ORIGINAL ARTICLE

Retrospective Study

Peri-operative score for elderly patients with resectable hepatocellular carcinoma

Maria Conticchio, Riccardo Inchingolo, Antonella Delvecchio, Francesca Ratti, Maximiliano Gelli, Massimiliano Ferdinando Anelli, Alexis Laurent, Giulio Cesare Vitali, Paolo Magistri, Giacomo Assirati, Emanuele Felli, Taiga Wakabayashi, Patrick Pessaux, Tullio Piardi, Fabrizio di Benedetto, Nicola de'Angelis, Javier Briceño, Antonio Rampoldi, Renè Adam, Daniel Cherqui, Luca Antonio Aldrighetti, Riccardo Memeo

Maria Conticchio, Antonella Delvecchio, Riccardo Memeo, Unit of Hepato-Pancreatic-Biliary Surgery, "F. Miulli" Regional General Hospital, Acquaviva Delle Fonti 70021, Italy

Riccardo Inchingolo, Interventional Radiology Unit, Department of Radiology, "F. Miulli" Regional General Hospital, Acquaviva Delle Fonti 75100, Italy

Francesca Ratti, Luca Antonio Aldrighetti, Hepatobiliary Surgery Division, IRCSS San Raffaele Scientific Institute, Milan 20132, Italy

Francesca Ratti, Luca Antonio Aldrighetti, Hepatobiliary Surgery Division, Vita-Salute San Raffaele University, Milan 20132, Italy

Maximiliano Gelli, Département de Chirurgie Viscérale, Gustave Roussy Cancer Campus Grand Paris, Paris 94800, France

Massimiliano Ferdinando Anelli, Unit of Oncologic and Pancreatic Surgery, Hospital University Reina Sofía, Cordoba 14004, Spain

Alexis Laurent, Department of Digestive and Hepatobiliary Surgery, Assistance Publique-Hôpitaux de Paris, Créteil 94000, France

Giulio Cesare Vitali, Service of Abdominal Surgery, Poliambulanza Foundation, Brescia 25124, Italy

Paolo Magistri, Giacomo Assirati, Fabrizio di Benedetto, Hepato-Pancreato-Biliary Surgery and Liver Transplantation Unit, University of Modena and Reggio Emilia, Modena 41121, Italy

Emanuele Felli, Taiga Wakabayashi, Department of Surgery, Institut de Recherche Contre les Cancers de l'Appareil Digestif (IRCAD), Strasbourg 67000, France

Patrick Pessaux, Service de Chirurgie Viscérale et Digestive, Nouvel Hôpital Civil, Unité INSERM U1110, Strasbourg 67000, France

Tullio Piardi, Department of Surgery, Hôpital Robert Debré, Reims 51092, France

Nicola de'Angelis, Assistance Publique-Hôpitaux de Paris, Centre Hospitalier Universitaire Henri Mondor, Paris 94000, France

Javier Briceño, Unit of Hepatobiliary Surgery and Liver Transplantation, Hospital University Reina Sofía, Cordoba 14004, Spain

Antonio Rampoldi, Interventional Radiology Unit, Niguarda Hospital, Milan 20162, Italy

Renè Adam, Daniel Cherqui, Department of Surgery, Centre Hepatobiliaire, Hopital Paul Brousse, Paris 94000, France

Corresponding author: Riccardo Inchingolo, MD, Director, Doctor, Interventional Radiology Unit, Department of Radiology, "F. Miulli" Regional General Hospital, Strada Per Santeramo, Acquaviva Delle Fonti 75100, Italy. riccardoin@hotmail.it

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
To identify new perioperative risk factors that could be associated with higher 90- and 180-d 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 70 years or older who electively underwent liver resection for HCC; several independent variables correlated with death from all causes at 90 and 180 d 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 (American Society of Anesthesiology score, high rate of comorbidities, Mayo end stage liver disease score and size of biggest lesion) that had independent correlations with increased 90- and 180-d 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

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 hepatobiliary centers during a 10-years period. A multivariate analysis was performed to find variables (American Society of Anesthesiology score, high rate of comorbidities, Mayo end stage liver disease score and size of biggest lesion) that had independent correlations with increased 90- and 180-d 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]. 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 d.

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 90 d and 180 d 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%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 validated 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 d after surgery, as shown in Table 1.

Two hundred fifty-seven patients, 60% presented an American Society of Anesthesiology (ASA) score III-IV, and the median range of Mayo end stage liver disease (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 score 2 to patients with score 6: Patients with 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).

Table 1 Characteristics of samples used to study the variables and deaths 180 d after surgery, *n* (%)

	All		Alive at 180 d		Death at 180 d		HR	P value
	N	n = 429	N	n = 409	N	n = 20		
Age, yr	429	75.3 ± 4.1	409	75.3 ± 4.1	20	76.9 ± 4.9	1.52 (0.94-2.47)	0.086
Male	429	319 (74.4)	409	306 (74.8)	20	13 (65.0)	0.61 (0.24-1.54)	0.296
BMI	429	26.9 ± 3.5	409	26.9 ± 3.6	20	26.9 ± 0.9	0.97 (0.52-1.82)	0.921
ASA score	429	2.60 ± 0.50	409	2.59 ± 0.50	20	2.90 ± 0.31	4.49 (1.47-13.74)	0.008
Comorbidity > 2	429	142 (33.1)	409	129 (31.5)	20	13 (65.0)	3.92 (1.56-9.82)	0.004
HBV	429	80 (18.6)	409	80 (19.6)	20	0 (0.0)	-	-
HCV	429	217 (50.6)	409	210 (51.3)	20	7 (35.0)	0.51 (0.2-1.28)	0.151
ALD	429	60 (14.0)	409	56 (13.7)	20	4 (20.0)	1.58 (0.53-4.72)	0.415
Others	429	72 (16.8)	409	63 (15.4)	20	9 (45.0)	4.3 (1.78-10.37)	0.001
F4 cirrhosis	429	178 (41.5)	409	173 (42.3)	20	5 (25.0)	0.46 (0.17-1.27)	0.134
CHILD A	429	370 (86.2)	409	353 (86.3)	20	17 (85.0)	0.92 (0.27-3.13)	0.891
MELD score	429	7.4 ± 2.1	409	7.4 ± 2.0	20	8.9 ± 2.7	1.25 (1.09-1.44)	0.001
Albumin	382	3.80 ± 0.60	367	3.80 ± 0.60	15	3.71 ± 0.77	0.75 (0.33-1.73)	0.504
Bilirubin	424	1.05 ± 0.64	404	1.05 ± 0.64	20	0.99 ± 0.54	0.81 (0.37-1.76)	0.587
Creatinin	425	1.03 ± 0.36	405	1.02 ± 0.36	20	1.17 ± 0.42	2.55 (0.9-7.2)	0.077
INR	422	1.20 ± 0.23	402	1.20 ± 0.23	20	1.17 ± 0.28	0.51 (0.07-3.8)	0.508
AST	424	68 ± 61	405	69 ± 61	19	48 ± 41	0.92 (0.85-1)	0.045
ALT	201	51 ± 80	182	52 ± 82	19	41 ± 48	0.98 (0.91-1.05)	0.540
GGT	192	145 ± 218	174	145 ± 218	18	146 ± 228	1 (0.98-1.02)	0.958
Platelets	425	191 ± 92	406	191 ± 92	19	177 ± 85	0.98 (0.93-1.04)	0.509
Number of lesions	429	1.09 ± 0.30	409	1.09 ± 0.31	20	1.05 ± 0.22	0.54 (0.08-3.77)	0.531
Size of biggest lesion (mm)	429	33 ± 10	409	32 ± 10	20	37 ± 13	1.26 (1.01-1.58)	0.043
Bilobar lesion	429	8 (1.9)	409	8 (2.0)	20	0 (0.0)	-	-
Preop treatment	429	53 (12.4)	409	50 (12.2)	20	3 (15.0)	1.24 (0.36-4.23)	0.732
Major HTC	429	56 (13.1)	409	55 (13.4)	20	1 (5.0)	0.34 (0.05-2.56)	0.297

BMI: Body mass index; ASA: American Society of Anesthesiology; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; Major HTC: Hepatectomy; ALD: Alcoholic liver disease; HBV: Hepatitis B virus; HCV: Hepatitis C virus; MELD: Mayo end liver disease score; INR: International normalized ratio; HR: Hazard ratio.

Table 2 Multivariate analysis

	Beta	HR	P value
ASA score	1.189	3.28 (1.04-10.34)	0.042
Comorbidity 2	1.071	2.92 (1.14-7.45)	0.025
MELD	0.202	1.22 (1.06-1.41)	0.005
Size of largest lesion	0.046	1.05 (1.01-1.09)	0.034
C-index = 0.807	-	-	-

ASA: American Society of Anesthesiology; MELD: Mayo end liver disease; HR: Hazard ratio.

Table 3 Score point system

	Values	Points
ASA score	1	0
	2	0
	3	2
	4	3
Comorbidity > 2	Yes	1
MELD	< 8	0
	8-12	1
	> 12	2
Size of largest lesion (mm)	≤ 10	0
	10-32	1
	> 32	2
	Max score	8

ASA: American Society of Anesthesiology; MELD: Mayo end liver disease.

Table 4 Stratification of mortality risk on preoperative score

Score	Number and prevalence, *n* (%)	Three-month mortality, %	Six-month mortality, %
≥ 2 *vs* ≤ 1	366 (85.3) *vs* 63 (14.7)	3.3 *vs* 0.0	5.7 *vs* 0.0
≥ 3 *vs* ≤ 2	296 (69.0) *vs* 133 (31.0)	4.1 *vs* 0.0	7.0 *vs* 0.0
≥ 4 *vs* ≤ 3	213 (49.7) *vs* 216 (50.3)	5.3 *vs* 0.5	9.3 *vs* 0.5
≥ 5 *vs* ≤ 4	102 (23.8) *vs* 327 (76.2)	5.0 *vs* 2.2	13.6 *vs* 2.2
≥ 6 *vs* ≤ 5	28 (6.5) *vs* 401 (93.5)	11.3 *vs* 2.3	22.9 *vs* 3.6

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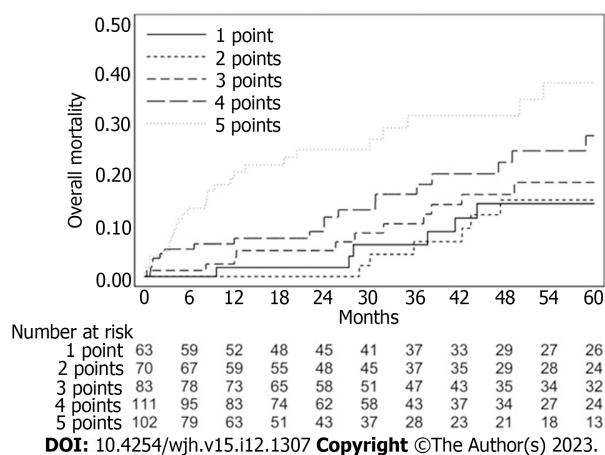
Figure 1 Overall mortality.

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 90 d and 180 d mortality rate.
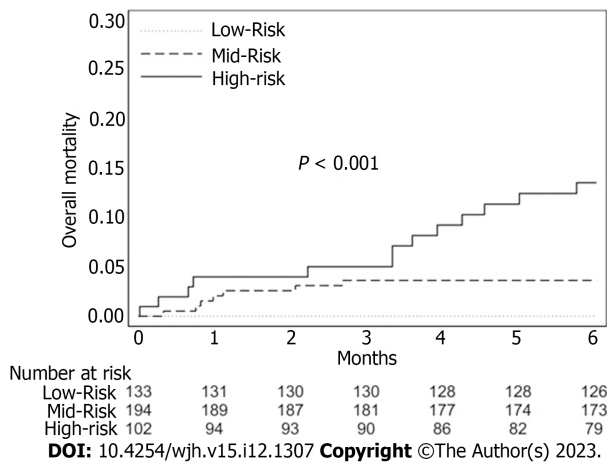
Figure 2 Profile risk of six-month mortality probability.

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[6-9]. 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 benefits and drawback.

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 30 d mortality after liver resection for HCC[10-13]. 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*[14] in a nationwide cohort study recognized the Platelet-Albumin-Bilirubin score had an higher sensitivity and specificity than MELD or Albumin-Bilirubin score[15].

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 [16,17], 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[13,18,19]. 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 > 32 mm 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[18] with 'Metroticket paradigm' before, and 'Up to7 criteria' after, more useful in the context of liver transplantation, but it had represented the substrate for comprehensive measures as reported by Tokumitsu *et al*[12] with its NxS score which provide a cut off value of tumor burden to predict the prognosis following hepatectomies for HCC[12]. 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[19-20] to better stratifying patients at risk and to implement preoperative and postoperative programs of rehabilitation which could bridge the gap of physiopathological state[21].

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 180 d 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 90 d and 180 d 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 180 d mortality.

ARTICLE HIGHLIGHTS

Research background

Liver resection represented one of the mainstay treatment for hepatocellular carcinoma (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 makes 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 d.

Research methods

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

Research results

The American Society of Anesthesiology (ASA) score, Mayo end stage liver disease 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.

Research perspectives

Randomized controlled studies are needed to better explore these results.

FOOTNOTES

ORCID number: Maria Conticchio 0000-0003-3177-5274; Riccardo Inchingolo 0000-0002-0253-5936; Antonella Delvecchio 0000-0002-7759-4340; Francesca Ratti 0000-0002-4710-6940; Maximiliano Gelli 0000-0001-9807-4021; Massimiliano Ferdinando Anelli 0000-0002-0916-1949; Alexis Laurent 0000-0003-1372-0843; Giulio Cesare Vitali 0000-0001-8956-0247; Paolo Magistri 0000-0001-8326-069X; Giacomo Assirati 0000-0001-8240-1497; Emanuele Felli 0000-0002-6510-1457; Taiga Wakabayashi 0000-0002-5074-0205; Patrick Pessaux 0000-0001-5635-7437; Tullio Piardi 0000-0001-6704-3206; Fabrizio di Benedetto 0000-0002-6718-8760; Nicola de'Angelis 0000-0002-1211-4916; Javier Briceño 0000-0001-7027-7898; Antonio Rampoldi 0000-0003-2494-5925; Renè Adam 0000-0003-2169-5449; Daniel Cherqui 0000-0001-5270-2731; Luca Antonio Aldrighetti 0000-0001-7729-2468.

REFERENCES

1   **Marosi C**, Köller M. Challenge of cancer in the elderly. *ESMO Open* 2016; **1**: e000020 [PMID: 27843603 DOI: 10.1136/esmoopen-2015-000020]

2   **Sav A**, McMillan SS, Akosile A. Burden of Treatment among Elderly Patients with Cancer: A Scoping Review. *Healthcare (Basel)* 2021; **9** [PMID: 34069688 DOI: 10.3390/healthcare9050612]

3   **Ferlay J**, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359-E386 [PMID: 25220842 DOI: 10.1002/ijc.29210]

4   **Petrick JL**, Florio AA, Znaor A, Ruggieri D, Laversanne M, Alvarez CS, Ferlay J, Valery PC, Bray F, McGlynn KA. International trends in hepatocellular carcinoma incidence, 1978-2012. *Int J Cancer* 2020; **147**: 317-330 [PMID: 31597196 DOI: 10.1002/ijc.32723]

5   **Galle PR**, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul JL, Schirmacher P, Vilgrain V; European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2018; **69**: 182-236 [PMID: 29628281 DOI: 10.1016/j.jhep.2018.03.019]

6   **Kaibori M**, Yoshii K, Yokota I, Hasegawa K, Nagashima F, Kubo S, Kon M, Izumi N, Kadoya M, Kudo M, Kumada T, Sakamoto M, Nakashima O, Matsuyama Y, Takayama T, Kokudo N; Liver Cancer Study Group of Japan. Impact of Advanced Age on Survival in Patients Undergoing Resection of Hepatocellular Carcinoma: Report of a Japanese Nationwide Survey. *Ann Surg* 2019; **269**: 692-699 [PMID: 28922205 DOI: 10.1097/SLA.0000000000002526]

7   **Smith BD**, Smith GL, Hurria A, Hortobagyi GN, Buchholz TA. Future of cancer incidence in the United States: burdens upon an aging, changing nation. *J Clin Oncol* 2009; **27**: 2758-2765 [PMID: 19403886 DOI: 10.1200/JCO.2008.20.8983]

8   **Conticchio M**, Inchingolo R, Delvecchio A, Laera L, Ratti F, Gelli M, Anelli F, Laurent A, Vitali G, 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. Radiofrequency ablation vs surgical resection in elderly patients with hepatocellular carcinoma in Milan criteria. *World J Gastroenterol* 2021; **27**: 2205-2218 [PMID: 34025074 DOI: 10.3748/wjg.v27.i18.2205]

9   **Conticchio M**, Delvecchio A, Ratti F, Gelli M, Anelli FM, Laurent A, Vitali GC, Magistri P, Assirati G, Felli E, Wakabayashi T, Pessaux P, Piardi T, Di Benedetto F, de'Angelis N, Javier Briceno DF, Rampoldi AG, Adam R, Cherqui D, Aldrighetti L, Memeo R. Laparoscopic surgery versus radiofrequency ablation for the treatment of single hepatocellular carcinoma ≤3 cm in the elderly: a propensity score matching analysis. *HPB (Oxford)* 2022; **24**: 79-86 [PMID: 34167892 DOI: 10.1016/j.hpb.2021.05.008]

10   **Takagi K**, Umeda Y, Yoshida R, Nobuoka D, Kuise T, Fushimi T, Fujiwara T, Yagi T. Preoperative Controlling Nutritional Status Score Predicts Mortality after Hepatectomy for Hepatocellular Carcinoma. *Dig Surg* 2019; **36**: 226-232 [PMID: 29672297 DOI: 10.1159/000488215]

11   **Shen J**, Tang L, Zhang X, Peng W, Wen T, Li C, Yang J, Liu G. A Novel Index in Hepatocellular Carcinoma Patients After Curative Hepatectomy: Albumin to Gamma-Glutamyltransferase Ratio (AGR). *Front Oncol* 2019; **9**: 817 [PMID: 31612101 DOI: 10.3389/fonc.2019.00817]

12   **Tokumitsu Y**, Shindo Y, Matsui H, Matsukuma S, Nakajima M, Suzuki N, Takeda S, Wada H, Kobayashi S, Eguchi H, Ueno T, Nagano H. Utility of scoring systems combining the product of tumor number and size with liver function for predicting the prognosis of patients with hepatocellular carcinoma after hepatectomy. *Oncol Lett* 2019; **18**: 3903-3913 [PMID: 31516601 DOI: 10.3892/ol.2019.10688]

13   **Moris D**, Shaw BI, Ong C, Connor A, Samoylova ML, Kesseli SJ, Abraham N, Gloria J, Schmitz R, Fitch ZW, Clary BM, Barbas AS. A simple scoring system to estimate perioperative mortality following liver resection for primary liver malignancy-the Hepatectomy Risk Score (HeRS). *Hepatobiliary Surg Nutr* 2021; **10**: 315-324 [PMID: 34159159 DOI: 10.21037/hbsn.2020.03.12]

14   **Lee SK**, Song MJ, Kim SH, Park M. Comparing various scoring system for predicting overall survival according to treatment modalities in hepatocellular carcinoma focused on Platelet-albumin-bilirubin (PALBI) and albumin-bilirubin (ALBI) grade: A nationwide cohort study. *PLoS One* 2019; **14**: e0216173 [PMID: 31048923 DOI: 10.1371/journal.pone.0216173]

15   **Okinaga H**, Yasunaga H, Hasegawa K, Fushimi K, Kokudo N. Short-Term Outcomes following Hepatectomy in Elderly Patients with Hepatocellular Carcinoma: An Analysis of 10,805 Septuagenarians and 2,381 Octo- and Nonagenarians in Japan. *Liver Cancer* 2018; **7**: 55-64 [PMID: 29662833 DOI: 10.1159/000484178]

16   **Tokumitsu Y**, Sakamoto K, Tokuhisa Y, Matsui H, Matsukuma S, Maeda Y, Sakata K, Wada H, Eguchi H, Ogihara H, Fujita Y, Hamamoto Y, Iizuka N, Ueno T, Nagano H. A new prognostic model for hepatocellular carcinoma recurrence after curative hepatectomy. *Oncol Lett* 2018; **15**: 4411-4422 [PMID: 29556288 DOI: 10.3892/ol.2018.7821]

17   **Tokumitsu Y**, Tamesa T, Matsukuma S, Hashimoto N, Maeda Y, Tokuhisa Y, Sakamoto K, Ueno T, Hazama S, Ogihara H, Fujita Y, Hamamoto Y, Oka M, Iizuka N. An accurate prognostic staging system for hepatocellular carcinoma patients after curative hepatectomy. *Int J Oncol* 2015; **46**: 944-952 [PMID: 25524574 DOI: 10.3892/ijo.2014.2798]

18   **Mazzaferro V**. Results of liver transplantation: with or without Milan criteria? *Liver Transpl* 2007; **13**: S44-S47 [PMID: 17969068 DOI: 10.1002/Lt.21330]

19   **McCorkle R**, Strumpf NE, Nuamah IF, Adler DC, Cooley ME, Jepson C, Lusk EJ, Torosian M. A specialized home care intervention improves survival among older post-surgical cancer patients. *J Am Geriatr Soc* 2000; **48**: 1707-1713 [PMID: 11129765 DOI: 10.1111/j.1532-5415.2000.tb03886.x]

20   **Kaibori M**, Matsushima H, Ishizaki M, Kosaka H, Matsui K, Ogawa A, Yoshii K, Sekimoto M. Perioperative Geriatric Assessment as A Predictor of Long-Term Hepatectomy Outcomes in Elderly Patients with Hepatocellular Carcinoma. *Cancers (Basel)* 2021; **13** [PMID: 33671388 DOI: 10.3390/cancers13040842]

21   **Melloul E**, Hübner M, Scott M, Snowden C, Prentis J, Dejong CH, Garden OJ, Farges O, Kokudo N, Vauthey JN, Clavien PA, Demartines N. Guidelines for Perioperative Care for Liver Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. *World J Surg* 2016; **40**: 2425-2440 [PMID: 27549599 DOI: 10.1007/s00268-016-3700-1]