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A nomogram predicting pulmonary metastasis of hepatocellular carcinoma following partial hepatectomy

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Background: Pulmonary metastasis (PM) following curative hepatectomy for hepatocellular carcinoma (HCC) is indicative of a poor prognosis. This study aimed to develop a nomogram to identify patients at high risks of PM.

Methods: A primary cohort of patients who underwent curative hepatectomy for HCC at the Eastern Hepatobiliary Surgery Hospital from 2002 to 2010 was prospectively studied. A nomogram predicting PM was constructed based on independent risk factors of PM. The predictive performance was evaluated by the concordance index (c-index), calibration curve and decision curve analysis (DCA). During the study period, a validation cohort was included at the First Affiliated Hospital of Fujian Medical University.

Results: Postoperative PMs were detected in 106 out of 620 and 45 out of 218 patients, respectively, in two cohorts. Factors included in the nomogram were microvascular invasion, serum alpha-fetoprotein, tumour size, tumour number, encapsulation and intratumoral CD34 staining. The nomogram had a c-index of 0.75 and 0.82 for the two cohorts for predicting PM, respectively. The calibration curves fitted well. In the two cohorts, the DCA demonstrated positive net benefits by the nomogram, within the threshold probabilities of PM $>10\%$.

Conclusion: The nomogram was accurate in predicting PM following curative hepatectomy for HCC.

Hepatocellular carcinoma (HCC) is the fifth common malignancy and a major cause of cancer-related mortality (Ferlay *et al*, 2010). Partial hepatectomy and transplantation still remain the major curative therapeutic options available to patients with HCC. However, following partial hepatectomy there is a significant chance of recurrence (Poon *et al*, 2000). Although intrahepatic recurrence is most common after operation, extrahepatic metastases (EHMs) still account for 14.0–25.5% of all recurrences. Pulmonary metastases (PMs) represent nearly 50% of all EHM (Hong *et al*, 2003; Yang *et al*, 2007; Li *et al*, 2012).

For most cancers, PM signifies systemic disease that is not curable with surgery. However, in the past two decades, data from some institutions suggested that pneumonectomy for PM of HCC could achieve a long-term survival, although it needs to be offered in well-selected patients with the lung as the only extrahepatic metastatic site and single PM lesion, and with a long disease-free interval (Chua and Morris, 2012). In addition, two recent studies with more than 22% of patients with PM showed sorafenib to prolong overall survival in patients with advanced HCC (Llovet *et al*, 2008; Cheng *et al*, 2009). In animals using orthotopic models, sorafenib also suppressed postresectional intrahepatic and distant metastasis of HCC, making it a potential choice in the prevention of postoperative PM (Feng *et al*, 2011), although the results of a phase III clinical trial that assesses the efficacy of sorafenib as an

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adjuvant therapy for HCC following partial hepatectomy are not yet available. Thus, the ability to identify HCC patients who are at high risks of developing postoperative PM facilitates not only early detection of PM lesions that are suitable for lung resection, but also identification of patients who might benefit from adjuvant therapies.

PM of HCC is hard to predict on clinical ground. A nomogram is a statistical tool that provides the overall probability of a specific outcome for an individual patient (Kattan and Scardino, 2007). In this study we constructed a nomogram from a primary cohort of patients to predict the likelihood of PM in patients with HCC after partial hepatectomy, and validated the nomogram with a validation cohort of patients.

MATERIALS AND METHODS

Patients. Consecutive patients with pathologically proven HCC after curative partial hepatectomy carried out between July 2002 and April 2010 at the fourth Department of Hepatic Surgery of the Eastern Hepatobiliary Surgery Hospital (EHBH) were enrolled into this study. The data of these patients were collected prospectively and analysed retrospectively. The definition of curative resection has been described in our previous study (Wang *et al*, 2010).

Data from another independent cohort of consecutive patients who underwent curative partial hepatectomy for HCC at the Department of Hepatobiliary Surgery, the First Affiliated Hospital of Fujian Medical University, during the same study period were collected retrospectively.

The clinical staging was based on the Barcelona Clinic Liver Cancer system and the seventh edition of the TNM/AJCC classification (Edge *et al*, 2009; European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer, 2012). Tumour differentiation was based on the Edmondson–Steiner classification. Paraffin-embedded tissue blocks were obtained after partial hepatectomy. Immunohistochemical staining of CD34, CK18, CK19 and HepPra-1 in tumour tissues was routinely performed in the pathological analysis. The status of these markers was considered positive if $\geqslant 50\%$ of cells stained positively.

The study was approved by the Institutional Ethics Committee from the two hospitals and it was censored on 19 October 2012. Informed consent was obtained from all the patients before surgery for using their data in research.

Hepatectomy and follow-up. Partial hepatectomy was carried out based on Couinaud's segments/sectors/hemilivers, tumour diameter, location, presence/absence of cirrhosis and estimated volume of future liver remnant. An anatomical hepatectomy was the preferred method if the tumour was within a segment/sector/hemiliver provided that the liver remnant could well compensate for the liver function. A non-anatomical resection was used for tumours situated at the junction of several segments, or for peripherally located tumours, or for patients who could not tolerate an anatomical resection.

Patients were followed up once every 2–3 months during the first 2 years after surgery, and once every 3–6 months thereafter. In each follow-up visit, the routine examination was carried out, including a detailed clinical history and physical examination, blood tests for hepatitis B and C immunology, hepatitis B virus (HBV)-DNA load, liver function and serum alpha-fetoprotein (AFP), chest X-ray and abdominal ultrasound (US). Computerised tomography (CT) of the chest, and contrast-enhanced CT and/or magnetic resonance imaging of the abdomen were performed every 6 months or earlier when tumour recurrence/metastasis was suspected. Hepatic angiography or 18F-fluorodeoxyglucose positron emission tomography was only carried out for patients whose recurrences were not well identified by the above methods. For the patient who survived for a disease-free interval $\geqslant 5$ years, the follow-up was performed less frequently as once every 6–12 months, with the examination of serum tests, abdominal US and chest X-ray.

The diagnosis of PM was mainly based clinically as previously reported (Bhattacharjya *et al*, 2006; Baek *et al*, 2012; Kong *et al*, 2012). The diagnostic criteria were: (a) new and growing lesions, especially multiple, round nodules in the periphery of lungs on dynamic chest CT scan; (b) elevation of serum AFP levels, especially in patients with initially raised serum AFP, which decreased after liver resection. Cytological examination of sputum, bronchofibrescopic brushing or bronchial perfusate was used in differentiating other lung lesions. Patients with PM diagnosed before or simultaneously with intrahepatic recurrence and/or extrapulmonary metastasis were included into this study. Patients with PM diagnosed later than any other recurrences were not analysed in this study because these cases could be metastases from these recurrent lesions instead of from the primary tumour, which had been resected.

Statistical analysis. The clinical end points were the time to PM and overall survival. The time to PM was calculated from the date of surgery to the date when PM was diagnosed or to the last follow-up visit. The overall survival was the interval between the date of liver resection to the date of death or the last follow-up. Categorical variables were compared using the χ^2-test or Fisher's exact test. Continuous variables were compared using the *t*-test or Mann–Whitney *U*-test. A competing risk survival analysis was conducted to identify risk factors of PM in the primary cohort, and treating deaths, intrahepatic and other EHMs before PM as competing events.

A final model selection for nomogram was performed by a backward step-down selection process using a threshold *P*-value of <0.05. The performance of the nomogram was measured by concordance index (*c*-index) and assessed by calibration. Aiming at more stability, a 10-fold cross-validation was done and repeated 100 times, and the average *c*-index was calculated. In calibration, the predicted probability of PM generated using 10-fold cross validation was compared with the observed cumulative incidence estimates of PM probability. The validation cohort and all the patients within the Milan criteria (Mazzaferro *et al*, 1996) were analysed using the method reported before (Wang *et al*, 2013).

The decision curve analysis (DCA) was used to evaluate the nomogram for the prediction of PM. This method incorporates the clinical consequences of the nomogram by applying a different weight to the true- and false-positive results. This weighting was varied to reflect the difference in patient preferences or differences in opinion on the risks of a procedure. These preferences were expressed in terms of a threshold probability for action. DCA provides a net benefit, which was calculated using the formula: net benefit $=$ true-positives/n $-$ false-positives/$n \times$ (pt/(1 $-$ pt)). In this formula, pt is the threshold probability of PM. Then, the net reduction in interventions per 100 patients could be calculated accordingly. The optimal model is one with a high net benefit as calculated within the favourable probability. This technique and the interpretation of the final result are available in a step-by-step tutorial online (Vickers and Elkin, 2006; Steyerberg and Vickers, 2008).

The statistical analysis was carried out using STATA 12 for Windows (Stata Press, College Station, TX, USA) and R 2.13.2 (http://www.r-project.org/) with library rms, cmprsk and QHScrnomo (Cahlon *et al*, 2012).

RESULTS

Of the 681 patients who received partial hepatectomy at the EHBH during the study period, we excluded patients with a history of

Table 1. Patients' characteristics

	Primary cohort		Validation cohort	
Variables	**No. of patients**	**%**	**No. of patients**	**%**
No. of patients	620	100	218	100
Age, years				
Median	51.4		53.0	
Range	17–78		16–77	
Sex				
Male	557	89.8	192	88.1
Female	63	10.2	26	11.9
HBsAg				
Negative	110	17.7	48	22.0
Positive	510	82.3	170	78.0
HCV-Ab				
Negative	601	96.9	210	96.3
Positive	19	3.1	8	3.7
PT, second				
Median	11.9		12	
Range	8–19.4		9.9–12.4	
ALB, g l^{-1}				
Median	41.5		42	
Range	28–80		30–50.9	
TBIL, μmol l^{-1}				
Median	14.7		15	
Range	4.9–80		6–40	
ALT, U l^{-1}				
Median	40.9		39.0	
Range	5.8–819.8		10–1689	
AFP, μg ml^{-1}				
Median	114.2		78.5	
Range	1–120 101		1–60 500	
Hepatectomy				
Anatomical	358	57.7	123	56.4
Non-anatomical	620	42.3	95	43.6
Cirrhosis				
No	409	66.0	159	72.9
Yes	211	34.0	59	27.1
Tumour size, cm				
Median	5		5.1	
Range	1–23.2		1–19	
No. of tumours				
Single	551	88.9	170	78.2
Multiple	69	11.1	48	12.8
Capsule				
Incomplete	382	61.6	126	57.8
Complete	238	38.4	92	42.2
Edmondson–Steiner classification				
I–II	133	21.5	43	19.7
III–IV	487	78.5	175	80.3
MVI				
Absence	449	72.4	150	68.8
Presence	171	27.6	68	31.2
Surgical margin, cm				
Median	0.9		0.8	
Range	0.1–3.5		0.1–2.0	
Blood transfusion				
No	510	82.3	187	85.8
Yes	110	17.7	31	14.2
CD34				
Negative	135	21.8	45	20.6
Positive	485	78.2	173	79.4
CK18				
Negative	202	32.6	55	25.2
Positive	418	67.4	163	74.8
CK19				
Negative	557	89.8	198	90.8
Positive	63	10.2	20	9.2
HepPar-1				
Negative	145	23.4	32	14.7
Positive	475	76.6	186	85.3
Milan criteria				
Within	318	51.3	110	50.5
Beyond	302	48.7	108	49.5

Abbreviations: AFP = alpha-fetoprotein; ALB = albumin; ALT = alanine aminotransferase; CD34 = cluster of differentiation 34; CK18 and 19 = Cytokeratin 18 and 19; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HepPar-1 = hepatocyte paraffin 1; MVI = microvascular invasion; PT = prothrombin time; TBIL = total bilirubin.

preoperative anti-cancer therapy ($n = 23$), uncertain preoperative pulmonary lesions ($n = 4$), other malignancies ($n = 6$; 4 diagnosed before and 2 after hepatectomy), tumours with major vascular invasion or EHM ($n = 13$), incomplete data ($n = 12$) and in-hospital mortality ($n = 3$). Finally, 620 patients formed the primary cohort.

Of the 249 patients who received partial hepatectomy at the First Affiliated Hospital of Fujian Medical University during the study period, we excluded patients who had a history of preoperative anti-cancer therapy ($n = 10$), other malignancies ($n = 3$), tumours with major vascular invasion and EHM ($n = 7$), incomplete data ($n = 9$) and in-hospital mortality ($n = 2$). Finally, 218 patients comprised the validation cohort.

Clinicopathological characteristics. The clinicopathological characteristics of the patients are shown in Table 1. Most patients were men (89.4%), were positive for HBV surface antigen (81.2%)

Table 2. Independent risk factors predicting PM in the primary cohort

	Univariate analysis			Multivariate analysis		
Variables	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Age, years	0.97	0.95–0.99	0.495			NA
Sex: male *vs* female	1.40	0.68–2.90	0.365			NA
HBsAg: positive *vs* negative	1.55	0.89–2.70	0.119			NA
PT, second	1.07	0.94–1.21	0.305			NA
ALB, $g\,l^{-1}$	1.01	0.97–1.05	0.588			NA
TBIL, $\mu mol\,l^{-1}$	1.00	0.98–1.02	0.921			NA
ALT, $U\,l^{-1}$	1.00	1.00–1.00	0.509			NA
Log (AFP)	1.37	1.14–1.65	**0.001**	1.34	1.10–1.62	**0.004**
Hepatectomy: anatomical *vs* non-anatomical	0.98	0.66–1.44	0.903			
Cirrhosis: yes *vs* no	1.02	0.69–1.52	0.908			NA
Tumour size, cm	1.10	1.06–1.14	**<0.001**	1.08	1.03–1.13	**0.001**
No. of tumours: multiple *vs* single	2.07	1.30–3.27	**0.002**	1.72	1.02–2.88	**0.041**
Capsule: incomplete *vs* complete	1.64	1.08–2.50	**0.021**	2.84	1.70–4.76	**<0.001**
Differentiation: III–IV *vs* I–II	1.55	0.92–2.62	0.103			NA
MVI: presence *vs* absence	4.08	2.78–5.99	**<0.001**	3.73	2.44–5.70	**<0.001**
Surgical margin, cm	0.69	0.51–0.94	0.017			NA
Blood transfusion: yes *vs* no	1.07	0.66–1.75	0.777			NA
CD34: positive *vs* negative	5.22	1.67–16.3	**0.004**	3.50	1.14–10.78	**0.029**
CK18: positive *vs* negative	1.03	0.68–1.54	0.903			NA
CK19: positive *vs* negative	0.82	0.42–1.62	0.573			NA
HEP-1: positive *vs* negative	1.44	0.88–2.36	0.150			NA

Abbreviations: AFP = alpha-fetoprotein; ALB = albumin; ALT = alanine aminotransferase; CD34 = cluster of differentiation 34; CI = confidence interval; CK18 and 19 = Cytokeratin 18 and 19; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; Hep-1 = hepatocyte paraffin 1; HR = hazard ratio; MVI = microvascular invasion; PM = pulmonary metastasis; PT = prothrombin time; TBIL = total bilirubin. Bold values indicate $P<0.05$.

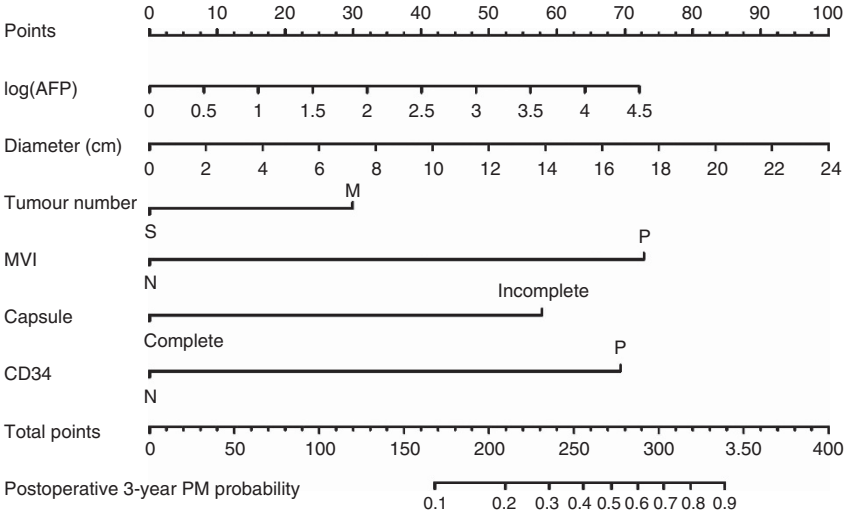

Figure 1. Nomogram for predicting PM of HCC patients following hepatectomy. To calculate the probability of PM, first determine the value for each factor by drawing a vertical line from that factor to the points scale. Then sum up all the individual values and draw a vertical line from the total points scale to the probability at the Probability at the year 3 line to obtain the PM estimates. AFP, preoperative level of serum α-fetoprotein; MVI, presence of MVI.

and 86.0% of the patients had a single tumour nodule at the time of resection (Table 1). There were no significant differences in the characteristics between the two cohorts of patients.

Prognosis of the primary cohort. The median follow-up of the patients was 2.4 years (range: 0.1–9.1 years) and the median time to PM was 1.7 years (range: 0.1–8.9 years). The postoperative

1-, 3- and 5-year recurrence and overall survival rates were 43.7%, 68.8% and 83.7%, and 90.7%, 61.2% and 43.9%, respectively.

At the time of diagnosis of the first recurrence or metastases after hepatic resection, 262 patients had intrahepatic recurrences only; 27 patients had synchronous intrahepatic recurrence and extrapulmonary metastases; 54 patients had extrapulmonary metastases only, including metastases to the peritoneal cavity ($n=19$), lymph node ($n=15$), bone ($n=13$), adrenal gland ($n=5$), brain ($n=3$) and other less common sites ($n=3$). For the 106 patients who presented with PM (91.5% within 3 years after surgery) either before or at the same time with recurrences at other sites, they were the subjects in this study.

Construction of the nomogram. Using multivariate analysis, the following six independent variables were selected in the nomogram to predict the 3-year rate of PM (Table 2; Figure 1): preoperative serum AFP level, tumour size, multiple tumour nodules, incomplete tumour encapsulation, presence of microvascular invasion (MVI) and positivity of intratumoral CD34 staining. The model demonstrated good accuracy for predicting a 3-year probability rate of PM, with a *c*-index of 0.75. Calibration curves revealed good model calibration between the PM estimates from the nomogram and those derived from cumulative incidence function estimates (Figure 2A).

Validation of the nomogram. The median follow-up time of patients was 2.3 years (range: 0.1–8.8 years), and the median time to PM was 1.5 years (range: 0.1–8.8 years) in the validation cohort. The recurrence and overall survival rates at 1, 3 and 5 years were 44.2%, 73.3% and 82.2%, and 88.0%, 61.0% and 38.5%, respectively. At the time of diagnosis of the first recurrence or metastasis after hepatic resection, 90 patients had intrahepatic recurrences alone; 7 patients had synchronous intrahepatic recurrence with extrapulmonary metastases; and 20 patients had extrapulmonary metastases only. There were 45 patients who presented with PM before or simultaneously with other tumour recurrences. The nomogram displayed a *c*-index of 0.82 and showed a good calibration curve for predicting the 3-year rate of PM (Figure 2B).

Predictive performance of the nomogram for patients within the Milan criteria. The predictive ability of this nomogram in 428 patients who were within the Milan criteria in the primary and validation cohorts was studied. PM occurred in 46 patients (10.8%), which was lower than the rate of PM in patients with more advanced HCC (25.6%, 105 out of 410). The nomogram displayed a good *c*-index (0.78) and calibration curve (Figure 2C) in predicting postoperative PM in these patients.

Clinical usefulness of nomogram as evaluated by DCA. DCA revealed that the nomogram provided superior net benefit and reduction than that of treating everyone or treating no one, with a probability threshold of 10% or greater (Figure 3).

DISCUSSION

Pulmonary metastasis following partial hepatectomy for HCC is common. Although progress has been made on the management of PM, there is no method for predicting PM, thus limiting its early detection. In this study, we developed a nomogram with a *c*-index >0.75 for such a prediction.

We also tested the role of this nomogram in PM prediction for patients with HCC within the Milan criteria. It is known that this group of patients have a relatively good prognosis after partial hepatectomy (Bolondi *et al*, 2001), although some still develop early tumour recurrence and metastasis. In our study, 7.0% of these patients developed PM within 2 years of surgery. Our results suggested that a subset of patients with early HCC who are likely to develop PM after surgery could be identified by this nomogram, which has a *c*-index of 0.78.

This nomogram included all the important variables of the pathological characteristics, and the serum and tissue tumour biomarkers of HCC, thus making it accurate in the prediction of PM. For the pathological variables, in addition to tumour size and

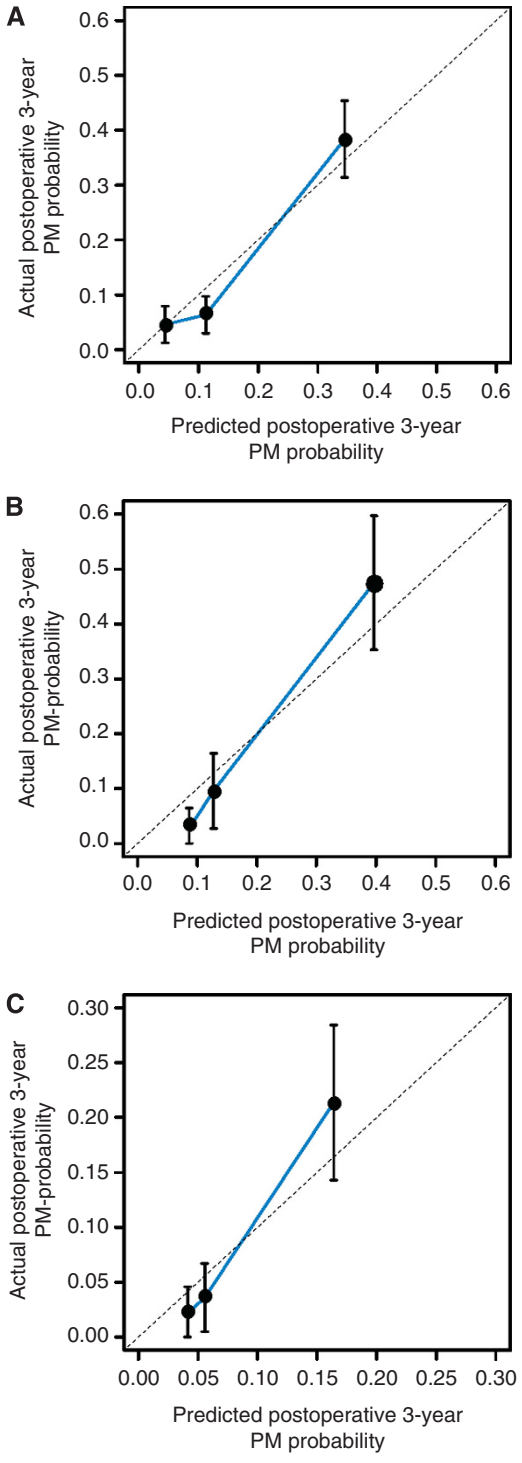

Figure 2. Calibration of the nomogram. The nomogram predicted the probabilities of postoperative PM within 3 years in the primary cohort (**A**), the validation cohort (**B**) and in patients who were within the Milan criteria in both the two cohorts, (**C**) the actual postoperative 3-year PM-probabilities are plotted on the *y* axis. The predicted postoperative 3-year PM-probabilities are plotted on the *x* axis.

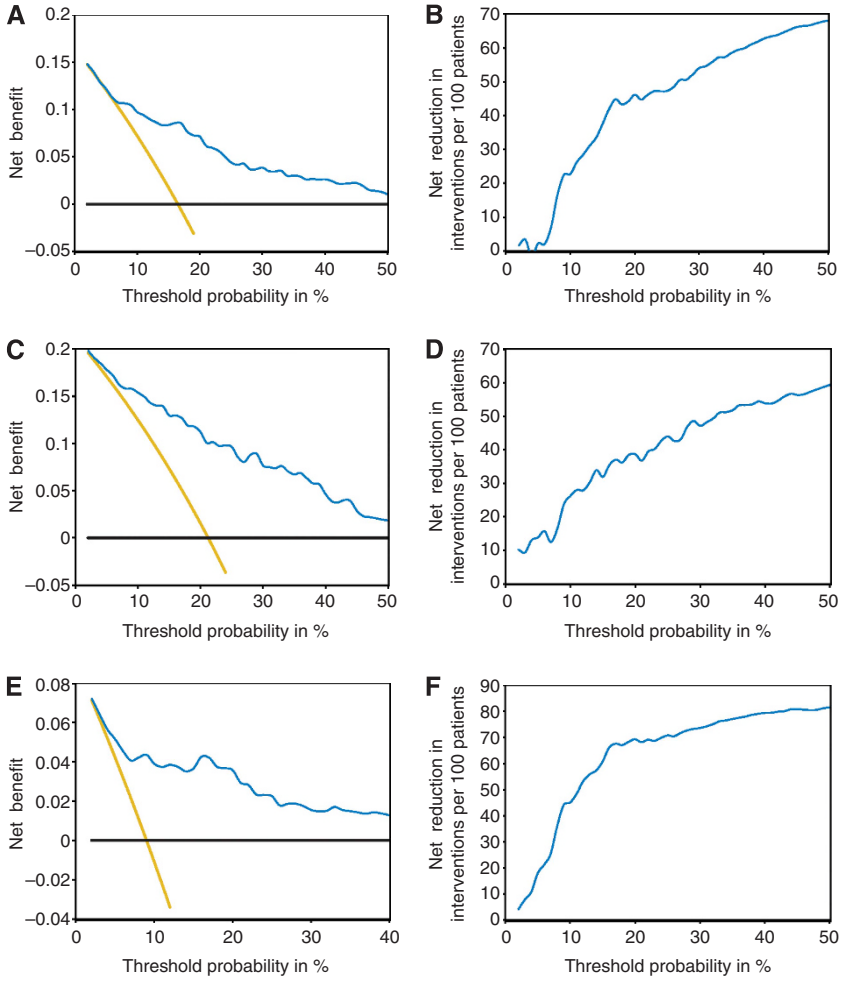

Figure 3. Decision curve analysis of the nomogram. The net benefits (*y* axis) as calculated in the primary cohort (**A**), the validation cohort (**C**) and in patients who were within the Milan criteria in both the two cohorts, (**E**) are plotted against the threshold probabilities of PM on the *x* axis; blue line: nomogram; yellow line: to assume all patients to have PM; horizontal black line: to assume no patients to have PM. Net reduction in interventions per 100 patients at different threshold probabilities of PM are shown in (**B**), (**D**) and (**F**) (the primary cohort, the validation cohort and in patients who were within the Milan criteria).

number, which reflect the stage of disease, MVI and the status of tumour encapsulation were also included. Many published reports have shown the presence of MVI to be correlated with EHM after curative resection for HCC and that MVI is a predictor of poor prognosis (Poon *et al*, 2000; Sonoyama *et al*, 2003; Li *et al*, 2012). Our study also revealed >60% of patients with MVI developed PM. Vascular invasion is an indication that the neoplasm has developed to a stage of tumour progression when its tumour cells have developed into a sufficiently evolved phenotype to invade blood vessels and begin the distant metastatic process (Hart, 1997). On the contrary, the influence of tumour encapsulation on distant spread of HCC is less studied, although well-encapsulated tumours are generally known to be associated with a low incidence of direct invasion, microsatellite formation and vascular invasion (Ng *et al*, 1992). For unencapsulated or incompletely encapsulated tumours, the cancer cells can directly invade into the surrounding liver parenchyma, causing destruction of the extra-cellular matrix and migration into the circulation (Iguchi *et al*, 2009). For HCC biomarkers, serum AFP level and intratumoral CD34 were included into the model. Recent studies have showed that a high level of serum AFP to be an independent factor of HCC invasiveness. Also, a high AFP level is closely correlated with both a decrease in immunological function in tumour host and an increase in the invasive ability of HCC cells, thus explaining the relatively poor surgical outcomes (Yamamoto *et al*, 2007; The Cancer of the Liver Italian Program (CLIP) Investigators, 1998). There have been very few studies on the AFP level of HCC patients with PM after partial hepatectomy. CD34 is an important biomarker of angiogenesis and microvascular density of HCC, and it is closely associated with HCC prognosis (Yang *et al*, 2010; Ding *et al*, 2011). A recent study showed that endothelium-coated tumour cell clusters (ECTCs) served as the origin of distant metastasis from HCC, and CD34 was closely involved in ECTC (Ding *et al*, 2011).

The diagnosis of PM in this study was based on medical imaging and serology, and we cannot completely rule out the possibility of primary pulmonary cancer (PPC) in this series. A previous study has reported the mean incidence of extrahepatic primary malignancy in HCC patients to be 6%; PPC accounted for 17.4%, and less than half of these PPCs occurred after the diagnosis of HCC (Fernández-Ruiz *et al*, 2009). On the basis of these figures, the calculated number of patients with PPC in our study should be <4. Furthermore, in the majority of cases, the diagnosis of PM from HCC was supported mainly by the changes in serum AFP level. In this study, all patients with a preoperative AFP $\geqslant 20\ \mathrm{ng\,ml^{-1}}$ ($n=112$, 74.2% of all patients with PM) presented with re-elevation of the tumour marker when postoperative PM was diagnosed. In addition, the clinical characteristic differences

between PM and PPC on CT scan can be used in the differentiation (Smith, 1998). It is our belief that the low incidence of PPC and our stringent diagnostic criteria for PM make the results reliable.

The DCA was initially used by Vickers and Elkin as a new analytical technique, incorporating the clinical consequences of a decision, to quantify the clinical usefulness of a prediction model (Vickers and Elkin, 2006). It can therefore determine whether the predictive models are clinically useful or not. In our study, the nomogram showed better net benefit and reduction at a threshold probability of 10% or greater. This suggested that if the patients were predicted with a probability of PM to be $>10\%$ by our nomogram, they should be classified to be a high-risk population. Measures to early detect or prevent PM should be instituted. Accordingly, the follow-up of these patients should be more intensive. Thus, regular chest CT scans instead of chest X-ray should be taken (Pomerri *et al*, 2012) in order to diagnose PM early. The nomogram may also be a useful tool in deciding organ allocation for secondary liver transplantation for HCC patients who have been initially treated with partial hepatectomy. A patient who is predicted to have a high risk of PM by the nomogram may not be an appropriate candidate for cadaveric liver transplantation.

This study has the following limitations: (a) most of our patients had a background of HBV infection (81.1%) and non-cirrhosis (67.8%). Although the proposed nomogram also produced good *c*-indexes (0.758 or 0.757) for prediction of PM in cirrhotic or HBV-negative patients, its performance in the patients with other underlying disease remains to be further studied. (b) Although the nomogram was based on competing risk analysis for the probability of postoperative PM, we still cannot conclude that the nomogram is absolutely specific for PM. However, the nomogram is relatively specific for PM because the *c*-indices of the nomogram in predicting PM-free EHM were 0.51 and 0.70 in the primary and validation cohorts, which were significantly lower than those in predicting PM (0.75 and 0.82, $P<0.01$).

In conclusion, we have developed a reliable nomogram to predict postoperative PM of HCC. This is a useful tool for the early diagnosis and prevention of PM. The identification of organ-specific biomarkers is still a challenge in cancer metastasis (Nguyen *et al*, 2009). With progress, a model with higher specificity and accuracy than our nomogram may be established in the future.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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