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Retrospective Study

Peri-operative score for elderly patients with resectable hepatocellular carcinoma

a clinical risk score

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Abstract

BACKGROUND

Liver resection is the mainstay for a curative treatment for patients with resectable hepatocellular carcinoma (HCC), also in elderly population. Despite this, the evaluation of patient condition, liver function and extent of disease remains a demanding process with the aim to reduce postoperative morbidity and mortality.

AIM

The aim of this study is to identify new perioperative risk factors that could be associated with higher 90- and 180- day mortality in elderly patients eligible for liver resection for HCC considering traditional perioperative risk scores and to develop a risk score.

METHODS

A multicentric, retrospective study was performed by reviewing the medical records of patients aged 70years or older who electively underwent liver resection for HCC; several independent variables correlated with death from all causes at 90 and 180 days were studied. The coefficients of Cox regression proportional-hazards model for six-month mortality were rounded to the nearest integer to assign risk factors' weights and derive the scoring algorithm.

RESULTS

Multivariate analysis found variables (ASA score, high rate of comorbidities , MELD score and size of biggest lesion)that had independent correlations with increased 90- and 180- day mortality. A clinical risk score was developed with survival profiles.

CONCLUSION

This score can aid in stratifying this population in order to assess who can benefit from surgical treatment in terms of postoperative mortality.

Key Words: Hepatocellular carcinoma; score; Laparoscopy; Surgical resection; Elderly patients; multivariate analysis

1 Conticchio M, Inchingolo R, Delvecchio A, Ratti F, Gelli M, Anelli MF, Laurent A, Vitali GC, Magistri P, Assirati G, Felli E, Wakabayashi T, Pessaux P, Piardi T, di Benedetto F, de'Angelis N, Briceño J, Rampoldi A, Adam R, Cherqui D, Aldrighetti LA, Memeo R. Peri-operative score for elderly patients with resectable hepatocellular carcinoma . *World J Hepatol* 2023; In press

Core Tip: To support the decision-making process in elderly patient with resectable hepatocellular carcinoma (HCC) and understand who can benefit from surgical treatment in terms of postoperative mortality, we analyzed data from 11 hepato-biliary centers during a 10-years period. A multivariate analysis was performed to find

variables (ASA score, high rate of comorbidities, MELD score and size of biggest lesion) that had independent correlations with increased 90- and 180- day mortality. The evaluation of elderly patients who underwent liver resection for HCC need to be supported by any form of possible analysis of risk.

INTRODUCTION

The life expectancy of the population has increased in recent years, and this led to an increased rate of malignant disease in elderly population [1,2]. Hepatocellular carcinoma (HCC) became even more frequent in elderly population [3,4].

According to current guidelines liver resection, ablation and liver transplant are still the mainstay treatments for HCC.

Liver resection presented better overall and disease-free survival than other curative treatments[5,6]. Despite this, liver resection presented a significant risk postoperative morbidity and mortality.

The approach of liver disease in elderly population needed of an accurate stratification of patients at risk, with the involvement of multidisciplinary preoperative assessment.

The aim of our study was to analyze a population of elderly patients who underwent liver resection for HCC, to investigate the possible presence of risk predictors of postoperative mortality at 90 and 180 days.

MATERIALS AND METHODS

Study Design

A multicentric, retrospective cohort study was carried out by reviewing the medical records of patients aged> 70 years or over undergoing liver resection for HCC from January 2009 to January 2019. We evaluated all preoperative independent variables linked with patients (demographics data), with lesion (number and size, calculated on the preoperative imaging) and preoperative clinical assessment in eligible patients. The primary endpoint was to define 90day and 180day mortality rate. The second one was to explore the association among variables and post operative mortality rate.

Statistical Analysis

All analyses were conducted using STATA software, version 16 (Stata-Corp LP, College Station, Tex). Data are reported as means (standard deviations) for continuous variables or numbers (percentages) of patients for categorical variables. Six-month follow-up was chosen to analyze at least 20 fatal events after the surgery. Associations between baseline pre-operative variables with six-month mortality were evaluated using a univariate Cox proportional-hazards model. A score point system was derived from the multivariable Cox proportional-hazards model including univariate predictors with $p<0.05$. For a dichotomous risk factor, the estimated regression coefficient was rounded to the nearest integer. For a non-dichotomous risk factor, continuous or discrete, the estimated regression coefficient was multiplied by observed values, rounded to the nearest integer and rescaled to assign zero points to the lowest risk-category. Hazard Ratios (HRs) with their 95% confidence intervals (CI) were reported. The discriminative ability of the models was assessed using the Harrell's concordance index (C-index). Patients were stratified into three groups of risk by the estimated six-month mortality probability (low-risk <5%, mid-risk 5-10%, and high-risk >10%). The cumulative mortality was displayed using Kaplan-Meier estimates with comparison between curves based on the Log-Rank statistic. The score was internally validated by resampling 1000 bootstrap replications. The bias was calculated as the difference between estimation and the mean of the bootstrap sample. Theoretical profiles were constructed by combining variables of the final model as well as a risk score for death in the period. The cut off of 6 mo as final follow up has been chosen to obtain an appropriate number of events, but its significance was validate at 3 mo. A p value <0.05 was considered statistically significant.

RESULTS

A total of 429 patients, who underwent liver resection for HCC were included (**Table 1**). The majority of patients were male (n = 319, 74.3%, and 110 females, 25.7%), aged ≥70

years (mean of 75.3±4.1 years); 20 deaths (4.7%) occurred up to 180 days after surgery, as shown in **Table 1**.

257 patients, 60% presented an ASA (American Society of Anesthesiology) score III-IV, and the median range of MELD score was 7 (7.4±2.1). Roughly one third of patients was affected by more of 2 comorbidities (n = 142, 33.1%). Most patients presented a single, unilobar lesion (n = 421, 98%). Most of patients underwent to a minor hepatectomy, while only 54 patients (13.1%) underwent to a major hepatectomy, according to Brisbane classification.

The overall survival curve calculated by the Kaplan–Meier estimator is shown in **Figure 1**. The ASA score, MELD score, the presence of Comorbidities>2 and the size of the biggest lesion presented in the univariate analysis an HR greater than 1, as shown in **Table 1**. They are used as predictor factors in the multivariate analysis (**Table 2**). Table 3 showed a score system which provides a balanced weight for each variable. Combining the four variables we obtained different profiles of patients with a different preoperative risk, based on personal score, groupable in a low-risk (<5% at 6 mo), mid-risk (5-10% at 6 mo) and high-risk class (>10% at 6 mo) (**Table 4** and **Figure 2**).

Figure 2 showed the curves of six-month mortality probability, according to the different profile created on various score. The rate of mortality probability significantly increased from patients with score2 to patients with score6: patients wtith a score ≥2 presented a 5.7% of mortality, patients with a score≥3 presented a 7%, patients with a score≥4 showed a 9.3% of mortality, patients with a score≥5 showed a 13.6%, patients with a score≥6 presented 22.9% of mortality.

We performed an Internal validation using a bootstrapping technique with 1000 resamples, the derived score point system had good discrimination as 0.803 of the Harrell C-Index (bootstrap 95%CI 0.741-0.875). The bias of the estimated risk assigned to 1 point of the score, as the difference between coefficient estimation in the derivation model (0.875) and the mean of the bootstrap sample (0.888), it was negligible (-0.013).

DISCUSSION

The present study observed a population of elderly patients (≥70 years) who underwent liver resection for HCC , and it showed that a simple preoperative score, resulting from the evaluation of presence and degree of ASA score, MELD score, the presence of more than 2 comorbidities and the size of the biggest lesion, can predict 90d and 180d mortality rate.

The process of 'aging society' resulted in an increasing rate of surgical oncological elderly patients and it made necessary to provide an accurate preoperative assessment to optimize the choice of the best possible treatment. Liver resection represented the treatment of choice for resectable HCC, even in elderly population[7,8,9,10]. Age itself should not be a contraindication to liver resection in treatment of HCC, but this population needed a more accurate selection and preoperative evaluation of benefit and drawnback.

The assessment of liver function needed to be linked with the identification of modifiable and not modifiable risk factors to improve surgical outcomes. There were several predictive of 30d mortality after liver resection for HCC[11,12,13,14,15]. MELD score was often considered a significant parameter, as well in our study where this score was ranged in 3 degrees with a different impact on final sum. Conversely Lee *et al* in a nationwide cohort study recognized the PALBI score had an higher sensitivity and specificity than MELD or ALBI score[16].

With the aim to better explore the concept of 'frailty' in this population also the ASA score gained more relevance. In our results an ASA score of 1-2 or 3-4 can weight in a different significantly way on the final score and so have impact on the post operative mortality probability. Not only the evaluation of the degree of pathological physical state, but also the presence of more of 2 comorbidities resulted significant as risk predictor in our score. The limit was represented by not knowing the type of comorbidity which made impossible to optimize the stratification. Preoperative evaluation of the physiological age could be more useful in predicting risk of postoperative morbidity and mortality than chronological age[17,18,19], but several external validation of comprehensive score are needed.

As previously reported the size of largest tumor was a useful factor to predict prognostic outcomes after liver resection for HCC[20,14,21,22]. Also our results showed in univariate and multivariate analysis how an increasing size could be a risk factor on postoperative mortality. In the setting of liver disease almost completely represented by a single nodule of HCC, a size>32mm could impact on postoperative mortality risk as a MELD score>12. The idea of the importance of morphological tumor data was yet explored by Mazzaferro with 'Metroticket paradigm'[23] before, and 'Up to7 criteria'[24] after, more useful in the context of liver transplantation, but it had represented the substrate for comprehensive measures as reported by Tokumitsu with its NxS score which provide a cut off value of tumor burden to predict the prognosis following hepatectomies for HCC[14]. Despite this, prognosis of HCC was more complex than other solid tumors because it depended not only from tumor burden but also from liver function reserve.

ASA score, MELD score, the presence of more than 2 comorbidities and the size of the lesion were all non-modifiable factor. Our work underlined how the process of decision making could be delicate in elderly patients with HCC. The association of evaluation of liver (functional and oncological) disease and the physiological age of patients needed to be assessed before surgery[25,26,27] to better stratifying patients at risk and to implement preoperative and postoperative programs of rehabilitation which could bridge the gap of physiopathological state[28,29].

3 However, this study had some limitations. First of all, because of its retrospective nature, there was a possibility of an unavoidable selection bias. Secondly, the surgical procedures included were laparoscopic and open approach without considering their different impact on the postoperative outcomes. In addition, our aim was to evaluate 90 and 180d mortality but another key point was represented by postoperative complications and their correlations with preoperative and intraoperative data. This could be the focus for future works.

CONCLUSION

In conclusion, our score resulted from granular evaluation of possible risk factors for the postoperative mortality at 90d and 180d in elderly patients resected for HCC.
It would be a simple and useful tool to provide a better cognition of patients who could benefit of liver resection and to improve 180d mortality.

ARTICLE HIGHLIGHTS

Research background

Liver resection represented one of the mainstay treatment for HCC. The approach of liver disease in elderly population needed of an accurate stratification of patients at risk, with the involvement of multidisciplinary preoperative assessment.

Research motivation

Liver resection is burdened by a variable rate of postoperative morbidity and mortality. Elderly patients represented more often the major rate of patients who underwent liver resection for HCC. This aspect make mandatory an accurate preoperative assessment and a specific evaluation of potential postoperative risk.

Research objectives

The aim of our study was to analyze a population of elderly patients who underwent liver resection for HCC, to investigate the possible presence of risk predictors of postoperative mortality at 90 and 180 days

Research methods

Associations between baseline pre-operative variables with six-month mortality were evaluated using a uni-variate Cox proportional-hazards model. A score point system was derived from the multi-variable Cox proportional-hazards model .

Research results

The ASA score, MELD score, the presence of Comorbidities>2 and the size of the biggest lesion are included in the stratification of the score. Combining the four variables we obtained different profiles of patients with a different preoperative risk at 6 mo: low-risk <5%, mid-risk 5-10% and high-risk class >10%

Research conclusions

This score can aid in stratifying this population in order to assess who can benefit from surgical treatment in terms of postoperative mortality

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Research perspectives

Randomized controlled studies are needed to better explore these results.

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