Emergency liver resection for non-traumatic lesions.
A systematic review

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AIM: *Primary liver tumors have an incidence of 20% regarding benign tumors respectively 5.7% of the overall incident cases of cancer. In any major hepatic injury, the surgical treatment has two main goals: hemostasis and excision of the affected liver segments. We aimed to systematic review the non-traumatic emergency liver resections, in order to raise concern about a rather rare, but difficult to treat hepatic pathology, which implies divergent therapeutical approach, and emergency liver surgery remains the first or backup option.*
METHODS: *A literature survey was performed guided by the words "liver resections", "major liver resections", "emergency liver resection". "hepatocellular carcinoma" using four databases: Pubmed, Scopus, Web of Science and Embase. All titles referred in English, published from 2000 until 2021, were checked for eligibility.*
RESULTS: *Six publications were considered relevant for major liver resections in emergency, from a total of 331 articles that were reviewed. Large hepatocellular carcinomas and adenomas were the most common types of tumors found at risk for spontaneous rupture. The patients with hemodynamic instability, reduced liver function and large tumors had lower long-term survival and disease-free survival. Major hepatectomy was indicated as a viable solution for prolonging survival rate, whenever the patient's general status permits it per primam.*
CONCLUSIONS: *Emergency major liver resection for tumoral causes prolongs survival even if the cause is usually malignant. The tumor can be resected with negative resection margins, respecting the correct oncological requirements, both per primam or staged approach according to each case specifically.*

KEY WORDS: Adenoma, Emergency, Hemorrhage, Hepatocellular Carcinoma, Liver Resection, Liver Tumors

Introduction

Primary malignant liver tumors have an incidence of 5.7% of the overall cases of cancer, placing it as the sixth type of cancer worldwide. It has a poor prognosis with less than 10% 5-year survival rate. On the other hand, the benign liver tumors have a demonstrated incidence of up to 20% of the hepatic pathology, usually incidentally diagnosed by imaging instruments and low chances of carcinogenesis [1,2]. Their treatment, depending on the stage of the neoplasms and the character of the benign tumors, consists mostly in liver resections, performed electively. Emergency surgery is necessary if life threatening complications occur, such as intraperitoneal hemorrhage and extensive intrahepatic hematomas occur. However emergency liver surgery in the absence of optimal preoperative preparation and neoadjuvant treatment (when required, for malignancies) might negatively affected long distance results.
Surgical treatment should be started with a quick approach to the organ, the access path being usually the median laparotomy, which can be enlarged in both direc-

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tions and eventually transformed into a thoraco-brake-laparotomy if needed [3].

Clinical exam, intraoperative cholangiography or ultrasonography, computed tomography (CT) and especially, selective arteriography of the hepatic artery are edifying for diagnosis.

In any major hepatic injury, the surgical treatment has two main goals: hemostasis and excision of the affected liver segments. From the therapeutical point of view, there are two possible attitudes. In case of hemodynamically stable patients, with CT characters of minor lesions (small dimension tumors, low amount of free intraperitoneal blood etc.), which do not change on repeated examinations, conservative approach can be advocated for, without surgery and close clinical and CT surveillance or exploratory laparoscopy with simple insertion of subhepatic drainage, without need for suturing. In case of hemodynamically and respiratory unstable patients, with clinical signs of active bleeding, CT scans showing severe lesions, immediate open surgery is recommended [4].

The technical procedures consist of removal of the affected tissue, recommended at the same time as direct hemostasis; in marginally located lesions, atypical liver resection is practiced, but for more extensive lesions, targeted liver resections are required: preferably anatomical resections (exposing the surgeon to less blood loss and more accurate oncologic results). In the face of massive, difficult to control hemorrhage, temporary inflow interruption, such as the Pringle maneuver or selective and supraselective vascular occlusion can be performed. Large vessels injuries (hepatic artery, portal vein or other main branches) require special techniques, in order to restore blood flow: vascular primary reconstruction and/ or vascular replacement with venous graft or synthetic prosthesis [5].

In low volume centers, safe liver resections with mortality and survival rates comparable with those from high-volume centers were reported [6]. Correct assessment of the remaining liver should be done whenever it is possible. Further, patients proposed for major liver resection should be maintained at a balanced nutritive and electrolyte level, good liver and renal function, not only before, but also during surgery. Low central venous pressure, under 5 mmHg during parenchymal transection is also cited to be indirectly proportional correlated with postoperative liver failure [7,8].

On the other hand, in emergency cases, the comfort of the surgical team disappears completely, decisions being made on the spot, lack of time representing a major issue; the expertise of the surgeon achieved on numerous previous cases is proved to be the decisive factor [9].

There are no studies in literature to compare major liver resections versus elective ones in terms of morbidity and mortality. However, there are studies comparing the surgical treatment options in emergency liver lesions: per primam resections versus staged hepatectomies, transarterial embolization or liver packing, followed by curative resection in the next 48 hours [10,11].

Predictive factors of the patients' outcome after major liver resections have been identified in the literature: blood loss with need of transfusions (red blood cell packs or fresh frozen plasma); elevated serum levels of total bilirubin, aspartate aminotransferase and alanine aminotransferase; coagulopathies and the presence of hypovolemic shock due to haemorrhage [12,13].

The purpose of the article is to analyze data from the literature on emergency liver resections performed for non-traumatic complications of liver pathology, to determine whether the prognosis being actively influenced by this approach, compared to the elective interventions.

Methods

A literature survey was performed guided by the words "liver resections", "major liver resections", "emergency liver resection", "hepatocellular carcinoma", "rupture", "bleeding" using four databases: Pubmed, Scopus, Web of Science and Embase (Figs. 1, 2).

All titles referred in English, published from 2000 until 2021, were checked for eligibility by title and abstract, by two different researchers, in order to remove double counting. Searching "major liver resections in emergency" on Pubmed, there were 97 results. The full texts of the eligible original articles were reviewed entirely. Searching on SCOPUS, there were identified 211 results; regarding Web of Science, there were 45 results; on Embase, 75 results.

Articles regarding liver trauma due to stab wounds, gunshot wounds, car accidents wounds and those regarding liver metastatic tumors, were excluded from the current study. They did not meet the inclusion criteria; there-

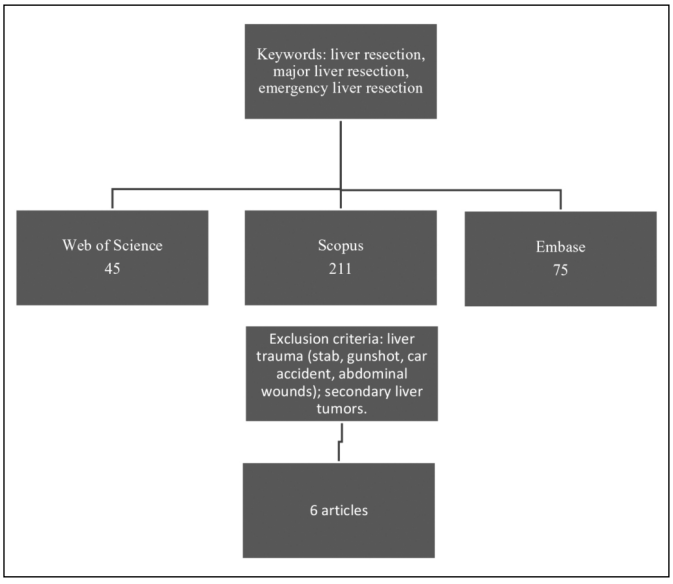

Fig. 1: Systematic review diagram (method).

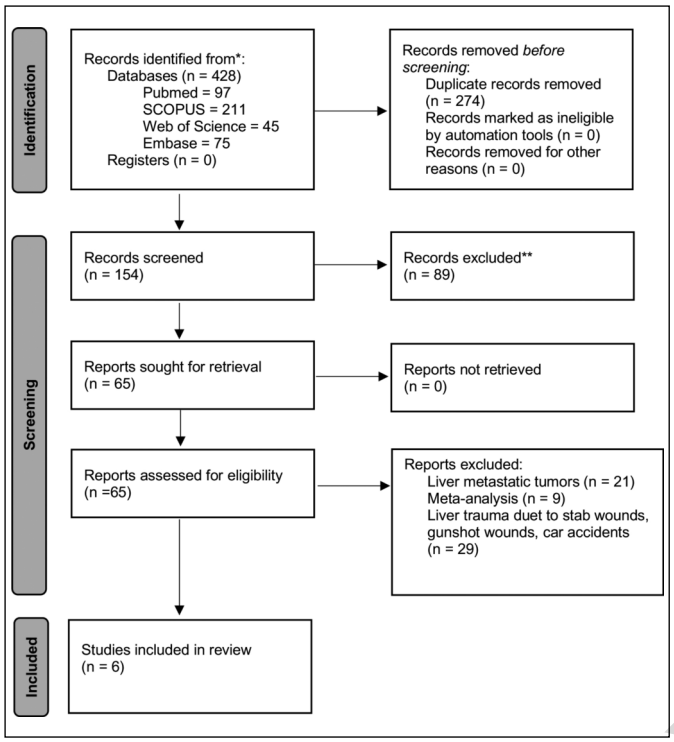

Fig. 2: PRISMA flow chart for the selected studies included in the systematic review.

fore, they were considered non-eligible. Following a comprehensive examination of all qualifying papers, two independent reviewers extracted data and double-checked all results based on a predefined set of criteria. An Excel extraction form was used to collect data. We gathered information on research design, data source, prognostic variables of interest, outcomes of interest and adjustment factors for all studies using Covidence workflow platform. Quality assessment used three tools: prognostic factor measurement, outcome measurement and study participation.

During the selection and extraction of data, any discrepancies between the two reviewers were reviewed with a third reviewer, in order to further reduce bias and any relating discrepancies. The reference lists of certain research were combed for prospective papers using the "snowball" technique. In order to express the degree of consistency in the evaluated article's findings, we used tables for quantitative data with textual description and content analysis for qualitative data.

We analyzed the patients' demographics (age, gender), type of admission, status at admission (hypovolemic shock, blood loss, transfusions needed), tumor specifications (localization, type of lesion, diameter), therapeutic attitude (emergency resection, staged intervention, surgical procedure), intraoperative conduct (blood loss, Pringle maneuver, resection type), tumor type (benign, malign, histopathological diagnosis) and patients' evolution (survival time, hospitalization, complications), by comparing the studies in connection with these elements considered core points for the aim of our study. We have used tables for quantitative data with textual description and content analysis for qualitative data, in order to express the degree of consistency in the evaluated article's findings.

Results

A total of 6 publications were considered relevant for major liver resections in emergency, from a total of 331 articles that were reviewed.

These six articles, published in internationally renowned journals, met the inclusion criteria of the present study. After thorough analysis, we highlight that a total of 237

Table I - *Patients' demographics and status at admission*

Authors	Year	Journal	Number of patients	Gender	Age (years)	Type of admission	Hypovolemic shock	Blood loss (ml)	Transfusions (RBC packs/FFP)
Dipengou, et al	2016	Digestive and Liver Disease	131	104 – male 27 – female	29-74 (mean 56,4)	direct hospitalization	62 patients (47,3%)	650 (500 - 2600)	1 - 9 RBC packs
Koray Kutluturk, et al	2013	Case Reports in Medicine	1	1 – female	72	direct hospitalization	1 patient (100%)	1500	6 RBC packs 4 FFP packs
P. Marini, et al	2002	Digestive Surgery	20	11 – male 9 – female	23-72 (mean 48,5)	direct hospitalization	3 patients (23%)	not specified	1 - 16 RBC packs
Kuan-chun Hsueh, et al	2012	World J Surg	54	39 – male 15 – female	28-85 (mean 61,5)	33 – transfer 21 – direct hospitalization	48 patients (88,8%)	not specified	not specified
Christine Leowardi, et al	2006	World J Gastroenterol	1	1 – male	76	direct hospitalization	0 patients	1000 - 2000	2 RBC packs
Fung, et al	2017	Hepatoma Res	30	26 – male 4 – female	54-71 (mean 56)	direct hospitalization	0 patients	390 - 1900	1 - 6 RBC packs

patients have undergone emergency major liver resections (Table I) [14-19].

Comparing the selected articles, in terms of demographic characteristics of the patients studied, they showed an increased number of males who underwent major liver resections, compared to females (181 males, 56 females; M: F = 3.2). The age of the patients in the studies, ranged from 23 to 85 years, resulting in an average age of 61.7 on all included studies. Most patients went directly to the emergency department (203 patients), while 33 patients were transferred from other medical services (Table I).

We analyzed the status of patients at admission. A number of 114 subjects were admitted with hypovolemic shock, representing 48.5% of the patients studied. Although some studies did not specify the blood loss experienced by the patient at the time of admission, the amount was between 390 and 2600 ml of blood loss. The average blood loss at admission, that we obtained, was approximately 1200 ml of fresh blood. All patients needed blood transfusions and received between 1 to 16 red blood cells packs (Table I).

Analyzing the characteristics of the tumors, we noticed that there were almost equally distributed between the right and left liver lobes and they suffered spontaneous rupture, with consecutive acute abdomen and eventually hypovolemic shock. Their size varied between 4 to 25 cm, with an average of 9.2 cm (Table II).

The therapeutic attitude consisted of emergency liver resections in 106 patients (44.3%) and staged interventions in 128 patients (54%). 1.7% of patients did not undergo any surgical intervention, conservative treatment and watch-full waiting being the approach of choice. There were performed: direct emergency hepatectomy or staged intervention, consisting in liver packing followed by emergency hepatectomy or transarterial embolization (TAE) followed by emergency hepatectomy (Table III). Intraoperatively, blood loss was evaluated between 50 and 1500 ml, with an average volume of 450 ml. Pringle manoeuvre was used for inflow control, for difficult haemostasias in patients included in the first two studies, meaning 132 patients (55.6%). The types of liver resections varied largely, depending on the patient's status and the location of the tumor. There were represented by left and right hepatectomy, central hepatectomy, bi- or trisegmentectomy, according to the Brisbane Classification (Table III).

Most tumors were malignant, proving hepatocellular carcinoma on histopathological evaluation, the benign ones were adenomas and one *Fasciola hepatica* infection.

Regarding the hospitalization period, patients ranged from 8 to 18 days, with an average of 12.7 days of hospitalization. Only one case was reported to be uncomplicated after surgery.

The short-term morbidity was reported between 20% and 50% and the in-hospital mortality was considered high, approximately 11%.

Synthesizing the postoperative complications, we noticed: wound infection, pulmonary infection, ascites, encephalopathy, bile leakage, subhepatic abscess and hemorrhage (12% accounting for major complications and 21% for minor complications) (Table III).

The 5-year survival rate of the patients studied in these publications ranged from 12 months to 45.7 months, highlighting the extreme case of one patient, who died on day 1 after surgery [20]. Calculating an average survival rate of all patients with major liver resections included in our study, we obtain a median of 24.6 months.

Discussion

Liver is one of the most affected organs by rupture or hemorrhage, despite it being a relatively well protected organ, due to its anatomical position. Management of liver emergency lesions has evolved over time from non-surgical treatment to selective surgery or major liver resections performed in emergency. Globally, hepatocellular carcinoma is the third leading cause of death, due to malignant tumors [21].

In our study, we analyzed six articles, that highlighted different emergency therapeutical approaches to liver tumors, complicated with rupture. As previously empha-

Table II - *Tumor specifications*

Authors	Localization	Trauma / spontaneous rupture	Diameter of lesion (cm)
Dipeng ou et all	Not specified	Not specified	10 (4 – 25)
Koray kutluturk et all	Right liver	Spontaneous rupture	4
P. Marini et all	Not specified	Spontaneous rupture	8,3 (4 – 17)
Kuan-chun hsueh et all	Right liver – 25 Left liver – 15 Bilateral – 14	Spontaneous rupture	10,3
Christine leowardi et all	Left	Spontaneous rupture	12,5
Fung et all	Right and left liver	Spontaneous rupture	10,5 (8,3 – 14,8)

Table III - *Therapeutic attitude*

Authors	Direct emergency resection	Staged intervention	Therapeutic procedure	Blood loss (ml)	Pringle maneuver	Resection type	Survival time (months)	Hospitalization period (days)	Postoperative complications
Dipengou, et al	73 patients	58 patients	Liver packing -> emergency hepatectomy	200 (150-450)	+	Left/ right hepatectomy Central hepatectomy Bi-/ trisegmentectomy	45.7	15,5	Wound infection Pulmonary infection Ascites Encephalopathy Bile leakage Subhepatic abscess
Koray Kutluturk, et al	1 patient	0 patients	Emergency hepatectomy	50	+	Trisegmentectomy (V,VI,VII)	not specified	8	No complications
P. Marini, et al	3 patients	13 patients	TAE -> emergency hepatectomy	not specified	not specified	not specified	12	not specified	not specified
Kuan-chun Hsueh, et al	19 patients	35 patients	TAEù -> emergency hepatectomy	not specified	not specified	Left/ right hepatectomy Bisegmentectomy	12	18	not specified
Christine Leowardi, et al	0 patients	1 patient	TAE -> hepatectomy	not specified	not specified	Left hepatectomy	1 day	10	Haemorrhage
Fung, et al	9 patients	21 patients	Emergency hepatectomy/ TAE -> emergency hepatectomy	850 - 1500	not specified	Left/ right hepatectomy Right posterior sectionectomy			

sized in literature, large hepatocellular carcinomas and adenomas were the most common types of tumors found at risk for spontaneous rupture [22].

Most patients, who have undergone emergency major liver resections were men. The average age of the patients evaluated was 61 years, as researchers have shown that the malignant transformation of liver tumors appears more commonly in elderly patients [23]. Most of the subjects were directly admitted in specialized medical centers; the others presented themselves to primary or secondary medical institutions, being subsequently transferred to tertiary centers, dedicated to hepato-biliary pathology. It is known that approximately 850,000 new cases of liver tumors are identified worldwide and the number of people who die from it is 800,000 per year. Studies have shown that patients with liver tumors are predominantly male and the age of patients with hepatocellular carcinoma is over 41 years [24].

Half of the patients were brought to the emergency room in hypovolemic shock. Clinically, they accused acute abdomen, rebound tenderness and marked pain. Contrast-enhanced CT examination is the gold standard in abdominal emergencies, quickly identifying the characteristics of the tumor, intraperitoneal fluid and reaching correct diagnosis. Active bleeding may indicate rupture of the liver tumor, which leads to fast general status alteration, with hemodynamical instability. Rapid body fluid resuscitation, blood transfusions and even ventilation assistance is necessary, in order to successfully stabilize these patients. Many studies emphasize the fact that the hemodynamic status of patients at admission is the most important factor influencing long term survival and prognosis [25].

Several articles have highlighted the fact that patients with hemodynamic instability, reduced liver function and large tumors present lower long-term survival and disease-free survival. Moreover, Trans-Arterial Embolization (TAE) treatment is also associated with 30-day mortality in patients with hepatocellular carcinoma. Other factors with significative impact on mortality include serum Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) and bilirubin levels, International normalized ratio (INR) and AST to Platelet Ratio Index (APRI) [26]. In contrast, a number of studies emphasize that TAE proves to be an essential factor for the long-term survival of patients with ruptured hepatocellular carcinoma, with demonstrated benefits. Consecutively, direct surgical intervention, such as major hepatectomy is indicated as a viable solution for prolonging survival rate, whenever the patient's general status permits it per primam [27,28]. Ruptured hepatocellular carcinoma determines not only bleeding from the affected liver parenchyma with following hemoperitoneum, but also diffuse intraperitoneal tumor spreading to impaired liver func-

tion. Emergency liver resections can eradicate the tumor, which is the bleeding source with clear, negative margins. Recent studies have shown that emergency liver resection is indicated in patients with preserved liver function, presenting single or a limited number of tumor formations localized in one lobe. But for those who have marked liver damage, at high risk for postoperative liver failure, emergency liver resection could further damage the precarious liver function. For this reason, Shimada et al. [29] and Miyamoto et al. [28] stressed out that delayed or post-TAE hepatectomy showed better survival rates and should be considered as the therapeutic course for spontaneously ruptured hepatocellular carcinoma. The role of TAE as stage treatment in case of liver tumor ruptures should be analyzed according to the patient's status and the infrastructure available in the medical center. Performance status, liver parameters, tumor characteristics should all be carefully considered before choosing a certain emergency therapeutic action, in order to prevent postoperative liver failure [30].

The general 30-day survival rate, cited in literature, for these kinds of patients was 85% and the one-year survival rate was 46%. For patients who have undergone emergency hepatectomy, the survival rate was higher, reaching 97% for 30 days and 62% for one year. The literature notes, that approximately 85% of patients with spontaneous liver rupture were diagnosed with hepatocellular carcinoma [19,20]. The need to treat these subjects in specialized centers is further emphasized. Conservative treatment is indicated for patients, who are not candidates for liver resection or embolization. TAE is noted as the first-line method for achieving hemostasis in these patients with close follow-up ulteriorly [18]. Patients with a stable hemodynamically and respiratory status, with acceptable liver function and resectable tumors on imaging, are the perfect candidates for liver resection as the first intention. Patients with questionable clinical and paraclinical data or with borderline tumors, could be treated with TAE as the first intention for hemostasis, followed by stabilization of hepatic functions and consecutive surgical resection [15]. The combination between TAE and major liver resections has significant advantages over the other therapeutical strategies, in regards with 5-year survival rate [23]. No study determines the survival rate in emergency resections compared to the elective ones, but considerable differences appear between emergency hepatectomies and staged interventions regarding mortality (11% versus 1%) and complications (12.3% versus 6.9%) [15].

The limitations of our study mostly reflect the rare conditions evaluated and scarcity of information regarding the subject approached, implying the small number of articles available in the literature. Therefore, the impossibility to apply an extremely strict exclusion criteria and the heterogeneity of the data based on the number of cases treated in each article, blood loss volume, blood transfusions and complications, impediments which are highly reliant on the investigator's preferences or resources.

Conclusions

The management of emergency liver interventions has increasingly developed over the last 20 years, succeeding in performing major liver interventions in emergency. The analyzed studies highlighted the predominance of male sex and advanced age in patients with malignancies. Most patients admitted to the emergency room end up in hypovolemic shock due to acute bleeding. This indicates a high rate of possible postoperative complications. It is highlighted that emergency major liver resection can prolong survival even if the cause is usually malignancy, when the tumor can be resected with negative resection margins, both per primam or staged approach according to each case specifically.

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