HCC who had liver resection surgery, regardless of age, sex, etiology, associated defects and the presence or no underlying chronic liver disease. The diagnosis was confirmed in all cases by the anatomopathological study on a preoperative biopsy or on an operative specimen.

The exclusion criteria were:

- Patients with a histological type other than hepatocellular carcinoma.
- Patients with hepatocholangiocarcinoma.
- Non-operated patients.
- Patients with distant metastases.
- Recurrent HCC.

The outcome measures were postoperative mortality and morbidity, defined respectively as the occurrence of death and/or a medical or surgical complication with or without reoperation, during the hospital stay or during the 30 days after discharge.

The severity of postoperative complications was measured according to the Clavien and Dindo classification developed in 2004.

In our study, the criterion chosen to define hepatocellular insufficiency was the “50-50” or “Beaujon criterion” [7], combining, on the 5th postoperative day, a prothrombin (PT) level < 50% and a total bilirubinemia > 50 µmol/L.

Data collection

Preoperative data

- Demographic and epidemiological data: Age, gender, body mass index.
- Comorbidities and lifestyle: Arterial hypertension, diabetes, dyslipidemia, metabolic syndrome, alcoholic intoxication, smoking, oral condition, presence or absence of scarifications.
- Clinical examination data: Functional signs, physical signs.
- Data from morphological and histological explorations: Presence or not of an underlying chronic hepatopathy as well as its aetiology, presence or not of cirrhosis, site, number and size of lesions, preoperative imaging, hepatic volumetry.
- Preoperative laboratory tests: Total bilirubinemia, AST/ALT, hemoglobin, PT, platelet count, Gamma-glutamyl transferase (GGT)/Alkaline phosphatase (ALP), albuminemia, alpha-fetoprotein level.
- Clinical, biological, endoscopic, and radiological signs of portal hypertension.
- Preoperative treatment: Arterial chemoembolization, embolization, or portal ligation.

Intraoperative data

- Surgical procedure performed: Type and extent of hepatic resection, associated procedure.
- Data of the operative act: Duration of the act, type, number and duration of pedicle clamping.
- Blood loss and transfusion.
- Mode of transection and treatment of the hepatic section.
- Per operative incidents.

Postoperative data

- Postoperative complications: Type and means of management.
- Mortality: Rate and cause.

- Results of the biological tests at Day 1, Day 3 and Day 5.
- Results of the anatomopathological examination according to the Edmondson grade, nature of the tumoral and non-tumoral liver tissues.
- Duration of hospitalization in the surgical department and in the intensive care unit.

Statistical study

Statistical analyzes were entered and analyzed using IBM SPSS version 25.

Qualitative variables were expressed as numbers and percentages. After being tested for the normal distribution using the Shapiro-Wilk tests, the normally distributed quantitative variables were expressed as the mean standard deviation and the non-normally distributed continuous variables were expressed as the median and interquartile range. Comparison of qualitative variables was done using the Chi-deux test or Fisher's exact test. Quantitative variables were compared using Student's T-test for independent samples or the Mann-Whitney-Wilcoxon test.

Multivariate logistic regression analyzes were performed to identify variables independently associated with postoperative morbidity and mortality. Variables that were significantly associated with the event studied in the univariate analysis ($p < 0.05$) were included in the multivariate model after checking for multicollinearity. In order to reduce the bials caused by the tiller of our sample and to produce fine and consistent estimates even in case of separation we used Firth logistic regression in the study of predictors of mortality.

The level of statistical significance was set at $p < 0.05$.

Results

Preoperative data

We collected 41 patients with HCC while respecting the aforementioned inclusion criteria. The median age of our patients was 61 years with extremes ranging from 20 to 77 years with a clear male predominance (sex ratio at 1.9). The most frequent comorbidity found in our series was arterial hypertension which was present in 17 patients (42%), followed by diabetes (39%), Thirty-three patients (81%) had developed HCC on a liver of cirrhosis or chronic hepatopathy, the main aetiology of which was mainly viral dominated by hepatitis C virus (32%) followed by hepatitis B virus. The proportion of HCC developed in healthy liver was 19% (8 patients). The median size of the nodules at preoperative imaging was 50 mm with extremes ranging from 16 to 190 mm. Eight patients had 2 nodules located in the same lobe. Twenty-seven patients (66%) had clinical, laboratory or endoscopic signs of portal hypertension, dominated by esophageal varices (17 patients). Twelve patients (29%) had chronic liver disease in the cirrhosis stage. Five were classified CHILD A and seven were CHILD B7 according to the Child-Turcotte-Pugh classification.

In univariate study, the preoperative variable significantly associated with mortality was the size of the HCC nodule ($p = 0.043$). The variables significantly associated with postoperative complications were diabetes ($p = 0.029$), CHILD B cirrhosis ($p = 0.003$) and hypoalbuminemia ($p = 0.002$).

In multivariate study, the only independent predictor of postoperative complications was preoperative hypoalbuminemia. No independent preoperative variable predicted postoperative mortality.

Intraoperative data

In our series, ten major hepatectomies were performed. Among the minor hepatectomies, 13 atypical resections or "wedge resection" and 15 segmentectomies were performed. The average operating time was 187 minutes with extremes ranging from 73 to 430 minutes. The mean blood loss was 610 ml (100-2400). Eleven patients benefited from intraoperative red blood cell transfusion. An intraoperative incident occurred in 6 cases, 5 of which resulted in complicated operative consequences and death in two patients. The most frequent incident was a hepatic vein wound followed by hemodynamic intolerance to pedicular clamping.

In univariate study, the preoperative variables significantly associated with mortality were major hepatectomy ($p = 0.039$), vascular clamping and particularly pedicle clamping ($p = 0.028$), intraoperative blood loss ($p = 0.031$) and transfusion of blood products intraoperative ($p = 0.003$). The variables significantly associated with postoperative complications were operative time ($p = 0.014$), blood loss (p-0.049) and blood product transfusion ($p = 0.014$).

In a multivariate study, the only independent predictor of postoperative complications was the operating time ($p = 0.015$). The intraoperative independent variable predictive of postoperative mortality was blood loss ($p = 0.013$).

Postoperative data

Mortality in our series concerned 4 patients (10%). The main cause of death was postoperative hepatocellular failure in 2 cases. Seventeen patients (41%) had a postoperative complication. According to Clavien Dindo's classification, severe morbidity (defined by a score greater than II) was 29% (Table 1). The most specific complication was hepatocellular failure. It was found in 4 patients, two of whom died. Oedemato-ascitic decompensation (2 patients), biliary fistulas (2 patients), bilomas and purulent intraperitoneal collections show the most common specific complications. The pulmonary complications mainly represented were present in the pneumopathies, of the examination cases. By pathology

Table 1: Summarizes the postoperative mortality rates of the main series in patients who have had hepatic resections for HCC as well as their main risk factors.

Author	Country	Year	Patients	Mortality rate	Risk factors
Filman, et al. [8]	Germany	2019	8364	9.3%	-
Neeff, et al. [10]	Germany	2008	93	8.6%	- Major hepatectomies - Blood lose
Gassmann, et al. [11]	Germany	2010	72	9.7%	- Hepatic failure
Shimada, et al. [12]	Japan	1998	388	2.8%	- Major hepatectomies
Lee, et al. [9]	Taiwan	2016	3386	1.8%	- Hypoalbuminemia - Intraoperative incident
Yang, et al. [13]	China	2011	305	2.6%	- Hepatic failure - Thrombopenia
Capussotti, et al. [14]	Italy	2005	216	8.3%	- Hepatic failure
Our study	Tunisia	2020	41	10%	- Hepatic failure - Blood lose

of the operative specimen showed that the proportion of fibrosis was minimal or moderate (F1-F2) according to the Metavir score in 14 patients (34%) and severe or at the stage of cirrhosis (F3-F4) in 19 cases (46%).

In univariate study, the preoperative variable significantly associated with mortality was hepatocellular failure (p = 0.041). The only postoperative variable significantly associated with postoperative complications was portal fibrosis 2 3 (p = 0.047).

In multivariate study, the only independent predictor of postoperative mortality was the occurrence of postoperative hepatocellular failure (p = 0.03). No postoperative independent variable predicted morbidity.

Discussion

The mortality rate after hepatic resection remains very variable in the literature. It is between 1.8 and 10% but is generally between 5 and 10%.

A German series [8] identified a plethora of patients (8364) having undergone liver resection for hepatocellular carcinoma on cirrhotic or non-cirrhotic liver over a period of 5 years, between 2010 and 2015. The mortality rate was 9, 3% for all types of resection.

A Taiwanese study [9], for its part, counted 3386 hepatic resections for curative purposes. The mortality rate was 1.8% and the significant predictors of death were preoperative albuminemia and the occurrence of intraoperative incidents.

In our series, the mortality rate was 10%. The main cause was hepatic failure, the occurrence of which was significantly predictive of death (p = 0.03, OR = 67.15 (1.44; 6, 1.10^{9}). The second independent predictor of postoperative death found in our series was intraoperative blood loss (p = 0.013, OR = 1.36 (1.05; 3.7)).

The main predictors of death found in the literature were enlarged hepatectomy, preoperative albuminemia, preoperative hemostasis disorders, intraoperative incidents and hepatocellular failure.

Table 1 summarizes the postoperative mortality rates of the main series in patients who have had hepatic resections for HCC as well as their main risk factors [8-14].

The rate and predictive factors of mortality in our series were comparable to those found in the literature.

Hepatocellular insufficiency is the first cause of death in the series, especially since most of these are pathological livers. Its prevention in preoperative by a rigorous and meticulous evaluation of the hepatic function and the volume of the future remaining liver is essential, particularly for pathological livers. Indeed, the occurrence of hepatocellular insufficiency can be fatal and require resuscitation. Its postoperative diagnosis must be made quickly by armed clinical-biological surveillance, even for minor hepatectomies.

In our series, we chose the "Beaujon criteria" in order to detect hepatocellular insufficiency on the 5^{th} postoperative day. However, it would be more interesting to perform a predictive score for postoperative hepatocellular failure. This is why some teams have looked into the issue in order to develop a new algorithm to predict the risk of hepatocellular failure. At present, several Asian teams have turned to the APRI score [15] (initially developed to screen for fibrosis lesions) and the ALBI grade [16] (initially developed for long-term prognostic purposes), or even a combination of these two scores in order to predict the onset of postoperative hepatocellular failure. It has been shown that a high ALBI grade was statistically correlated with the occurrence of hepatocellular insufficiency in patients with HCC [17]. Likewise, a new mathematical algorithm coupling the two scores (ALBI + APRI) was developed, predicting in a precise and statistically significant

Table 2: Summarizes the morbidity rate in the main series on liver resection for patients with HCC.

Authors	Country	Year	Patients	Morbidity rate	Risk factors
Shimada, et al. [12]	Japan	1998	388	21.9%	- Blood lose - Operative time
Lee, et al. [9]	China	2011	305	37%	- Thrombopénia - Blood lose > 800 cc
Kusano, et al. [20]	Japan	2009	291	42.6%	- CHILD B - Blood lose > 1200 cc
Kabir, et al. [21]	Singapore	2020	888	26.7%	- Blood lose - Comorbidity - Hepatitis B virus
Chok, et al. [22]	China	2017	1710	27%	- Blood lose - Blood transfusion - Intraoperative incident
Okamura, et al. [23]	Japan	2011	376	47.1	- Blood lose - Blood transfusion - Operative time - Pringle
Harimoto, et al. [24]	Japan	2015	966	17%	- Operative time - Hypoalbuminemia
Tomimaru, et al. [25]	Japan	2018	158	17.7%	- Operative time - Hypoalbuminemia
Amisaki, et al. [26]	Japan	2018	145	26%	- Operative time
Margonis, et al. [27]	USA Japan	2017	774	47.7%	- Blood lose - Multiple tumors - BMI ≥ 30 Kg/m^2
Our study	Tunisia	2020	41	41%	- Operative time - Hypoalbuminemia

manner the occurrence of hepatocellular insufficiency [18,19]. The advantage of these two scores is that they do not include no subjective variables (unlike the CHILD score), which could help the clinician easily predict the risk of developing hepatocellular failure. This algorithm is not yet common practice in our establishment, and other larger-scale studies will have to be carried out in this direction so that it can establish its possible future legitimacy.

The best treatment for IHC so far remains prevention and careful selection of candidates for liver resection.

In our series, the overall morbidity rate was 41%. The rate of serious complications (> grade II of the Clavien-Dindo classification) was 29%.

In the literature, the morbidity rate varies between 15 and 61%. The non-specific complications were mainly of a pleuro-pulmonary and infectious nature (abscess of the wall, urinary tract infections, etc.). The specific complications were represented by hepatocellular insufficiency, oedemato-ascitic decompensation, intra-abdominal collections and postoperative bleeding.

In our series, the most frequent complications were hepatocellular failure in 4 patients, two of whom died from it, and pleuropulmonary complications in 7 patients.

The predictive factors significantly associated with complicated postoperative complications found in our series were preoperative albuminemia ($p = 0.008$, OR = 0.68 (0.52, 0.9)) and operative time ($p = 0.015$, OR = 1.14 (1.03, 1.28)).

Table 2 summarizes the morbidity rate in the main series on liver resection for patients with HCC [9,12,20-27].

Conclusion

Liver resection remains the major therapeutic weapon for the management of patients with hepatocellular carcinoma. The indications have continued to expand in recent years, thanks to better patient selection, better prevention, and more adequate screening for patients at risk, in parallel with advances in imaging, surgical techniques and anesthesia and resuscitation measures.

Conflict of Interest

We declare that we have no conflict of interest.

Acknowledgements

None.

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