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REVIEW

Serum biomarkers and risk of hepatocellular carcinoma recurrence after liver transplantation

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Abstract

Liver transplantation (LT) is the only potentially curative treatment for selected patients with cirrhosis and hepatocellular carcinoma (HCC) who are not candidates for resection. When the Milan criteria are strictly applied, 75% to 85%of 3- to 4-year actuarial survival rates are achieved, but up to 20% of the patients experience HCC recurrence after transplantation. The Milan criteria are based on the preoperative tumor macromorphology, tumor size and number on computed tomography or magnetic resonance imaging that neither correlate well with posttransplant histological study of the liver explant nor accurately predict HCC recurrence after LT, since they do not include objective measures of tumor biology. Preoperative biological markers, including alpha-fetoprotein, des-gamma-carboxiprothrombin or neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio, can predict the risk for HCC recurrence after transplantation. These biomarkers have been proposed as surrogate markers of tumor differentiation and vascular invasion, with varied risk magnitudes depending on the defined cutoffs. Different studies have shown that the combination of one or several biomarkers integrated into prognostic models predict the risk of HCC recurrence after LT more accurately than Milan criteria alone. In this review, we focus on the potential utility of these serum biological markers to improve the performance of Milan criteria to identify patients at high risk of tumoral

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recurrence after LT.

Key words: Hepatocellular carcinoma; Liver transplantation; Recurrence; Selection criteria; Prognostic score; Biomarker; Alpha-fetoprotein; Systemic inflammatory marker

Core tip: The Milan criteria for liver transplantation have improved survival of patients with small hepatocellular carcinoma (HCC), but up to 20% of patients still experience HCC recurrence after transplantation. Microvascular invasion and tumors with poor histologic grade of differentiation are the most important risk factors for HCC recurrence, but they are evidenced after surgery on explant pathology examination. Several surrogate pretransplant biomarkers, directly related with tumor biology or systemic inflammation markers conditioning tumor progression, have been suggested to identify, alone or integrated in pretransplant prognostic scores, patients at high risk of HCC recurrence after liver transplantation.

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INTRODUCTION

Liver transplantation (LT) is the best treatment option for selected patients with cirrhosis and small hepatocellular carcinoma (HCC) who are not candidates for resection. Mazzaferro *et al*[1] proposed the Milan criteria in 1996 for selection of patients with HCC for LT (defined as single lesion ≤ 5 cm, up to three separate lesions with none larger than 3 cm, no evidence of gross vascular invasion, and no regional nodal or distant metastases), and since then they have been applied worldwide. Patients fulfilling these criteria achieve similar survival rates as patients with LT without malignancies, of about 75% to 85% at 3 and 4 years respectively[2]. However, albeit that the Milan criteria are considered too restrictive and limiting for the transplantation option, HCC recurrence develops after LT in up to 20% of the patients[1-3], having adverse negative impact on patient survival. A poor histologic grade of differentiation, presence of vascular invasion, nodule size of > 5 cm, lymph nodes metastases and bilobar tumor involvement are classically associated with an increased risk of HCC recurrence after LT.

The Milan criteria are based on the preoperative tumor macromorphology on computed tomography or magnetic resonance imaging, that neither correlate well with posttransplant histologic study of the liver explant[4,5] nor accurately predict HCC recurrence after LT, since they do not include objective measures of tumor biology. In fact, small HCC may present biological aggressive features with unfavorable post-LT outcome, while other patients with HCC beyond Milan criteria but fulfilling the University of California San Francisco (UCSF) criteria[6] or the Up-to-7 criteria[7] could have a low risk of HCC recurrence in the presence of favorable tumor biology and could benefit from LT.

Liver biopsy is still the gold standard for determining the molecular biology of the tumor, its behavior and invasive characteristics. Some centers deny LT to patients with poorly differentiated tumors on needle biopsy, irrespective of number and size of tumoral nodules, and they have reported an excellent overall survival and low recurrence rates after LT even in patients exceeding Milan criteria[8-10]. However, preoperative biopsy often underestimates poorly differentiated tumors and does not accurately predict microvascular invasion, when compared with the final specimen examination after liver resection or LT[11,12]. Due to these limitations and because of the risk of needle tract tumor seeding, preoperative biopsy is not currently recommended for routine HCC evaluation; although, it is still needed in patients with atypical radiological features and in doubtful cases.

Preoperative biological markers can predict the risk for recurrence after transplantation. Biological markers can be categorized as: (1) serum markers directly

related with tumor biology, such as alpha-fetoprotein (AFP) and des-gamma-carboxyprothrombin (DCP); or (2) systemic inflammation markers, such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) conditioning tumor progression. In this review, we focus on the utility of these serum biological markers to improve the performance of Milan criteria for predicting recurrence after LT for HCC.

SERUM BIOLOGICAL MARKERS RELATED WITH TUMOR BIOLOGY

AFP

AFP is a 67-kDa glycoprotein that is produced by the liver in early fetal life. In adults, AFP production is restricted to a variety of liver tumors, including HCC, because of the dedifferentiation of hepatocytes. First considered a reliable marker for HCC diagnosis, at present the joined committees of the European Association for the Study of the Liver (commonly known as EASL) and the European Organization for Research and Treatment of Cancer (commonly known as EORTC) consider AFP testing as suboptimal for routine screening of early HCC (2B)[13]. In fact, about 80% of small HCC (< 2 cm) do not show high levels of serum AFP[14,15]. In the other hand, AFP level can be increased in patients with chronic liver disease, with a degree of hepatocytes regeneration in absence of malignancy[16].

Nevertheless, AFP is a surrogate marker of tumor differentiation and vascular invasion[17-20] and has proven a useful biomarker to identify patients at a higher risk for HCC recurrence[21], with varied risk magnitudes depending on the defined AFP cutoffs[22-33]. AFP has been integrated into several prognostic models for predicting recurrence after LT for HCC, by combining AFP level with tumor size and number, at different cutoffs for each variable (Table 1). Integration of AFP into the selection criteria was first proposed for patients receiving living donor (LD) LT in Asian countries, since the fast-track to LDLT may result in inclusion of patients with biologically aggressive HCC.

In the score proposed by Yang *et al*[34] patients were awarded between 1 and 4 points for each feature, with three different cutoffs: tumor size of 3, 5 and 6.5 cm; tumor number = 1, 3 and 5; and, AFP of 20, 200 and 1000 ng/mL. With a maximum score of 12 points, patients with a score ≥ 7 were considered as nontransplantable patients. In contrast, the Hangzhou criteria[35] consider transplantable patients as those with well or moderately differentiated HCC and having a total tumor diameter of > 8 cm and AFP of < 400 ng/mL. A large study conducted in 6487 patients registered in the Scientific Registry of Transplant Recipients database[36] showed that total tumor volume of ≤ 115 cm^3 and pretransplant AFP of ≤ 400 ng/mL identified patients at low risk of HCC recurrence after LT more effectively than both the Milan and UCSF criteria. This prognostic score has been validated both retrospectively in Poland[37] and prospectively in a multicenter study carried out in Canada, Switzerland and the United Kingdom[38].

The Liver Transplantation French Study Group developed and validated a prognostic model, known as the AFP model, for predicting recurrence after LT that combines AFP level, tumor size and number, at different cutoffs for each variable[17]. Tumor size was assigned: 0, 1 or 4 points when the largest tumor size was ≤ 3 cm, between 3-6 cm or ≥ 6 cm respectively; 0 or 2 points for ≤ 3 nodules or ≥ 4 nodules; and, AFP level added 0, 2 or 3 points for AFP ≤ 100, between 100-1000 or > 1000 ng/mL respectively; with a maximum score of 9 points. A cutoff of 2 points classified patients at low or high risk for HCC recurrence after LT. Thus, AFP > 1000 ng/mL provides enough points for excluding patients from LT whatever the size and number of nodules.

The AFP model better discriminated patients at high and low risk than Milan criteria. This model identifies patients within Milan criteria but with high risk of 5-year HCC recurrence as those having AFP > 1000 ng/mL (37.7% *vs* 13.3%), while patients beyond Milan criteria but with AFP < 100 have a low risk of HCC recurrence (14.4% *vs* 47.6%). Indeed, this model has been officially adopted in the liver allocation policy in France since 2013. This score has been validated in a single center from Spain[39] and in two multicenter studies, respectively from Italy[20] and Latin America[40], with similar results. Moreover, the AFP model has also been validated in a cohort of 400 patients with LDLT from Korea, in whom this model showed an improvement in predicting no HCC recurrence but not the occurrence of HCC recurrence[41].

All these models have been proved successful for selecting patients beyond the Milan criteria who will achieve similar outcomes to patients within Milan criteria.

Table 1 Main selection criteria for liver transplantation including alpha-fetoprotein

Reference	Country	*n*	AFP cutoff, ng/mL	Criteria	Validated in
Yang *et al*[34], 2007	Korea	63	20, 200 and 1000	Tumor number, tumor size and AFP level with different cutoffs	
Zheng *et al*[35], 2008	China	195	400	Hangzhou criteria: (1) TTD ≤ 8 or (2) TTD > 8, well or moderately differentiated and AFP < 400	
Toso *et al*[36], 2009	SRTR database	6487	400	TTV/AFP criteria for overall survival after LT: TTV ≤ 115cm^3 and AFP ≤ 400	Validated for recurrence after LT: Grat *et al*[37], 2013; Toso *et al*[38],2015.
Duvoux *et al*[17], 2012	France	537 (training cohort); 435 (validation cohort)	100 and 1000	AFP model: tumor number, tumor size and AFP level with different cutoffs	Varona *et al*[39], 2015; Notarpaolo *et al*[20], 2017; Piñero *et al*[40], 2016; Rhu *et al*[41], 2018
Lai *et al*[45], 2012	Italy	158	400	AFP-TTD criteria: TTD < 8 cm and AFP < 400	
Grąt *et al*[42], 2014	Poland	101	100	Warsaw criteria: (I) fulfillment of Milan criteria; or (II) Up-to-7 or UCSF criteria and AFP < 100	Piñero *et al*[43], 2016; Grat *et al*[44], 2017
Kim *et al*[46], 2014	Korea	180	1000	Samsung criteria: Up to 7 tumors ≤ 6 cm, and AFP ≤ 1000	

AFP: Alpha-fetoprotein; LT: Liver transplantation; SRTR: Scientific Registry of Transplant Recipients; TTD: Total tumor diameter; TTV: Total tumor volume; UCSF: University of California San Francisco.

Also, in a recent study[42] evaluating the role of AFP as predictor of HCC recurrence with respect to the fulfillment of Milan, UCSF or Up-to-7 criteria, patients beyond Milan criteria but within UCSF or Up-to-7 and with AFP < 100 ng/mL had a minimal risk of HCC recurrence after LT, criteria that have been validated in other studies[43,44].

Albeit AFP has proved to be a useful biomarker for identifying patients at a higher risk for HCC recurrence, there is no consensus about the best cutoff value to be considered. While different cutoffs have been proposed in several scores[17,34], other criteria include a sole cutoff at 400 ng/mL[35,36,45] or 1000 ng/mL[46]. Also, serial measurements of AFP (accounting for AFP variations) have been considered to better reflect the dynamic variations in the tumor biological behavior than a cutoff value of AFP level in a single assessment. Progression of AFP level while on the waiting list exceeding 15 ng/mL per mo[47,48], 50 ng/mL per mo[49] or 0.1 ng/mL per d[50] have been suggested as strong predictors of HCC recurrence after LT. In contrast, Grąt *et al*[42] found AFP > 100 ng/mL to better identify patients at risk of HCC recurrence than AFP slope.

DCP

Increased levels of DCP or prothrombin induced by vitamin K absence or antagonist II (PIVKA-II) are found in patients with HCC[51-43]. This abnormal form of prothrombin, produced during malignant transformation of hepatocytes, induces expression of angiogenic factors such as endothelial growth factor receptor and vascular endothelial growth factor (VEGF)[54,55]. Up-regulation of DCP has been found to correlate with the degree of malignancy of HCC, as DCP-positive tumors are characterized by increased likelihoods of intrahepatic metastasis, capsule infiltration, and portal venous invasion[56,57]. Moreover, the DCP-positive and AFP-negative tumors are more aggressive, for high risk of recurrence after treatment, since they are usually larger tumors with a poor grade of differentiation and vascular invasion[58,59].

DCP has been suggested as a stronger predictor of HCC recurrence after LT than AFP[57,60] and some centers from Asia have proposed the combined use of DCP level with tumor number and/or size in selection of candidates for LDLT with or without consideration of the AFP value (Table 2). The Kyoto criteria[61] and the Kyushu criteria[62] have been retrospectively and prospectively validated in the same centers where these scores were proposed[63-65]. Patients beyond Milan criteria but meeting Kyoto criteria had similar recurrence rate as patients within Milan criteria[61], while

Kyushu criteria was more powerful than UCSF, Tokyo and Kyoto criteria in predicting HCC recurrence[65].

Other centers have proposed different scores combining AFP and DCP levels with different cutoffs for both serum biomarkers that have improved Milan criteria for selection of patients at higher risk of HCC recurrence after LT. The A-P level criteria[66] included AFP ≤ 200 ng/mL "and" DCP ≤ 100 AU/mol, while the A-P 200 criteria[67] considered AFP ≤ 200 ng/mL "or" DCP ≤ 200 AU/molto identify patients at lower risk of HCC recurrence. Kim *et al*[68] found AFP > 150 ng/mL and DCP > 100 AU/mol to be associated with a higher risk of HCC recurrence after LT.

Lee *et al*[69] from Seoul, Korea developed and validated a model to predict recurrence after LDLT for HCC beyond the Milan criteria. Using a multivariate Cox proportional hazard model, the authors derived the model of recurrence after LT (commonly known as MoRAL) score using serum levels of AFP and DCP. Patients with a low MoRAL score (≤ 314.8) and no extrahepatic metastasis, even though their tumors exceeded the Milan criteria, had a lower tumor recurrence risk than patients within the Milan criteria with a high MoRAL score (> 314.8). Finally, the only study carried out in a non-Asiatic center found AFP ≥ 250 ng/mL and DCP ≥ 7.5 ng/mL to be associated with a higher risk of HCC recurrence[70], and added predictive information to the Milan criteria [hazard ratio (HR): 4.5 *vs* 2.6 with Milan criteria alone].

SYSTEMIC INFLAMMATION MARKERS

NLR and PLR

Two inflammation markers, the NLR and the PLR, have an important role in predicting outcome in several malignancies and have been associated with HCC recurrence after LT. Both the NLR and the PLR measure the proportion of peripheral blood neutrophils or platelets, respectively, to lymphocytes.

The link between NLR and liver malignancies was first demonstrated by Halazun *et al*[71] in patients who underwent surgery for colorectal liver metastasis. Same authors also reported that patients within Milan criteria and NLR ≥ 5 had a poorer recurrence-free survival than those with NLR < 5 (25% *vs* 75%) and proposed a pre-LT score for HCC recurrence after LT including NLR and tumor size > 3 cm (C-statistics: 0.74)[72]. Since then, NLR has been identified as an independent risk factor for HCC recurrence, along with microvascular invasion and/or tumor size and number in some studies[73-77], but not in others[78-80]. A recent systematic review by Najjar *et al*[81] and a meta-analysis by Xu *et al*[82] showed that elevated NLR is associated with a lower recurrence-free survival after LT (pooled HR: 3.77, 95%CI: 2.01-7.06) and with vascular invasion. Because of the different NLR cutoffs considered in the studies included in the meta-analysis (ranging from 2.6 to 6), Xu *et al*[82] recommend a cutoff NLR value of 4.

The prognostic significance of PLR for HCC recurrence after LT has been less extensively studied than that of NLR, but in a recent systematic review and meta-analysis including 899 patients from five studies, high PLR was associated with a significant increase of HCC recurrence after LT[83]. However, this association must be taken in consideration with great caution since a moderate level of heterogeneity was found among the studies included. In a recent study by Xia *et al*[84], PLR failed to predict HCC recurrence in patients meeting Milan criteria, but the 5-year recurrence-free survival in patients with HCC beyond Milan criteria but within Hangzhou criteria (total tumor diameter of ≤ 8 cm or > 8 cm, well or moderately differentiated and pretransplant AFP of < 400 ng/mL and PLR < 120) was comparable to the figure for patients within Milan criteria (73.3% *vs* 72.8%).

Han *et al*[85] also found that PLR was associated with HCC recurrence after LT, but interestingly a stronger association was found when considering the absolute platelet count. HCC recurrence rate after LT was higher in patients with platelet count of 75 × 10^9/L or greater at the day before surgery compared to patients with platelet count lower than 75 × 10^9/L (28.2% *vs* 13.2%). Moreover, the proportion of poorly differentiated tumors, microvascular invasion and bile duct invasion were higher in patients with platelet count of 75 × 10^9/L or greater. In the experience of those authors, the incorporation of platelet count at 75×10^9/L into the Milan criteria significantly increased the predictive power for HCC recurrence, over that of Milan criteria alone.

The molecular mechanisms through which the NLR and PLR are associated with HCC recurrence after LT remain unknown, but several hypotheses have been proposed. Both neutrophils and platelets are involved in vascular invasion and metastatization by increasing the production of proangiogenic factors such as

Table 2 Main selection criteria for liver transplantation including des-gamma-carboxyprothrombin

Reference	Country	*n*	Cutoff values	Criteria	Validated in
Takada *et al*[61],2007	Japan	125	DCP: 400	Kyoto criteria: up to 10 tumors ≤ 5 cm and DCP ≤ 400	Fujiki *et al*[63], 2009; Kaido *et al*[64], 2013
Soejima *et al*[62], 2007	Japan	60	DCP: 300	Kyushu criteria: any number of tumors < 5 cm and DCP < 300	Shirabe *et al*[65], 2011
Todo *et al*[66], 2007	Japan	551	AFP:200, DCP: 100	A-P level: AFP ≤ 200 and DCP ≤ 100	
Chaiteerakij *et al*[70], 2015	United States	127	AFP:250, DCP: 7.5		
Yang *et al*[67], 2016	Korea	88 (training cohort); 198 (validation cohort)	AFP: 200; DCP: 200	A-P 200: AFP ≤ 200 or DCP ≤ 200	
Kim *et al*[68], 2016	Korea	461	AFP: 150; DCP:100	--	

AFP: Alpha-fetoprotein; DCP: Des-gamma-carboxyprothrombin; MoRAL: Model of recurrence after liver transplantation.

VEGF[86,87]. Moreover, neutrophils, the common inflammatory infiltrate in tumors, have been found to be enriched predominantly in the peritumoral stroma of HCC tissue[75,88], correlating with angiogenesis and disease progression[89]. Within the circulatory system, platelets could help to establish metastatic lesions by blocking tumor cell removal[90,91]. On the other hand, low lymphocyte numbers, which also increase NLR and PLR values, could result in an impaired immunosurveillance against disease development and progression.

C-reactive protein

The C-reactive protein (CRP) is an acute-phase reactant synthesized by hepatocytes in response to systemic inflammation that has been related with the prognosis of various malignancies, including HCC[92]. Two independent groups from Korea have reported that high CRP level (with cutoff values at 1 mg/dL[93] or 0.3 mg/dL[94]) is an independent risk factor for HCC recurrence after LT, but only in patients beyond Milan criteria.

COMBINATION OF SERUM BIOLOGICAL MARKERS

In recent years, several studies have showed that the combination of several systemic inflammation biomarkers and tumor biomarkers predict the risk of HCC recurrence after LT more accurately (Table 3). In all the nine studies summarized, the relationship among tumor features and HCC recurrence was evidenced, and interestingly all studies analyzing pre-LT AFP level, except for one[95], found AFP to be an independent risk factor for HCC recurrence[80,96-98]. Also, Lai *et al*[78] found that although AFP and PLR were associated with HCC recurrence in univariate analysis, AFP > 200 ng/mL was the best prognostic factor with an area under the receiver operating characteristic curve (AUC) of 70.6 compared to 66.1 for PLR. Similarly, only two studies[80,99] out of three, found DCP to be an independent factor for HCC recurrence.

Regarding the systemic inflammation markers, NLR was found to be associated with HCC recurrence in six[82,95-99] out of nine studies and CRP in one[96] of two studies, while PLR was not shown as an independent risk factor in any of the four studies in which it was analyzed[78,79,99,100]. The two studies that analyzed inflammation marker sonly, found none of the biomarkers included to be independent risk factors for HCC recurrence[79,100]. Parisi *et al*[79] analyzed NLR, PLR and the inflammation-based index score (CRP ≥ 10 mg/dL and albumin < 35 gr/L; one point each) in 150 patients within Milan criteria before LT and found that absence of neoadjuvant therapy before LT and exceeding Milan criteria on explant pathology were the only risk factors for HCC recurrence. Fu *et al*[100] investigated the prognostic role of the systemic inflammation index (SII; absolute platelet count × absolute neutrophil count/absolute lymphocyte count) compared with PLR, NLR and monocyte-to-lymphocyte ratio in patients fulfilling the Hangzhou criteria for LDLT. At a cutoff of 226 × 10^9/mL, high SSI was associated with larger tumor size, greater total tumor volume, poorer differentiation grade and higher AFP level. Nevertheless, although SII was the best prognostic factor for overall survival, neither SSI nor the other systemic inflammatory markers

Table 3 Main studies analyzing several pre-liver transplantation systemic inflammation biomarkers and proposed scores

Reference	Country	LT type	*n*	Biomarkers	Time of biomarker test	Risk factors by multivariate analysis	Risk score
Yoshizumi *et al*[95], 2013	Japan	LDLT	104	AFP > 400, DCP > 300, NLR ≥ 4	Not specified	NLR, tumor size + number ≥ 8	No
Na *et al*[96], 2014	Korea	LDLT	224	AFP ≥ 100, NLR ≥ 6, CRP ≥ 1,	Day of LT	NLR ≥ 6 and AFP ≥ 100	Prognostic factor score: NLR ≥ 6 and CRP ≥ 1 (one point each)
Shindoh *et al*[80], 2014	Japan	LDLT	124	AFP, DCP, NLR	Day before LT, maximum and mean values within 90 d before LT	Tumor ≥ 5, MVI, mean NLR and maximum AFP and DCP before LT	Tokyo criteria, AFP > 250 and DCP > 450 (one point each)
Lai *et al*[78], 2014	Belgium	DDLT	146	AFP > 200, NLR > 5.4, PLR > 150	At inclusion on the waiting list, at LT,	AFP, NLR and PLR in univariate analysis	No
Parisi *et al*[79], 2014	UK	DDLT	150	NLR ≥ 5, PLR ≥ 150, IBI score	Day of LT	Absence of neoadjuvant therapy, beyond Milan criteria on explant	No
Harimoto *et al*[99], 2016	Japan	LDLT	190	DCP ≥ 300, NLR ≥ 2.66, PLR ≥ 70.4, CRP ≥ 0.27	Not specified	NLR, DCP, and tumor number ≥ 5	No
Wang *et al*[97], 2016	China	DDLT/LDLT	248	NLR continuous, AFP > 400	Within 1 wk before LT	NLR , AFP > 400, age, tumor number and size	Model TFS: 1.094 × tumor number (≤ 3, 0 points; > 3 (1 point) + 0.094 × maximum tumor diameter + 0.754 × AFP (≤ 400, 0 points; > 400, 1 point) + 0.085 × NLR -0.024 × age
Halazun *et al*[98], 2017	United States	DDLT/LDLT	339	NLR ≥ 5, AFP	NLR at day of LT; serial AFP at HCC diagnosis, before pre-LT treatment and at LT.	Tumor size and number, NLR ≥ 5, maximum pre-LT AFP, vascular invasion and poor differentiated tumors	MoRAL score: (1) pre-MoRAL: NLR ≥ 5 (6 points) + AFP > 200 (4 points) + largest tumor size > 3 cm by imaging (3 points); (2) post-MoRAL: grade IV tumors (6 points) + vascular invasion (2 points) + tumor size > 3 on pathology (3 points) + tumor number > 3 on pathology (2 points); and (3) combined score.
Fu *et al*[100], 2018	China	LDLT	150	NLR, PLR, MLR, SII	Within 1 wk before LT	No association	No

AFP: Alpha-fetoprotein; CRP: C-reactive protein; DCP: Des-gamma-carboxyprothrombin; DDLT: Deceased donor liver transplantation; IBI: Inflammation based index; LDLT: Living donor liver transplantation; LT: Liver transplantation; MVI: Microvascular invasion; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic inflammation index; TFS: Tumor-free survival.

analyzed were associated with recurrence-free survival.

Prognostic scores including inflammatory markers for HCC recurrence after LDLT have been proposed by three different groups from Asia and one group from the United States. Na *et al*[96] proposed a prognostic factor score assigning 1 point for pre-LT NLR ≥ 6 and CRP ≥ 1 each, and Wang *et al*[97], who included only males receiving a LDLT, proposed the model tumor free survival, combining tumor morphological features with tumor biological information. Interestingly, both scores were

informative only in patients beyond Milan criteria, and not predictive of HCC recurrence in patients within Milan criteria.

The score proposed by Shindoh *et al*[80] incorporates pre-LT maximum AFP and DCP in the Tokyo criteria (≤ 5 tumors of ≤ 5 cm) to better stratify patients at risk of HCC recurrence after LT. After evaluating three different pre-LT values for NLR, AFP and DCP (the last value before LT, and the maximum and mean values within the 90 d before LDLT), the maximum AFP and DCP values and the mean value of NLR were independently associated with HCC recurrence. However, NLR had a limited prognostic impact (AUC: 0.62) and only maximum AFP and DCP values had sufficient discriminative power (AUC: 0.88 and 0.76 respectively). So, the authors proposed extending the Tokyo criteria by adding AFP > 250 and DCP > 450 (1 point for each variable; maximum score of 3). Patients with a score 0-1 had a 5-year disease-free survival rate of 97%, opposed to only 20% of patients with a score 2-3.

In 2017, Halazun *et al*[98] carried out a prospective study of 339 patients to identify predictors of HCC recurrence after LT. Preoperative NLR > 5 ($P < 0.0001$, HR: 6.2), AFP > 200 ($P < 0.0001$, HR: 3.8) and tumor size > 3 cm ($P < 0.001$, HR: 3.2) were found to be independently associated with a worse recurrence-free survival. The authors developed a new MoRAL score for predicting HCC recurrence after LT, mainly in individuals receiving a liver from deceased donors[98]. They constructed three scores: the pre-MoRAL, the post-MoRAL and the combined-MoRAL score, the latter including both pre-MoRAL and post-MoRAL scores. The pre-MoRAL score, included the three preoperative significant variables with a minimum of 0 points (no factors) and a maximum of 13 points (all 3 factors). The highest risk patients in the pre-MoRAL (score > 10) had a 5-year recurrence-free survival of 17.9% compared with 98.6% for the low risk group ($P < 0.0001$). The post-MoRAL score included four postoperatively available factors related to pathological features in liver explant, namely grade 4 HCCs, vascular invasion, tumor size > 3 cm and tumor number > 3. The pre-MoRAL, post-MoRAL and combo-MoRAL better predicted HCC recurrence after LT than Milan criteria with C-statistics of 0.82, 0.87 and 0.91 respectively.

LIMITATIONS OF PRETRANSPLANT SERUM BIOMARKERS

Most of the studies to date have been retrospective and include a small sample size; moreover, the included patients in the different studies are highly heterogeneous regarding indications for LT, handling of incidental tumors or inclusion of salvage LT. Also, frequent exclusion of patients who died within 1 mo or even 3 mo after LT could have restricted data about the most aggressive tumors. Besides, there is a great variation of time elapsed between the measurement of the markers and LT. Most studies considered these markers from the analytical data of the day before LT, while others considered these values within 1 wk before LT or did not specify it. Also, there is no consensus about the best cutoff value for each biomarker, and it maybe those different cutoffs should be considered in different populations or centers. In addition, comparison of results from multiple laboratories is uncertain because of different laboratory methods and processing techniques for measuring these biomarkers. Another limitation of the different studies reviewed here relies on the analyses of HCC recurrence as a time-dependent variable, such as recurrence or disease-free survival, without accounting for competing risk, such as death. So, patients who died early after LT or whose death was not related to HCC may never have had the chance to experience HCC recurrence.

Albeit the serum markers reviewed here are potential markers to be included in patient selection for LT, their utility is limited and they cannot be universally applied in all patients. Although AFP is considered the most useful pretransplant marker of HCC recurrence after LT, its utility is restricted by the existence of non-AFP secreting HCC. More restricted is the utility of systemic inflammatory markers, for different reasons. Although some meta-analyses have suggested NLR[82] and PLR[83] as useful pretransplant biomarkers for HCC recurrence, they are based on very few retrospective studies (four and five studies respectively), with most having small sample size. However, the most important limitation may be that these inflammatory serum biomarkers can be affected by other conditions, such an acute infection, hematologic disorders, hypersplenism, gastrointestinal tract bleeding or systemic inflammatory diseases, which are frequent in patients with end-stage liver diseases.

OTHER POTENTIAL SERUM BIOMARKERS

In addition to the serum biomarkers reviewed here, some other markers have been

proposed as potential risk factors for HCC recurrence after LT.

AFP-L3%, which represents a serum AFP fraction reactive with lens culinaris agglutinin, has been associated with HCC diagnosis[101,102]. In the LT context, an AFP-L3% level > 50 ng/mL combined with Milan criteria improved HCC recurrence prediction, when compared with Milan criteria alone[70]. Interestingly, AFP-L3% has been suggested as a highly specific marker of HCC in patients with low AFP level[102], which could overcome the limitation of AFP usefulness as a biomarker of HCC recurrence in patients with AFP-negative HCC. However, more studies are needed for this promising biomarker.

Liquid biopsy has attracted much attention as a feasible and noninvasive tool to identify tumoral markers in peripheral blood for diagnosis, monitoring and prognosis of cancer, overcoming tissue biopsy limitations. Circulating tumoral cells and tumoral cell free nucleic acids in peripheral blood could be advisory of micro metastasis, and their utility has been explored in HCC diagnosis and prognosis[103]. Very few data are available about the potential role of these circulating tumoral components as preoperative predictors of HCC recurrence after LT, and it is still a controversial issue. Although circulating HCC cells have been detected before LT, they have not been associated with HCC recurrence after LT[104]. Regarding circulating nucleic acids, AFP mRNA expression in peripheral blood has been suggested as a surrogate of circulating tumoral cells and has been associated with an increased risk of HCC recurrence after LT[105]. However, their utility is controversial and some authors consider AFP mRNA to be nonspecific for HCC micro metastases.

Some other circulating RNA have been explored, but none of them has been widely recognized as valuable marker of HCC recurrence, probably because none of them are specific for HCC[103]. Circulating tumor DNA has been isolated in patients with HCC, and has been associated with microvascular invasion[106]. However, much effort is still needed in order to consider these circulating tumor components as valuable markers in clinical practice since some limitations still need to be overcome. Although the complex methodology to isolate these tumoral components has improved dramatically, their extremely low frequencies in peripheral blood require more sensitive and cost effective techniques. Also, HCC-specific biomarkers should be validated and evidence of their association with HCC recurrence after LT should be proven.

Finally, different micro (mi) RNA signatures in liver tissue have been associated with HCC recurrence after LT[107,108]. However, the necessity of liver tissue samples limits their application preoperatively, and circulating miRNAs are at present being explored. Several circulating miRNAs have been suggested as potential biomarkers for HCC diagnosis[109], vascular invasion and prognosis[110,111]. To date, to the best of our knowledge, there is no data about the association of miRNAs with HCC recurrence after LT, and future studies are warranted to explore the utility of these promising biomarkers in preoperative prediction of HCC recurrence after LT.

CONCLUSION

Although the Milan criteria have improved survival of patients receiving a LT for small HCC, tumor recurrence after transplantation still develops in about 15% of patients. On the other hand, patients with less aggressive tumors and at lower risk of recurrence have proven benefit of LT. Since the Milan criteria are based on morphological tumor feature sonly, combination of these criteria with other preoperative available biomarkers related with tumor biology could better predict HCC recurrence after LT. Some serum biomarkers have been proposed but there is no consensus about their use, mainly due to the several limitations commented on in this review. In addition, considering that tumor growth patterns are highly variable among individuals, there probably is no perfect single biomarker for HCC prognosis after LT; thus, the combination of biomarkers could be more informative than any single biomarker alone.

For those reasons and taking into account the limitations highlighted here, multicenter prospective studies are demanded and an international consensus is mandatory in order to provide practical recommendations to guide the implementation of serum biomarkers combined with morphological criteria to better stratify patients at high or low risk of HCC recurrence after LT.

REFERENCES

1 **Mazzaferro V**, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M,

Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699 [PMID: 8594428 DOI: 10.1056/NEJM199603143341104]

2 **Maggs JR**, Suddle AR, Aluvihare V, Heneghan MA. Systematic review: the role of liver transplantation in the management of hepatocellular carcinoma. *Aliment Pharmacol Ther* 2012; **35**: 1113-1134 [PMID: 22432733 DOI: 10.1111/j.1365-2036.2012.05072.x]

3 **Molmenti EP**, Klintmalm GB. Liver transplantation in association with hepatocellular carcinoma: an update of the International Tumor Registry. *Liver Transpl* 2002; **8**: 736-748 [PMID: 12200772 DOI: 10.1053/jlts.2002.34879]

4 **Ecker BL**, Hoteit MA, Forde KA, Hsu CC, Reddy KR, Furth EE, Siegelman ES, Habibollahi P, Ben-Josef E, Porrett PM, Abt PL, Shaked A, Olthoff KM, Levine MH. Patterns of Discordance Between Pretransplant Imaging Stage of Hepatocellular Carcinoma and Posttransplant Pathologic Stage: A Contemporary Appraisal of the Milan Criteria. *Transplantation* 2018; **102**: 648-655 [PMID: 29319629 DOI: 10.1097/TP.0000000000002056]

5 **Piñero F**, Costa P, Boteon YL, Duque SH, Marciano S, Anders M, Varón A, Zerega A, Poniachik J, Soza A, Machaca MP, Menéndez J, Zapata R, Vilatoba M, Muñoz L, Maraschio M, Fauda M, McCormack L, Gadano A, Boin IS, García JHP, Silva M. Results of Liver Transplantation for Hepatocellular Carcinoma in a Multicenter Latin American Cohort Study. *Ann Hepatol* 2018; **17**: 256-267 [PMID: 29469048 DOI: 10.5604/01.3001.0010.8648]

6 **Yao FY**, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001; **33**: 1394-1403 [PMID: 11391528 DOI: 10.1053/jhep.2001.24563]

7 **Mazzaferro V**, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, Camerini T, Roayaie S, Schwartz ME, Grazi GL, Adam R, Neuhaus P, Salizzoni M, Bruix J, Forner A, De Carlis L, Cillo U, Burroughs AK, Troisi R, Rossi M, Gerunda GE, Lerut J, Belghiti J, Boin I, Gugenheim J, Rochling F, Van Hoek B, Majno P; Metroticket Investigator Study Group. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol* 2009; **10**: 35-43 [PMID: 19058754 DOI: 10.1016/S1470-2045(08)70284-5]

8 **Cillo U**, Vitale A, Bassanello M, Boccagni P, Brolese A, Zanus G, Burra P, Fagiuoli S, Farinati F, Rugge M, D'Amico DF. Liver transplantation for the treatment of moderately or well-differentiated hepatocellular carcinoma. *Ann Surg* 2004; **239**: 150-159 [PMID: 14745321 DOI: 10.1097/01.sla.0000109146.72827.76]

9 **DuBay D**, Sandroussi C, Sandhu L, Cleary S, Guba M, Cattral MS, McGilvray I, Ghanekar A, Selzner M, Greig PD, Grant DR. Liver transplantation for advanced hepatocellular carcinoma using poor tumor differentiation on biopsy as an exclusion criterion. *Ann Surg* 2011; **253**: 166-172 [PMID: 21294289 DOI: 10.1097/SLA.0b013e31820508f1]

10 **Irtan S**, Barbier L, Francoz C, Dondero F, Durand F, Belghiti J. Liver transplantation for hepatocellular carcinoma: is zero recurrence theoretically possible? *Hepatobiliary Pancreat Dis Int* 2016; **15**: 147-151 [PMID: 27020630 DOI: 10.1016/S1499-3872(16)60069-3]

11 **Pawlik TM**, Gleisner AL, Anders RA, Assumpcao L, Maley W, Choti MA. Preoperative assessment of hepatocellular carcinoma tumor grade using needle biopsy: implications for transplant eligibility. *Ann Surg* 2007; **245**: 435-442 [PMID: 17435551 DOI: 10.1097/01.sla.0000250420.73854.ad]

12 **Court CM**, Harlander-Locke MP, Markovic D, French SW, Naini BV, Lu DS, Raman SS, Kaldas FM, Zarrinpar A, Farmer DG, Finn RS, Sadeghi S, Tomlinson JS, Busuttil RW, Agopian VG. Determination of hepatocellular carcinoma grade by needle biopsy is unreliable for liver transplant candidate selection. *Liver Transpl* 2017; **23**: 1123-1132 [PMID: 28688158 DOI: 10.1002/lt.24811]

13 **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]

14 **Zhang XF**, Qi X, Meng B, Liu C, Yu L, Wang B, Lv Y. Prognosis evaluation in alpha-fetoprotein negative hepatocellular carcinoma after hepatectomy: comparison of five staging systems. *Eur J Surg Oncol* 2010; **36**: 718-724 [PMID: 20538423 DOI: 10.1016/j.ejso.2010.05.022]

15 **Agopian VG**, Harlander-Locke MP, Markovic D, Zarrinpar A, Kaldas FM, Cheng EY, Yersiz H, Farmer DG, Hiatt JR, Busuttil RW. Evaluation of Patients With Hepatocellular Carcinomas That Do Not Produce α-Fetoprotein. *JAMA Surg* 2017; **152**: 55-64 [PMID: 27706479 DOI: 10.1001/jamasurg.2016.3310]

16 **Toyoda H**, Kumada T, Kiriyama S, Sone Y, Tanikawa M, Hisanaga Y, Hayashi K, Honda T, Kitabatake S, Kuzuya T, Nonogaki K, Kasugai T, Shimizu J. Changes in the characteristics and survival rate of hepatocellular carcinoma from 1976 to 2000: analysis of 1365 patients in a single institution in Japan. *Cancer* 2004; **100**: 2415-2421 [PMID: 15160346 DOI: 10.1002/cncr.20289]

17 **Duvoux C**, Roudot-Thoraval F, Decaens T, Pessione F, Badran H, Piardi T, Francoz C, Compagnon P, Vanlemmens C, Dumortier J, Dharancy S, Gugenheim J, Bernard PH, Adam R, Radenne S, Muscari F, Conti F, Hardwigsen J, Pageaux GP, Chazouillères O, Salame E, Hilleret MN, Lebray P, Abergel A, Debette-Gratien M, Kluger MD, Mallat A, Azoulay D, Cherqui D; Liver Transplantation French Study Group. Liver transplantation for hepatocellular carcinoma: a model including α-fetoprotein improves the performance of Milan criteria. *Gastroenterology* 2012; **143**: 986-94.e3; quiz e14-5 [PMID: 22750200 DOI: 10.1053/j.gastro.2012.05.052]

18 **Liu C**, Xiao GQ, Yan LN, Li B, Jiang L, Wen TF, Wang WT, Xu MQ, Yang JY. Value of α-fetoprotein in association with clinicopathological features of hepatocellular carcinoma. *World J Gastroenterol* 2013; **19**: 1811-1819 [PMID: 23555170 DOI: 10.3748/wjg.v19.i11.1811]

19 **Hameed B**, Mehta N, Sapisochin G, Roberts JP, Yao FY. Alpha-fetoprotein level > 1000 ng/mL as an exclusion criterion for liver transplantation in patients with hepatocellular carcinoma meeting the Milan criteria. *Liver Transpl* 2014; **20**: 945-951 [PMID: 24797281 DOI: 10.1002/lt.23904]

20 **Notarpaolo A**, Layese R, Magistri P, Gambato M, Colledan M, Magini G, Miglioresi L, Vitale A, Vennarecci G, Ambrosio CD, Burra P, Di Benedetto F, Fagiuoli S, Colasanti M, Maria Ettorre G, Andreoli A, Cillo U, Laurent A, Katsahian S, Audureau E, Roudot-Thoraval F, Duvoux C. Validation of the AFP model as a predictor of HCC recurrence in patients with viral hepatitis-related cirrhosis who had received a liver transplant for HCC. *J Hepatol* 2017; **66**: 552-559 [PMID: 27899297 DOI: 10.1016/j.jhep.2016.10.038]

21 **Hakeem AR**, Young RS, Marangoni G, Lodge JP, Prasad KR. Systematic review: the prognostic role of alpha-fetoprotein following liver transplantation for hepatocellular carcinoma. *Aliment Pharmacol Ther* 2012; **35**: 987-999 [PMID: 22429190 DOI: 10.1111/j.1365-2036.2012.05060.x]

22 **She WH**, Chan ACY, Cheung TT, Lo CM, Chok KSH. Survival outcomes of liver transplantation for

hepatocellular carcinoma in patients with normal, high and very high preoperative alpha-fetoprotein levels. *World J Hepatol* 2018; **10**: 308-318 [PMID: 29527266 DOI: 10.4254/wjh.v10.i2.308]

23 **Levi DM**, Tzakis AG, Martin P, Nishida S, Island E, Moon J, Selvaggi G, Tekin A, Madrazo BL, Narayanan G, Garcia MT, Feun LG, Tryphonopoulos P, Skartsis N, Livingstone AS. Liver transplantation for hepatocellular carcinoma in the model for end-stage liver disease era. *J Am Coll Surg* 2010; **210**: 727-734, 735-736 [PMID: 20421039 DOI: 10.1016/j.jamcollsurg.2010.01.007]

24 **O'Connor DB**, Burke JP, Hegarty J, McCormick AP, Nolan N, Hoti E, Maguire D, Geoghegan J, Traynor O. Liver transplantation for hepatocellular carcinoma in Ireland: Pre-operative alpha-fetoprotein predicts tumour recurrence in a 14-year single-centre national experience. *World J Transplant* 2016; **6**: 396-402 [PMID: 27358785 DOI: 10.5500/wjt.v6.i2.396]

25 **Onaca N**, Davis GL, Jennings LW, Goldstein RM, Klintmalm GB. Improved results of transplantation for hepatocellular carcinoma: a report from the International Registry of Hepatic Tumors in Liver Transplantation. *Liver Transpl* 2009; **15**: 574-580 [PMID: 19479800 DOI: 10.1002/lt.21738]

26 **Abdel-Wahab M**, Sultan AM, Fathy OM, Salah T, Elshobary MM, Elghawalby NA, Yassen AM, Elsarraf WM, Elsaadany MF, Zalatah K. Factors affecting recurrence and survival after living donor liver transplantation for hepatocellular carcinoma. *Hepatogastroenterology* 2013; **60**: 1847-1853 [PMID: 24719918]

27 **Schraiber Ldos S**, de Mattos AA, Zanotelli ML, Cantisani GP, Brandão AB, Marroni CA, Kiss G, Ernani L, Marcon Pdos S. Alpha-fetoprotein Level Predicts Recurrence After Transplantation in Hepatocellular Carcinoma. *Medicine (Baltimore)* 2016; **95**: e2478 [PMID: 26817881 DOI: 10.1097/MD.0000000000002478]

28 **Xu X**, Ke QH, Shao ZX, Wu J, Chen J, Zhou L, Zheng SS. The value of serum alpha-fetoprotein in predicting tumor recurrence after liver transplantation for hepatocellular carcinoma. *Dig Dis Sci* 2009; **54**: 385-388 [PMID: 18563566 DOI: 10.1007/s10620-008-0349-0]

29 **Ciccarelli O**, Lai Q, Goffette P, Finet P, De Reyck C, Roggen F, Sempoux C, Doffagne E, Reding R, Lerut J. Liver transplantation for hepatocellular cancer: UCL experience in 137 adult cirrhotic patients. Alpha-foetoprotein level and locoregional treatment as refined selection criteria. *Transpl Int* 2012; **25**: 867-875 [PMID: 22716073 DOI: 10.1111/j.1432-2277.2012.01512.x]

30 **Wong LL**, Naugler WE, Schwartz J, Scott DL, Bhattacharya R, Reyes J, Orloff SL. Impact of locoregional therapy and alpha-fetoprotein on outcomes in transplantation for liver cancer: a UNOS Region 6 pooled analysis. *Clin Transplant* 2013; **27**: E72-E79 [PMID: 23278701 DOI: 10.1111/ctr.12056]

31 **Sapisochin G**, Goldaracena N, Laurence JM, Dib M, Barbas A, Ghanekar A, Cleary SP, Lilly L, Cattral MS, Marquez M, Selzner M, Renner E, Selzner N, McGilvray ID, Greig PD, Grant DR. The extended Toronto criteria for liver transplantation in patients with hepatocellular carcinoma: A prospective validation study. *Hepatology* 2016; **64**: 2077-2088 [PMID: 27178646 DOI: 10.1002/hep.28643]

32 **Zou WL**, Zang YJ, Chen XG, Shen ZY. Risk factors for fatal recurrence of hepatocellular carcinoma and their role in selecting candidates for liver transplantation. *Hepatobiliary Pancreat Dis Int* 2008; **7**: 145-151 [PMID: 18397848]

33 **Lao OB**, Weissman J, Perkins JD. Pre-transplant therapy for hepatocellular carcinoma is associated with a lower recurrence after liver transplantation. *Clin Transplant* 2009; **23**: 874-881 [PMID: 19453644 DOI: 10.1111/j.1399-0012.2009.00993.x]

34 **Yang SH**, Suh KS, Lee HW, Cho EH, Cho JY, Cho YB, Kim IH, Yi NJ, Lee KU. A revised scoring system utilizing serum alphafetoprotein levels to expand candidates for living donor transplantation in hepatocellular carcinoma. *Surgery* 2007; **141**: 598-609 [PMID: 17462459 DOI: 10.1016/j.surg.2006.11.006]

35 **Zheng SS**, Xu X, Wu J, Chen J, Wang WL, Zhang M, Liang TB, Wu LM. Liver transplantation for hepatocellular carcinoma: Hangzhou experiences. *Transplantation* 2008; **85**: 1726-1732 [PMID: 18580463 DOI: 10.1097/TP.0b013e31816b67e4]

36 **Toso C**, Asthana S, Bigam DL, Shapiro AM, Kneteman NM. Reassessing selection criteria prior to liver transplantation for hepatocellular carcinoma utilizing the Scientific Registry of Transplant Recipients database. *Hepatology* 2009; **49**: 832-838 [PMID: 19152426 DOI: 10.1002/hep.22693]

37 **Grat M**, Kornasiewicz O, Hołówko W, Lewandowski Z, Zieniewicz K, Paczek L, Krawczyk M. Evaluation of total tumor volume and pretransplantation α-fetoprotein level as selection criteria for liver transplantation in patients with hepatocellular cancer. *Transplant Proc* 2013; **45**: 1899-1903 [PMID: 23769067 DOI: 10.1016/j.transproceed.2012.12.010]

38 **Toso C**, Meeberg G, Hernandez-Alejandro R, Dufour JF, Marotta P, Majno P, Kneteman NM. Total tumor volume and alpha-fetoprotein for selection of transplant candidates with hepatocellular carcinoma: A prospective validation. *Hepatology* 2015; **62**: 158-165 [PMID: 25777590 DOI: 10.1002/hep.27787]

39 **Varona MA**, Soriano A, Aguirre-Jaime A, Garrido S, Oton E, Diaz D, Portero J, Bravo P, Barrera MA, Perera A. Risk factors of hepatocellular carcinoma recurrence after liver transplantation: accuracy of the alpha-fetoprotein model in a single-center experience. *Transplant Proc* 2015; **47**: 84-89 [PMID: 25645778 DOI: 10.1016/j.transproceed.2014.12.013]

40 **Piñero F**, Tisi Baña M, de Ataide EC, Hoyos Duque S, Marciano S, Varón A, Anders M, Zerega A, Menéndez J, Zapata R, Muñoz L, Padilla Machaca M, Soza A, McCormack L, Poniachik J, Podestá LG, Gadano A, Boin IS, Duvoux C, Silva M; Latin American Liver Research, Education and Awareness Network (LALREAN). Liver transplantation for hepatocellular carcinoma: evaluation of the alpha-fetoprotein model in a multicenter cohort from Latin America. *Liver Int* 2016; **36**: 1657-1667 [PMID: 27169841 DOI: 10.1111/liv.13159]

41 **Rhu J**, Kim JM, Choi GS, Kwon CHD, Joh JW. Validation of the α-fetoprotein Model for Hepatocellular Carcinoma Recurrence After Transplantation in an Asian Population. *Transplantation* 2018; **102**: 1316-1322 [PMID: 29470357 DOI: 10.1097/TP.0000000000002136]

42 **Grąt M**, Kornasiewicz O, Lewandowski Z, Hołówko W, Grąt K, Kobryń K, Patkowski W, Zieniewicz K, Krawczyk M. Combination of morphologic criteria and α-fetoprotein in selection of patients with hepatocellular carcinoma for liver transplantation minimizes the problem of posttransplant tumor recurrence. *World J Surg* 2014; **38**: 2698-2707 [PMID: 24858191 DOI: 10.1007/s00268-014-2647-3]

43 **Piñero F**, Marciano S, Anders M, Orozco Ganem F, Zerega A, Cagliani J, Andriani O, de Santibañes E, Gil O, Podestá LG, McCormack L, Gadano A, Silva M. Identifying patients at higher risk of hepatocellular carcinoma recurrence after liver transplantation in a multicenter cohort study from Argentina. *Eur J Gastroenterol Hepatol* 2016; **28**: 421-427 [PMID: 26684693 DOI: 10.1097/MEG.0000000000000551]

44 **Grąt M**, Wronka KM, Stypułkowski J, Bik E, Krasnodębski M, Masior Ł, Lewandowski Z, Grąt K, Patkowski W, Krawczyk M. The Warsaw Proposal for the Use of Extended Selection Criteria in Liver

Transplantation for Hepatocellular Cancer. *Ann Surg Oncol* 2017; **24**: 526-534 [PMID: 27531306 DOI: 10.1245/s10434-016-5500-0]

45 **Lai Q**, Avolio AW, Manzia TM, Sorge R, Agnes S, Tisone G, Berloco PB, Rossi M. Combination of biological and morphological parameters for the selection of patients with hepatocellular carcinoma waiting for liver transplantation. *Clin Transplant* 2012; **26**: E125-E131 [PMID: 22192083 DOI: 10.1111/j.1399-0012.2011.01572.x]

46 **Kim JM**, Kwon CH, Joh JW, Park JB, Lee JH, Kim GS, Kim SJ, Paik SW, Lee SK. Expanded criteria for liver transplantation in patients with hepatocellular carcinoma. *Transplant Proc* 2014; **46**: 726-729 [PMID: 24767334 DOI: 10.1016/j.transproceed.2013.11.037]

47 **Vibert E**, Azoulay D, Hoti E, Iacopinelli S, Samuel D, Salloum C, Lemoine A, Bismuth H, Castaing D, Adam R. Progression of alphafetoprotein before liver transplantation for hepatocellular carcinoma in cirrhotic patients: a critical factor. *Am J Transplant* 2010; **10**: 129-137 [PMID: 20070666 DOI: 10.1111/j.1600-6143.2009.02750.x]

48 **Lai Q**, Avolio AW, Graziadei I, Otto G, Rossi M, Tisone G, Goffette P, Vogel W, Pitton MB, Lerut J; European Hepatocellular Cancer Liver Transplant Study Group. Alpha-fetoprotein and modified response evaluation criteria in solid tumors progression after locoregional therapy as predictors of hepatocellular cancer recurrence and death after transplantation. *Liver Transpl* 2013; **19**: 1108-1118 [PMID: 23873764 DOI: 10.1002/lt.23706]

49 **Han K**, Tzimas GN, Barkun JS, Metrakos P, Tchervenkov JL, Hilzenrat N, Wong P, Deschênes M. Preoperative alpha-fetoprotein slope is predictive of hepatocellular carcinoma recurrence after liver transplantation. *Can J Gastroenterol* 2007; **21**: 39-45 [PMID: 17225881 DOI: 10.1155/2007/206383]

50 **Dumitra TC**, Dumitra S, Metrakos PP, Barkun JS, Chaudhury P, Deschênes M, Paraskevas S, Hassanain M, Tchervenkov JI. Pretransplantation α-fetoprotein slope and milan criteria: strong predictors of hepatocellular carcinoma recurrence after transplantation. *Transplantation* 2013; **95**: 228-233 [PMID: 23222895 DOI: 10.1097/TP.0b013e31827743d7]

51 **Fujiyama S**, Morishita T, Hashiguchi O, Sato T. Plasma abnormal prothrombin (des-gamma-carboxy prothrombin) as a marker of hepatocellular carcinoma. *Cancer* 1988; **61**: 1621-1628 [PMID: 2450634 DOI: 10.1002/1097-0142(19880415)61:8<1621::AID-CNCR2820610820>3.0.CO;2-C]

52 **Okuda H**, Obata H, Nakanishi T, Furukawa R, Hashimoto E. Production of abnormal prothrombin (des-gamma-carboxy prothrombin) by hepatocellular carcinoma. A clinical and experimental study. *J Hepatol* 1987; **4**: 357-363 [PMID: 3036940 DOI: 10.1016/S0168-8278(87)80546-9]

53 **Bertino G**, Ardiri AM, Boemi PM, Ierna D, Interlandi D, Caruso L, Minona E, Trovato MA, Vicari S, Li Destri G, Puleo S. A study about mechanisms of des-gamma-carboxy prothrombin's production in hepatocellular carcinoma. *Panminerva Med* 2008; **50**: 221-226 [PMID: 18927526]

54 **Gao FJ**, Cui SX, Chen MH, Cheng YN, Sun LR, Ward SG, Kokudo N, Tang W, Qu XJ. Des-gamma-carboxy prothrombin increases the expression of angiogenic factors in human hepatocellular carcinoma cells. *Life Sci* 2008; **83**: 815-820 [PMID: 18976674 DOI: 10.1016/j.lfs.2008.10.003]

55 **Wang SB**, Cheng YN, Cui SX, Zhong JL, Ward SG, Sun LR, Chen MH, Kokudo N, Tang W, Qu XJ. Des-gamma-carboxy prothrombin stimulates human vascular endothelial cell growth and migration. *Clin Exp Metastasis* 2009; **26**: 469-477 [PMID: 19263229 DOI: 10.1007/s10585-009-9246-y]

56 **Poté N**, Cauchy F, Albuquerque M, Voitot H, Belghiti J, Castera L, Puy H, Bedossa P, Paradis V. Performance of PIVKA-II for early hepatocellular carcinoma diagnosis and prediction of microvascular invasion. *J Hepatol* 2015; **62**: 848-854 [PMID: 25450201 DOI: 10.1016/j.jhep.2014.11.005]

57 **Shirabe K**, Itoh S, Yoshizumi T, Soejima Y, Taketomi A, Aishima S, Maehara Y. The predictors of microvascular invasion in candidates for liver transplantation with hepatocellular carcinoma-with special reference to the serum levels of des-gamma-carboxy prothrombin. *J Surg Oncol* 2007; **95**: 235-240 [PMID: 17323337 DOI: 10.1002/jso.20655]

58 **Okuda H**, Nakanishi T, Takatsu K, Saito A, Hayashi N, Yamamoto M, Takasaki K, Nakano M. Comparison of clinicopathological features of patients with hepatocellular carcinoma seropositive for alpha-fetoprotein alone and those seropositive for des-gamma-carboxy prothrombin alone. *J Gastroenterol Hepatol* 2001; **16**: 1290-1296 [PMID: 11903749 DOI: 10.1046/j.1440-1746.2001.02610.x]

59 **Hong YM**, Cho M, Yoon KT, Chu CW, Yang KH, Park YM, Rhu JH. Risk factors of early recurrence after curative hepatectomy in hepatocellular carcinoma. *Tumour Biol* 2017; **39**: 1010428317720863 [PMID: 29034775 DOI: 10.1177/1010428317720863]

60 **Taketomi A**, Sanefuji K, Soejima Y, Yoshizumi T, Uhciyama H, Ikegami T, Harada N, Yamashita Y, Sugimachi K, Kayashima H, Iguchi T, Maehara Y. Impact of des-gamma-carboxy prothrombin and tumor size on the recurrence of hepatocellular carcinoma after living donor liver transplantation. *Transplantation* 2009; **87**: 531-537 [PMID: 19307789 DOI: 10.1097/TP.0b013e3181943bee]

61 **Takada Y**, Ito T, Ueda M, Sakamoto S, Haga H, Maetani Y, Ogawa K, Ogura Y, Oike F, Egawa H, Uemoto S. Living donor liver transplantation for patients with HCC exceeding the Milan criteria: a proposal of expanded criteria. *Dig Dis* 2007; **25**: 299-302 [PMID: 17960063 DOI: 10.1159/000106908]

62 **Soejima Y**, Taketomi A, Yoshizumi T, Uchiyama H, Aishima S, Terashi T, Shimada M, Maehara Y. Extended indication for living donor liver transplantation in patients with hepatocellular carcinoma. *Transplantation* 2007; **83**: 893-899 [PMID: 17460559 DOI: 10.1097/01.tp.0000259015.46798.ec]

63 **Fujiki M**, Takada Y, Ogura Y, Oike F, Kaido T, Teramukai S, Uemoto S. Significance of des-gamma-carboxy prothrombin in selection criteria for living donor liver transplantation for hepatocellular carcinoma. *Am J Transplant* 2009; **9**: 2362-2371 [PMID: 19656125 DOI: 10.1111/j.1600-6143.2009.02783.x]

64 **Kaido T**, Ogawa K, Mori A, Fujimoto Y, Ito T, Tomiyama K, Takada Y, Uemoto S. Usefulness of the Kyoto criteria as expanded selection criteria for liver transplantation for hepatocellular carcinoma. *Surgery* 2013; **154**: 1053-1060 [PMID: 24074704 DOI: 10.1016/j.surg.2013.04.056]

65 **Shirabe K**, Taketomi A, Morita K, Soejima Y, Uchiyama H, Kayashima H, Ninomiya M, Toshima T, Maehara Y. Comparative evaluation of expanded criteria for patients with hepatocellular carcinoma beyond the Milan criteria undergoing living-related donor liver transplantation. *Clin Transplant* 2011; **25**: E491-E498 [PMID: 21518000 DOI: 10.1111/j.1399-0012.2011.01463.x]

66 **Todo S**, Furukawa H, Tada M; Japanese Liver Transplantation Study Group. Extending indication: role of living donor liver transplantation for hepatocellular carcinoma. *Liver Transpl* 2007; **13**: S48-S54 [PMID: 17969069 DOI: 10.1002/lt.21334]

67 **Yang K**, Lee TB, Choi BH, Park YM, Ryu JH, Joo DJ, Chu CW. Development and Applicability of the A-P 200 Criteria for Liver Transplantation for Hepatocellular Carcinoma. *Transplant Proc* 2016; **48**: 3317-3322 [PMID: 27931576 DOI: 10.1016/j.transproceed.2016.08.050]

68 **Kim SH**, Moon DB, Kim WJ, Kang WH, Kwon JH, Jwa EK, Cho HD, Ha SM, Chung YK, Lee SG. Preoperative prognostic values of α-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA-II) in patients with hepatocellular carcinoma for living donor liver transplantation. *Hepatobiliary Surg Nutr* 2016; **5**: 461-469 [PMID: 28124000 DOI: 10.21037/hbsn.2016.11.05]

69 **Lee JH**, Cho Y, Kim HY, Cho EJ, Lee DH, Yu SJ, Lee JW, Yi NJ, Lee KW, Kim SH, Kim JM, Joh JW, Teperman LW, Park JS, Kim YJ, Suh KS, Yoon JH. Serum Tumor Markers Provide Refined Prognostication in Selecting Liver Transplantation Candidate for Hepatocellular Carcinoma Patients Beyond the Milan Criteria. *Ann Surg* 2016; **263**: 842-850 [PMID: 26779979 DOI: 10.1097/SLA.0000000000001578]

70 **Chaiteerakij R**, Zhang X, Addissie BD, Mohamed EA, Harmsen WS, Theobald PJ, Peters BE, Balsanek JG, Ward MM, Giama NH, Moser CD, Oseini AM, Umeda N, Venkatesh S, Harnois DM, Charlton MR, Yamada H, Satomura S, Algeciras-Schimnich A, Snyder MR, Therneau TM, Roberts LR. Combinations of biomarkers and Milan criteria for predicting hepatocellular carcinoma recurrence after liver transplantation. *Liver Transpl* 2015; **21**: 599-606 [PMID: 25789635 DOI: 10.1002/lt.24117]

71 **Halazun KJ**, Aldoori A, Malik HZ, Al-Mukhtar A, Prasad KR, Toogood GJ, Lodge JP. Elevated preoperative neutrophil to lymphocyte ratio predicts survival following hepatic resection for colorectal liver metastases. *Eur J Surg Oncol* 2008; **34**: 55-60 [PMID: 17448623 DOI: 10.1016/j.ejso.2007.02.014]

72 **Halazun KJ**, Hardy MA, Rana AA, Woodland DC 4th, Luyten EJ, Mahadev S, Witkowski P, Siegel AB, Brown RS Jr, Emond JC. Negative impact of neutrophil-lymphocyte ratio on outcome after liver transplantation for hepatocellular carcinoma. *Ann Surg* 2009; **250**: 141-151 [PMID: 19561458 DOI: 10.1097/SLA.0b013e3181a77e59]

73 **Bertuzzo VR**, Cescon M, Ravaioli M, Grazi GL, Ercolani G, Del Gaudio M, Cucchetti A, D'Errico-Grigioni A, Golfieri R, Pinna AD. Analysis of factors affecting recurrence of hepatocellular carcinoma after liver transplantation with a special focus on inflammation markers. *Transplantation* 2011; **91**: 1279-1285 [PMID: 21617590 DOI: 10.1097/TP.0b013e3182187cf0]

74 **Wang GY**, Yang Y, Li H, Zhang J, Jiang N, Li MR, Zhu HB, Zhang Q, Chen GH. A scoring model based on neutrophil to lymphocyte ratio predicts recurrence of HBV-associated hepatocellular carcinoma after liver transplantation. *PLoS One* 2011; **6**: e25295 [PMID: 21966488 DOI: 10.1371/journal.pone.0025295]

75 **Motomura T**, Shirabe K, Mano Y, Muto J, Toshima T, Umemoto Y, Fukuhara T, Uchiyama H, Ikegami T, Yoshizumi T, Soejima Y, Maehara Y. Neutrophil-lymphocyte ratio reflects hepatocellular carcinoma recurrence after liver transplantation via inflammatory microenvironment. *J Hepatol* 2013; **58**: 58-64 [PMID: 22925812 DOI: 10.1016/j.jhep.2012.08.017]

76 **Limaye AR**, Clark V, Soldevila-Pico C, Morelli G, Suman A, Firpi R, Nelson DR, Cabrera R. Neutrophil-lymphocyte ratio predicts overall and recurrence-free survival after liver transplantation for hepatocellular carcinoma. *Hepatol Res* 2013; **43**: 757-764 [PMID: 23193965 DOI: 10.1111/hepr.12019]

77 **Xiao GQ**, Liu C, Liu DL, Yang JY, Yan LN. Neutrophil-lymphocyte ratio predicts the prognosis of patients with hepatocellular carcinoma after liver transplantation. *World J Gastroenterol* 2013; **19**: 8398-8407 [PMID: 24363533 DOI: 10.3748/wjg.v19.i45.8398]

78 **Lai Q**, Castro Santa E, Rico Juri JM, Pinheiro RS, Lerut J. Neutrophil and platelet-to-lymphocyte ratio as new predictors of dropout and recurrence after liver transplantation for hepatocellular cancer. *Transpl Int* 2014; **27**: 32-41 [PMID: 24118272 DOI: 10.1111/tri.12191]

79 **Parisi I**, Tsochatzis E, Wijewantha H, Rodríguez-Perálvarez M, De Luca L, Manousou P, Fatourou E, Pieri G, Papastergiou V, Davies N, Yu D, Luong T, Dhillon AP, Thorburn D, Patch D, O'Beirne J, Meyer T, Burroughs AK. Inflammation-based scores do not predict post-transplant recurrence of hepatocellular carcinoma in patients within Milan criteria. *Liver Transpl* 2014; **20**: 1327-1335 [PMID: 25088400 DOI: 10.1002/lt.23969]

80 **Shindoh J**, Sugawara Y, Nagata R, Kaneko J, Tamura S, Aoki T, Sakamoto Y, Hasegawa K, Tanaka T, Kokudo N. Evaluation methods for pretransplant oncologic markers and their prognostic impacts in patient undergoing living donor liver transplantation for hepatocellular carcinoma. *Transpl Int* 2014; **27**: 391-398 [PMID: 24472068 DOI: 10.1111/tri.12274]

81 **Najjar M**, Agrawal S, Emond JC, Halazun KJ. Pretreatment neutrophil-lymphocyte ratio: useful prognostic biomarker in hepatocellular carcinoma. *J Hepatocell Carcinoma* 2018; **5**: 17-28 [PMID: 29404284 DOI: 10.2147/JHC.S86792]

82 **Xu ZG**, Ye CJ, Liu LX, Wu G, Zhao ZX, Wang YZ, Shi BQ, Wang YH. The pretransplant neutrophil-lymphocyte ratio as a new prognostic predictor after liver transplantation for hepatocellular cancer: a systematic review and meta-analysis. *Biomark Med* 2018; **12**: 189-199 [PMID: 29327595 DOI: 10.2217/bmm-2017-0307]

83 **Lai Q**, Melandro F, Larghi Laureiro Z, Giovanardi F, Ginanni Corradini S, Ferri F, Hassan R, Rossi M, Mennini G. Platelet-to-lymphocyte ratio in the setting of liver transplantation for hepatocellular cancer: A systematic review and meta-analysis. *World J Gastroenterol* 2018; **24**: 1658-1665 [PMID: 29686473 DOI: 10.3748/wjg.v24.i15.1658]

84 **Xia W**, Ke Q, Guo H, Wang W, Zhang M, Shen Y, Wu J, Xu X, Yan S, Yu J, Zhang M, Zheng S. Expansion of the Milan criteria without any sacrifice: combination of the Hangzhou criteria with the pre-transplant platelet-to-lymphocyte ratio. *BMC Cancer* 2017; **17**: 14 [PMID: 28056901 DOI: 10.1186/s12885-016-3028-0]

85 **Han S**, Lee S, Yang JD, Leise MD, Ahn JH, Kim S, Jung K, Gwak MS, Kim GS, Ko JS. Risk of posttransplant hepatocellular carcinoma recurrence is greater in recipients with higher platelet counts in living donor liver transplantation. *Liver Transpl* 2018; **24**: 44-55 [PMID: 29024412 DOI: 10.1002/lt.24961]

86 **Kusumanto YH**, Dam WA, Hospers GA, Meijer C, Mulder NH. Platelets and granulocytes, in particular the neutrophils, form important compartments for circulating vascular endothelial growth factor. *Angiogenesis* 2003; **6**: 283-287 [PMID: 15166496 DOI: 10.1023/B:AGEN.0000029415.62384.ba]

87 **Bambace NM**, Holmes CE. The platelet contribution to cancer progression. *J Thromb Haemost* 2011; **9**: 237-249 [PMID: 21040448 DOI: 10.1111/j.1538-7836.2010.04131.x]

88 **Kuang DM**, Zhao Q, Wu Y, Peng C, Wang J, Xu Z, Yin XY, Zheng L. Peritumoral neutrophils link inflammatory response to disease progression by fostering angiogenesis in hepatocellular carcinoma. *J Hepatol* 2011; **54**: 948-955 [PMID: 21145847 DOI: 10.1016/j.jhep.2010.08.041]

89 **Li XF**, Chen DP, Ouyang FZ, Chen MM, Wu Y, Kuang DM, Zheng L. Increased autophagy sustains the survival and pro-tumourigenic effects of neutrophils in human hepatocellular carcinoma. *J Hepatol* 2015; **62**: 131-139 [PMID: 25152203 DOI: 10.1016/j.jhep.2014.08.023]

90 **Gay LJ**, Felding-Habermann B. Contribution of platelets to tumour metastasis. *Nat Rev Cancer* 2011; **11**:

123-134 [PMID: 21258396 DOI: 10.1038/nrc3004]
91 **Bihari C**, Rastogi A, Shasthry SM, Bajpai M, Bhadoria AS, Rajesh S, Mukund A, Kumar A, Sarin SK. Platelets contribute to growth and metastasis in hepatocellular carcinoma. *APMIS* 2016; **124**: 776-786 [PMID: 27457354 DOI: 10.1111/apm.12574]
92 **Zheng Z**, Zhou L, Gao S, Yang Z, Yao J, Zheng S. Prognostic role of C-reactive protein in hepatocellular carcinoma: a systematic review and meta-analysis. *Int J Med Sci* 2013; **10**: 653-664 [PMID: 23569429 DOI: 10.7150/ijms.6050]
93 **An HJ**, Jang JW, Bae SH, Choi JY, Yoon SK, Lee MA, You YK, Kim DG, Jung ES. Serum C-reactive protein is a useful biomarker for predicting outcomes after liver transplantation in patients with hepatocellular carcinoma. *Liver Transpl* 2012; **18**: 1406-1414 [PMID: 22821639 DOI: 10.1002/lt.23512]
94 **Kim YK**, Kim SH, Lee SD, Hong SK, Park SJ. Pretransplant serum levels of C-reactive protein predict prognoses in patients undergoing liver transplantation for hepatocellular carcinoma. *Transplant Proc* 2015; **47**: 686-693 [PMID: 25891712 DOI: 10.1016/j.transproceed.2014.11.048]
95 **Yoshizumi T**, Ikegami T, Yoshiya S, Motomura T, Mano Y, Muto J, Ikeda T, Soejima Y, Shirabe K, Maehara Y. Impact of tumor size, number of tumors and neutrophil-to-lymphocyte ratio in liver transplantation for recurrent hepatocellular carcinoma. *Hepatol Res* 2013; **43**: 709-716 [PMID: 23190306 DOI: 10.1111/hepr.12016]
96 **Na GH**, Kim DG, Han JH, Kim EY, Lee SH, Hong TH, You YK. Inflammatory markers as selection criteria of hepatocellular carcinoma in living-donor liver transplantation. *World J Gastroenterol* 2014; **20**: 6594-6601 [PMID: 24914382 DOI: 10.3748/wjg.v20.i21.6594]
97 **Wang W**, Ye Y, Wang T, Zhang F, Geng L, Yu J, Zhou L, Yan S, Zheng S. Prognostic prediction of male recipients selected for liver transplantation: With special attention to neutrophil to lymphocyte ratio. *Hepatol Res* 2016; **46**: 899-907 [PMID: 26666880 DOI: 10.1111/hepr.12633]
98 **Halazun KJ**, Najjar M, Abdelmessih RM, Samstein B, Griesemer AD, Guarrera JV, Kato T, Verna EC, Emond JC, Brown RS. Recurrence After Liver Transplantation for Hepatocellular Carcinoma: A New MORAL to the Story. *Ann Surg* 2017; **265**: 557-564 [PMID: 27611615 DOI: 10.1097/SLA.0000000000001966]
99 **Harimoto N**, Yoshizumi T, Shimagaki T, Nagatsu A, Motomura T, Harada N, Okabe H, Itoh S, Ikegami T, Uchiyama H, Soejima Y, Maehara Y. Inflammation-based Prognostic Score in Patients with Living Donor Liver Transplantation for Hepatocellular Carcinoma. *Anticancer Res* 2016; **36**: 5537-5542 [PMID: 27798927 DOI: 10.21873/anticanres.11137]
100 **Fu H**, Zheng J, Cai J, Zeng K, Yao J, Chen L, Li H, Zhang J, Zhang Y, Zhao H, Yang Y. Systemic Immune-Inflammation Index (SII) is Useful to Predict Survival Outcomes in Patients After Liver Transplantation for Hepatocellular Carcinoma within Hangzhou Criteria. *Cell Physiol Biochem* 2018; **47**: 293-301 [PMID: 29768257 DOI: 10.1159/000489807]
101 **Taketa K**, Endo Y, Sekiya C, Tanikawa K, Koji T, Taga H, Satomura S, Matsuura S, Kawai T, Hirai H. A collaborative study for the evaluation of lectin-reactive alpha-fetoproteins in early detection of hepatocellular carcinoma. *Cancer Res* 1993; **53**: 5419-5423 [PMID: 7693340]
102 **Kuromatsu R**, Tanaka M, Tanikawa K. Serum alpha-fetoprotein and lens culinaris agglutinin-reactive fraction of alpha-fetoprotein in patients with hepatocellular carcinoma. *Liver* 1993; **13**: 177-182 [PMID: 7690873 DOI: 10.1111/j.1600-0676.1993.tb00627.x]
103 **Li J**, Han X, Yu X, Xu Z, Yang G, Liu B, Xiu P. Clinical applications of liquid biopsy as prognostic and predictive biomarkers in hepatocellular carcinoma: circulating tumor cells and circulating tumor DNA. *J Exp Clin Cancer Res* 2018; **37**: 213 [PMID: 30176913 DOI: 10.1186/s13046-018-0893-1]
104 **Wang S**, Zheng Y, Liu J, Huo F, Zhou J. Analysis of circulating tumor cells in patients with hepatocellular carcinoma recurrence following liver transplantation. *J Investig Med* 2018; **66**: 1-6 [PMID: 29632031 DOI: 10.1136/jim-2017-000655]
105 **Marubashi S**, Dono K, Nagano H, Sugita Y, Asaoka T, Hama N, Miyamoto A, Takeda Y, Umeshita K, Monden M. Detection of AFP mRNA-expressing cells in the peripheral blood for prediction of HCC recurrence after living donor liver transplantation. *Transpl Int* 2007; **20**: 576-582 [PMID: 17425725 DOI: 10.1111/j.1432-2277.2007.00480.x]
106 **Ono A**, Fujimoto A, Yamamoto Y, Akamatsu S, Hiraga N, Imamura M, Kawaoka T, Tsuge M, Abe H, Hayes CN, Miki D, Furuta M, Tsunoda T, Miyano S, Kubo M, Aikata H, Ochi H, Kawakami YI, Arihiro K, Ohdan H, Nakagawa H, Chayama K. Circulating Tumor DNA Analysis for Liver Cancers and Its Usefulness as a Liquid Biopsy. *Cell Mol Gastroenterol Hepatol* 2015; **1**: 516-534 [PMID: 28210698 DOI: 10.1016/j.jcmgh.2015.06.009]
107 **Liese J**, Peveling-Oberhag J, Doering C, Schnitzbauer AA, Herrmann E, Zangos S, Hansmann ML, Moench C, Welker MW, Zeuzem S, Bechstein WO, Ulrich F. A possible role of microRNAs as predictive markers for the recurrence of hepatocellular carcinoma after liver transplantation. *Transpl Int* 2016; **29**: 369-380 [PMID: 26697811 DOI: 10.1111/tri.12733]
108 **Han ZB**, Zhong L, Teng MJ, Fan JW, Tang HM, Wu JY, Chen HY, Wang ZW, Qiu GQ, Peng ZH. Identification of recurrence-related microRNAs in hepatocellular carcinoma following liver transplantation. *Mol Oncol* 2012; **6**: 445-457 [PMID: 22552153 DOI: 10.1016/j.molonc.2012.04.001]
109 **Bharali D**, Jebur HB, Baishya D, Kumar S, Sarma MP, Masroor M, Akhter J, Husain SA, Kar P. Expression Analysis of Serum microRNA-34a and microRNA-183 in Hepatocellular Carcinoma. *Asian Pac J Cancer Prev* 2018; **19**: 2561-2568 [PMID: 30256056]
110 **Cho HJ**, Kim SS, Nam JS, Kim JK, Lee JH, Kim B, Wang HJ, Kim BW, Lee JD, Kang DY, Kim JH, Jae YM, Hwang JC, Shin SJ, Lee KM, Cho SW, Cheong JY. Low levels of circulating microRNA-26a/29a as poor prognostic markers in patients with hepatocellular carcinoma who underwent curative treatment. *Clin Res Hepatol Gastroenterol* 2017; **41**: 181-189 [PMID: 27839726 DOI: 10.1016/j.clinre.2016.09.011]
111 **Zhang J**, Lin H, Wang XY, Zhang DQ, Chen JX, Zhuang Y, Zheng XL. Predictive value of microRNA-143 in evaluating the prognosis of patients with hepatocellular carcinoma. *Cancer Biomark* 2017; **19**: 257-262 [PMID: 28436387 DOI: 10.3233/CBM-160357]

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