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Original Research

Nomograms Predicting Extra- and Early Intrahepatic Recurrence After Hepatic Resection of Hepatocellular Carcinoma

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Running head: Nomogram for extra- and early intrahepatic HCC recurrence

Abbreviations

HCC = Hepatocellular carcinoma

EHR = Extrahepatic recurrence

IHR -= Intrahepatic recurrence

AFP = α-fetoprotein

C-index = The concordance index

Article Summary

We have developed reliable nomograms to predict extra- and early intrahepatic recurrence of hepatocellular carcinoma after hepatic resection. The importance of this is that these nomograms are useful for the early diagnosis of extra- and early intrahepatic recurrences and could assist surgeons in decision-making for clinical management of hepatocellular carcinoma patients.

Abstract

Background: Extrahepatic recurrence (EHR) and early intrahepatic recurrence (IHR) of hepatocellular carcinoma (HCC) after hepatic resection are indicative of poor prognoses. We aimed to develop nomograms to predict EHR and early IHR after hepatic resection.

Methods: The participants of this study were 1206 patients who underwent initial and curative hepatic resection for HCC. Multivariate logistic regression analyses using the Akaike information criterion were used to construct nomograms to predict EHR and early IHR (within one year of surgery) at the first recurrence sites after hepatic resection. Performance of each nomogram was evaluated by calibration plots with bootstrapping.

Results: EHR was identified in 95 patients (7.9%) and early IHR in 296 patients (24.5%). Three predictive factors α-fetoprotein >200 ng/mL, tumor size (3–5 cm or > 5 cm vs. ≤ 3 cm), and image-diagnosed venous invasion by computed tomography were adopted in the final model of the EHR nomogram with a concordance index of 0.75. Tumor size and two additional predictors, i.e., multiple tumors and image-diagnosed portal invasion, were adopted in the final model of the early IHR nomogram with a concordance index of 0.67. The calibration plots showed good agreement between the nomogram predictions of EHR and early IHR and the actual observations of EHR and early IHR, respectively.

Conclusions: We have developed reliable nomograms to predict EHR and early IHR of HCC after hepatic resection. These are useful for the diagnostic prediction of EHR and early IHR and could guide the surgeon's selection of treatment strategies for HCC patients.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and a major cause of cancer-related death in the world.[1] Although hepatic resection has been accepted as a curative treatment for patients with HCC, the long-term outcome remains unsatisfactory because of the high incidence of postoperative recurrence.[2,3-5] The recurrence rate of HCC reaches more than 75% at five years after hepatic resection.[2] HCC recurrences are categorized into intrahepatic recurrences (IHR) and extrahepatic recurrences (EHR). Of these, IHR have been identified in more than 80% of HCC recurrences.[6] The types of IHR is considered to be divided into early and late recurrences. Early IHR is mainly derived from intrahepatic metastasis from primary cancer, [7] and is associated with a poor survival. [8] Meanwhile, EHR is identified in 14%–25.5% of HCC recurrent cases.[9-11] Because treatment options for EHR have been limited, especially for diffuse EHRs, the survival outcome of patients with EHR is reportedly very poor.[9-11] However, the management of EHR has recently been improved, and the survival benefit from locoregional therapy, including metastasetectomy and radiation therapy, has been reported in selected patients.[12, 13] Systemic therapy using molecular targeted agents or immune checkpoint inhibitors also provides long-term survival in HCC patients with extrahepatic spread.[14] Although a phase III clinical trial showed that sorafenib, the first molecular targeted agent, provided no survival benefit in an adjuvant therapy setting,[15] several molecular targeted agents and immune checkpoint inhibitors have recently been applied as adjuvant or neoadjuvant therapies.[16] Considering the high risk of EHR after hepatic resection, early detection of EHR and the identification of patients who may benefit from adjuvant or neoadjuvant therapy are very important.

Previous studies demonstrated individualized factors predicting EHR[17-19] and early IHR[20, 21] of HCC after hepatic resection, such as tumor size, microvascular invasion, multiple tumors, and serum α-fetoprotein (AFP) level. Because early IHR is mainly derived from intrahepatic metastasis through hematogenous tumor spread, [7] early IHR, like EHR, provides a significant measure of judgement for the therapeutic effects of hepatic resection in HCC. However, there have been few reports assessing the incidence probability of EHR and early IHR after hepatic resection and the probability weight of individual predictive factors for EHR and early IHR. Nomograms have been accepted as reliable tools to assess for oncological prognosis. By developing a statistical predictive model, a nomogram gives rise to a numerical probability of a clinical event, such as cancer recurrence and survival time.[22] It is expected that nomograms predicting EHR and early IHR are useful to predict the therapeutic effect of hepatic resection for HCC.

In the current study, we aimed to develop nomograms predicting EHR and early IHR after hepatic resection in patients with HCC.

METHODS

Patients

We identified 1206 patients who underwent initial and curative hepatic resection for HCC at Osaka City University Hospital from June 1990 to December 2018. Curative hepatic resection was defined as the histological absence of tumor cells along the parenchymal transection line. Exposure of only the tumor capsule with a surgical margin of 0 mm is defined as negative surgical margin.[23 24] However, patients with tumor recurrence connected to the cut surface of the remnant liver were excluded because this recurrence situation is considered as regrowth of residual tumor which was

part of the original tumor at surgery. None of the patients in this study received neoadjuvant or adjuvant therapy. This study was conducted in accordance with the guidelines of the Ethics Committee of our institution (No.3815) and the Declaration of Helsinki.

Hepatic Resection and Patient Follow-Up

Hepatic resection was carried out according to an algorithm consisting of the presence or absence of ascites, the serum total bilirubin level, and the results of the indocyanine green retention test.[25] Patients were followed up once every 3 months after surgery. At each follow-up visit, the routine examination included the measurement of HCC-specific tumor markers. In addition, ultrasonography, dynamic computed tomography (CT), or magnetic resonance imaging was conducted. The diagnostic criteria for EHRs were follows: (1) raised tumor markers that had decline to normal range after hepatic resection, (2) evidence of new extrahepatic lesions not identified preoperatively, and (3) histological diagnosis of extrahepatic lesions in patients undergoing metastasetectomy for EHR. The nomogram endpoints were the development of EHR for the first recurrence site during the follow-up time after surgery. Extrahepatic metastasis diagnosed later than IHR was excluded from the EHR as an endpoint.

Early IHR is mainly derived from intrahepatic metastasis through hematogenous tumor spread. [7] To focus on intrahepatic recurrence from primary cancer almost exclusively, the nomogram endpoints for early IHR were the development of IHR for the first recurrence site within one year after surgery.[26]

Preoperative CT findings

In this study, pathological findings pertaining to tumor progression (including microscopic vascular invasion and tumor differentiation) were not included because decision-making for clinical management of HCC, such as neoadjuvant therapy and surgical indication, are determined by preoperative factors. Several preoperative CT findings that are predictive of microscopic portal and venous invasion, and poor differentiation were included in this analysis as follows: (1) image-diagnosed portal invasion and venous invasion[27] based on the guidelines of the Liver Cancer Study Group of Japan[28]; (2) image -diagnosed non-smooth tumor margin (simple nodular type with extranodular growth and confluent multinodular type).[29]

Histology

The histological classifications of the tumor and the degree of the background liver were evaluated based on the guidelines of the Liver Cancer Study Group of Japan.[28] The grade (severity of active hepatitis) and stage (degree of hepatic fibrosis) of noncancerous hepatic tissue were determined by scoring based on the histological activity index.[30, 31]

Statistical Analysis

Background characteristics were summarized as the median and interquartile range for continuous variables and frequency and percentage for categorical variables. The presumptive nomogram prognosticators were selected based on previous study results [27, 29, 32-34] or our own clinical experience and included the age, sex, Child–Pugh class (A or B), alanine aminotransferase activity, tumor size (≤ 3 cm, 3–5 cm, or > 5 cm), multiple tumors, image-diagnosed portal invasion, image-diagnosed venous invasion,

image-diagnosed non-smooth tumor margin, liver cirrhosis, AFP (≤ 200 ng/mL or > 200 ng/mL), and intraoperative blood loss. Final models were selected using the dredge function with the Akaike information criterion in the MuMIn package of R software, version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria), which automatically calculates Akaike information criterion values for all possible combinations of fixed predictive factors. Based on the results of the multivariate logistic regression analyses for the final models, the nomograms were developed using the rms package of R software.[35] The performance of the nomograms was evaluated using the concordance index (C-index). Bootstrap validation was performed with 150 resamples to validate and calibrate the prediction models. The bootstrap bias-corrected C-indices were reported as measures of the predictive performance of the models.

RESULTS

Background characteristics for all 1206 patients are shown in Table 1. The median follow-up time was 49.9 months (interquartile range, 23.7–88.6 months). IHR was identified in 750 patients (62.1%), and 296 patients (24.5%) had early IHR (within one year after surgery), whereas 95 patients (7.9%) experienced EHR during the study period. Supplementary Table 1 shows the prevalence of the sites of EHR.

Table 2 shows the results of the multivariate logistic regression analysis for the final model predicting EHR. Three predictive factors, i.e., AFP >200 ng/mL, tumor size (3–5 cm or > 5 cm vs. ≤ 3 cm), and image-diagnosed venous invasion were adopted in the final model for the construction of the nomogram. The established nomogram is shown in Figure 1. By summing the points from each factor, locating the total points on the scale, and drawing a straight line down to the end point scales, the nomogram

indicates the incidence probability of EHR after hepatic resection.

Figure 2 shows the calibration plot using bootstrapping. The X-axis indicates the predicted EHR probability estimated by the nomogram, and the Y-axis demonstrates the actual rates of EHR. The actual EHR probability corresponded closely to the prediction of the nomogram. The calibration plot showed good agreement between the prediction by nomogram and actual observation. In terms of discriminative ability, the C-index was 0.75 (Fig. 3). The bootstrap validation with 150 resamples resulted in a C-index of 0.74. The bias-corrected C-index closely matched the initial C-index.

Table 3 shows the results of the multivariate logistic regression analysis for the final model predicting early IHR. Four predictive factors, i.e., tumor size (3–5 cm or > 5 cm vs. ≤ 3 cm), tumor exposure, multiple tumors, and image-diagnosed portal invasion were adopted in the final model for the construction of the nomogram. The established nomogram is shown in Figure 4.

Figure 5 shows the calibration plot using bootstrapping. The actual early IHR probability corresponded closely to the prediction of the nomogram. The calibration plot showed good agreement between the nomogram prediction and the actual observation. In terms of discriminative ability for early IHR, the C-index was 0.67 (Fig. 6). The bootstrap validation with 150 resamples resulted in a C-index of 0.67. The bias-corrected C-index closely matched the initial C-index.

DISCUSSION

In the present study, we developed a nomogram for EHR after hepatic resection of HCC that contains four independent predictive factors including AFP >200 ng/mL, tumor size (3–5 cm or > 5 cm vs. ≤ 3 cm), and image-diagnosed venous invasion. This nomogram

was shown to have high accuracy in the prediction of EHR with a C-index of 0.75. Tumor size and three additional predictors, i.e., tumor exposure, multiple tumors, and image-diagnosed portal invasion were adopted in the final model of the early IHR nomogram with a concordance index of 0.67. The nomograms were further validated internally using the bootstrapping technique. While, to the best of our knowledge, no previous reports have assessed the predictive value of nomograms for EHR and early IHR after hepatic resection, since the nomograms include major preoperative indicators of tumor progression and aggressiveness based on imaging findings and serum tumor biomarker, these provide an accurate prediction of EHR and early IHR.

Tumor size and hepatic venous invasion are tumor staging parameters and reportedly correlated with EHR of HCC after hepatic resection.[19, 36] The main presumed mechanism of extrahepatic tumor metastasis is systemic hematogenous tumor dissemination. Tumor size is considered with the increased risk of potentially hematogeneous tumor spread.[37] Carr et al reported that tumor size was associated with a proportional increase in the extrahepatic metastasis rate.[38] In the current study, image-diagnosed venous invasion was accorded the highest weighted score of 100 points and tumor size greater than 5 cm was accorded the score of approximately 60 points; therefore, tumor size and image-diagnosed venous invasion may be the main predictors of EHR of HCC.

Neither multiple tumors nor image-diagnosed portal invasion were adopted as predictors in the final model for the EHR nomogram. This may be explained by considering the metastatic mechanisms with affinity for intrahepatic recurrence. Portal invasion is considered to be associated with intrahepatic metastasis from the original tumor and thus increases the risk of IHR.[39, 40] Likewise, the presence of multiple tumor

nodules would include intrahepatic metastasis and multicentric development[41] and, as such, is considered a risk factor of IHR derived from both intrahepatic micrometastasis and multicentric carcinogenesis.[20, 42] Therefore, in this study, image-diagnosed portal invasion and multiple tumor were enrolled as predictors in the final model for the nomogram predicting early IHR.

AFP is the most widely accepted and used serum biomarker in HCC. Studies have demonstrated the association of AFP level with tumor growth and progression of HCC including vascular invasion and poor cellular differentiation.[33, 43] Overexpression of AFP promotes invasion and distant metastasis by upregulating the expression of metastasis-related proteins.[43] AFP is reportedly associated with distant metastasis of HCC[44] and is recognized as a predictor of recurrence after liver transplantation for HCC.[45] Incorporation of serum tumor biomarkers may help improve the accuracy of the current nomogram for EHR.

This nomogram is based on parameters that are routinely assessed during preoperative workup. Thus, it is a convenient tool for assessing the risk of EHR and establishing individualized case management plans after hepatic resection. Indications of high risk may induce doctors to increase the frequency of patient visits, and to include extrahepatic metastasis work-up including a chest CT, brain CT, and whole-body bone scintigraphy in addition to routine abdominal imaging tests in order to can detect EHR at an early stage during the follow-up period after surgery. Surgical resection of EHR in selected patients, such as those with one or two isolated extrahepatic metastases, [46] well-controlled IHR, [47] and preserved liver function[46] can offer improved long-term survival. More frequent follow-up visits with shortened intervals between examinations may therefore lead to a timely therapeutic strategy regarding surgical resection.[48] Hence,

the current nomogram may provide prognostic benefits to the patients at high risk of EHR, through more frequent follow-up visits accompanied by extrahepatic metastasis work-ups. Furthermore, a nomogram predicting EHR would allow clinicians to identify patients with promising survival prospects as potential candidates for adjuvant therapy or neoadjuvant therapy. In an adjuvant therapy setting, the results of a phase III clinical trial of sorafenib showed no survival benefits for patients undergoing curative treatment for HCC.[15] No effective therapies currently exist in adjuvant or neoadjuvant settings.[14, 49] However, several immune checkpoint inhibitors, including nivolumab and pembrolizumab, have recently demonstrated durable response effects for advanced HCC patients.[14] Many trials of immune checkpoint inhibitors are ongoing in the adjuvant or neoadjuvant setting.[49] Moreover, several combination therapies with immune checkpoint inhibitors and molecular targeted agents have shown synergistic effects.[14] Therefore, the current nomogram for EHR could be used to guide decisions around adjuvant or neoadjuvant therapy.

This nomogram shows an incidence probability of EHR of up to 70%. In other words, there is up to 30% chance that no EHR will occur after surgery. Hence, the nomogram for EHR should not be used to decide surgical indication in HCC patients. Instead, hepatic resection should be adopted as a locoregional therapy for patients at high risk for EHR. However, the nomogram predicting early IHR within one year after surgery indicated the incidence probability of early IHR up to 80%. It incorporated four predictive factors, i.e., tumor exposure, tumor size, multiple tumors, and image-diagnosed portal invasion. In this study, patients with tumor recurrence connected to the cut surface of the remnant liver were excluded. In a previous study, IHR due to tumor exposure was shown to be derived from residual micrometastasis

surrounding the original tumor.[50] Furthermore, early IHR within one year after surgery is likely attributable to preexisting intrahepatic hematogenous tumor spread at diagnosis.[7, 17] Therefore, patients at high risk for both EHR and early IHR in the current nomograms would be at a potentially advanced stage of HCC. For such patients, hepatic resection alone would not offer a sufficient therapeutic effect. Thus, by combining the risk assessments for EHR and early IHR obtained from the current nomograms, physicians may devise alternate treatment strategies. Survival benefits for patients at high risk for both EHR and early IHR by the current nomograms might be provided through neoadjuvant therapy using molecular targeted agents and/or immune checkpoint inhibitors, which are proven to be effective in advanced HCC.

Intraoperative blood loss was reported as a predictor of HCC recurrence.[32] However, in this study, intraoperative blood loss was not adopted in the final model for the nomograms predicting EHR and early IHR. The lack of association between intraoperative blood loss and recurrence may be attributable to improvement in surgical instruments (including hemostasis devices) and perioperative management during the study period of 28 years. The characteristics of patients with large amount of intraoperative blood loss may have changed over the years. Along with the improvement of perioperative management, the clinical impact of blood loss on the body after surgery may also have changed over the years. Therefore, the long study period may have obscured the prognostic impact of blood loss on postoperative recurrence.

Among the preoperative CT-image-diagnosed variables, image-diagnosed non-smooth tumor margin was not adopted for either EHR or early IHR. In a previous study, non-smooth tumor margins (simple nodular type with extranodular growth and

confluent multinodular type) were found to correlate with pathological vascular invasion.[29] In addition, contiguous multinodular type lesions showed a correlation with poor differentiation.[51] However, image-diagnosed venous invasion and portal invasion were only adopted in the final model for EHR and early IHR, respectively. This indicated that image-diagnosed venous invasion and portal invasion would have a more significant predictive ability for EHR and early IHR, respectively, than image-diagnosed non-smooth tumor margin.

The current study has several limitations. First, this study had a retrospective design and enrolled a rather small number of patients with EHR. Second, the study period was approximately 28 years. However, the long study period in a single institution might contribute to establish a consistent and robust nomogram based on detailed clinical data. Third, although the proposed nomograms had good C-indices of 0.75 and 0.67, their performance was not validated by using external data sets. However, calibration plots for internal validation using bootstrapping showed favorable performance with a closely matched bias-corrected C-indices.

In conclusion, we have developed reliable nomograms to predict EHR and early IHR of HCC after hepatic resection. These are useful for the diagnostic prediction of EHR and early IHR and could guide the surgeon's selection of treatment strategies for HCC patients.

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REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893-917.
2. Tung-Ping Poon R, Fan ST, Wong J. Risk factors, prevention, and management of postoperative recurrence after resection of hepatocellular carcinoma. Ann Surg 2000;232:10-24.
3. Vauthey JN, Lauwers GY, Esnaola NF, Do KA, Belghiti J, Mirza N, et al. Simplified staging for hepatocellular carcinoma. J Clin Oncol 2002;20:1527-36.
4. Kudo M, Izumi N, Kubo S, Kokudo N, Sakamoto M, Shiina S, et al. Report of the 20th Nationwide follow-up survey of primary liver cancer in Japan. Hepatol Res 2020;50:15-46.
5. Koda M, Tanaka S, Takemura S, Shinkawa H, Kinoshita M, Hamano G, et al. Long-term prognostic factors after hepatic resection for hepatitis c virus-related hepatocellular carcinoma, with a special reference to viral status. Liver Cancer 2018;7:261-76.
6. Shah SA, Cleary SP, Wei AC, Yang I, Taylor BR, Hemming AW, et al. Recurrence after liver resection for hepatocellular carcinoma: risk factors, treatment, and outcomes. Surgery 2007;141:330-9.
7. Kumada T, Nakano S, Takeda I, Sugiyama K, Osada T, Kiriyama S, et al. Patterns of recurrence after initial treatment in patients with small hepatocellular carcinoma. Hepatology 1997;25:87-92.
8. Portolani N, Coniglio A, Ghidoni S, Giovanelli M, Benetti A, Tiberio GA, et al. Early and late recurrence after liver resection for hepatocellular carcinoma:

prognostic and therapeutic implications. Ann Surg 2006;243:229-35.

9. Lee YT, Geer DA. Primary liver cancer: pattern of metastasis. J Surg Oncol 1987;36:26-31.

10. Hong SS, Kim TK, Sung KB, Kim PN, Ha HK, Kim AY, et al. Extrahepatic spread of hepatocellular carcinoma: a pictorial review. Eur Radiol 2003;13:874-82.

11. Poon RT, Fan ST, O'Suilleabhain CB, Wong J. Aggressive management of patients with extrahepatic and intrahepatic recurrences of hepatocellular carcinoma by combined resection and locoregional therapy. J Am Coll Surg 2002;195:311-8.

12. Mizuguchi S, Nishiyama N, Izumi N, Tsukioka T, Komatsu H, Iwata T, et al. Clinical significance of multiple pulmonary metastasectomy for hepatocellular carcinoma. World J Surg 2016;40:380-7.

13. Han B, Li C, Meng H, Gomes Romeiro F, Mancuso A, Zhou Z, et al. Efficacy and safety of external-beam radiation therapy for hepatocellular carcinoma: An overview of current evidence according to the different target population. Biosci Trends 2019;13:10-22.

14. Kudo M. Targeted and immune therapies for hepatocellular carcinoma: Predictions for 2019 and beyond. World J Gastroenterol 2019;25:789-807.

15. Bruix J, Takayama T, Mazzaferro V, Chau GY, Yang J, Kudo M, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol 2015;16:1344-54.

16. Akateh C, Black SM, Conteh L, Miller ED, Noonan A, Elliott E, et al. Neoadjuvant and adjuvant treatment strategies for hepatocellular carcinoma.

World J Gastroenterol 2019;25:3704-21.

17. Taketomi A, Toshima T, Kitagawa D, Motomura T, Takeishi K, Mano Y, et al. Predictors of extrahepatic recurrence after curative hepatectomy for hepatocellular carcinoma. Ann Surg Oncol 2010;17:2740-6.
18. Li J, Liu Y, Yan Z, Wan X, Xia Y, Wang K, et al. A nomogram predicting pulmonary metastasis of hepatocellular carcinoma following partial hepatectomy. Br J Cancer 2014;110:1110-7.
19. Chen S, Gao Y, Li Z, Jia J, Fang M, Wang M, et al. A Nomogram predicting extrahepatic metastases for patients with adjuvant transarterial chemoembolization after hepatectomy. J Cancer 2018;9:4223-33.
20. Imamura H, Matsuyama Y, Tanaka E, Ohkubo T, Hasegawa K, Miyagawa S, et al. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. J Hepatol 2003;38:200-7.
21. Poon RT, Fan ST, Ng IO, Lo CM, Liu CL, Wong J. Different risk factors and prognosis for early and late intrahepatic recurrence after resection of hepatocellular carcinoma. Cancer 2000;89:500-7.
22. Yap WK, Shih MC, Kuo C, Pai PC, Chou WC, Chang KP, et al. Development and validation of a nomogram for assessing survival in patients with metastatic lung cancer referred for radiotherapy for bone metastases. JAMA Netw Open 2018;1:e183242.
23. Matsui Y, Terakawa N, Satoi S, Kaibori M, Kitade H, Takai S, et al. Postoperative outcomes in patients with hepatocellular carcinomas resected with exposure of the tumor surface: clinical role of the no-margin resection. Arch Surg 2007;142:596-602; discussion 603.

24. Aoki T, Kubota K, Hasegawa K, Kubo S, Izumi N, Kokudo N, et al. Significance of the surgical hepatic resection margin in patients with a single hepatocellular carcinoma. Br J Surg 2020;107:113-20.
25. Makuuchi M, Kosuge T, Takayama T, Yamazaki S, Kakazu T, Miyagawa S, et al. Surgery for small liver cancers. Semin Surg Oncol 1993;9:298-304.
26. Cho JY, Han HS, Choi Y, Yoon YS, Kim S, Choi JK, et al. Association of remnant liver ischemia with early recurrence and poor survival after liver resection in patients with hepatocellular carcinoma. JAMA Surg 2017;152:386-92.
27. Matsuda M, Suzuki T, Kono H, Fujii H. Predictors of hepatic venous trunk invasion and prognostic factors in patients with hepatocellular carcinomas that had come into contact with the trunk of major hepatic veins. J Hepatobiliary Pancreat Surg 2007;14:289-96.
28. Liver Cancer Study Group of Japan. The general rules for the clinical and pathological study of primary liver cancer. Jpn J Surg 1989;19:98-129.
29. Yoneda N, Matsui O, Kobayashi S, Kitao A, Kozaka K, Inoue D, et al. Current status of imaging biomarkers predicting the biological nature of hepatocellular carcinoma. Jpn J Radiol 2019;37:191-208.
30. Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, Kaplowitz N, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology 1981;1:431-5.
31. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. Hepatology 1994;19:1513-20.
32. Cho CS, Gonen M, Shia J, Kattan MW, Klimstra DS, Jarnagin WR, et al. A novel

prognostic nomogram is more accurate than conventional staging systems for predicting survival after resection of hepatocellular carcinoma. J Am Coll Surg 2008;206:281-91.

33. Liu C, Xiao GQ, Yan LN, Li B, Jiang L, Wen TF, et al. Value of alpha-fetoprotein in association with clinicopathological features of hepatocellular carcinoma. World J Gastroenterol 2013;19:1811-9.
34. Pawlik TM, Delman KA, Vauthey JN, Nagorney DM, Ng IO, Ikai I, et al. Tumor size predicts vascular invasion and histologic grade: Implications for selection of surgical treatment for hepatocellular carcinoma. Liver Transpl 2005;11:1086-92.
35. Harrell FE. Regression modeling strategies, with applications to linear models, survival analysis and logistic regression. New York, NY: Springer-Verlag; 2001.
36. Jun L, Zhenlin Y, Renyan G, Yizhou W, Xuying W, Feng X, et al. Independent factors and predictive score for extrahepatic metastasis of hepatocellular carcinoma following curative hepatectomy. Oncologist 2012;17:963-9.
37. Shinkawa H, Tanaka S, Takemura S, Ishihara T, Yamamoto K, Kubo S. Tumor size drives the prognosis after hepatic resection of solitary hepatocellular carcinoma without vascular invasion. J Gastrointest Surg 2020;24:1040-48.
38. Carr BI, Guerra V. Hepatocellular carcinoma extrahepatic metastasis in relation to tumor size and alkaline phosphatase levels. Oncology 2016;90:136-42.
39. Shirabe K, Kanematsu T, Matsumata T, Adachi E, Akazawa K, Sugimachi K. Factors linked to early recurrence of small hepatocellular carcinoma after hepatectomy: univariate and multivariate analyses. Hepatology 1991;14:802-5.
40. Ogawa M, Yamamoto T, Kubo S, Uenishi T, Tanaka H, Shuto T, et al. Clinicopathologic analysis of risk factors for distant metastasis of hepatocellular

carcinoma. Hepatol Res 2004;29:228-34.

41. Takenaka K, Adachi E, Nishizaki T, Hiroshige K, Ikeda T, Tsuneyoshi M, et al. Possible multicentric occurrence of hepatocellular carcinoma: a clinicopathological study. Hepatology 1994;19:889-94.
42. Hao S, Fan P, Chen S, Tu C, Wan C. Distinct recurrence risk factors for intrahepatic metastasis and multicenter occurrence after surgery in patients with hepatocellular carcinoma. J Gastrointest Surg 2017;21:312-20.
43. Mizejewski GJ. Does alpha-fetoprotein contribute to the mortality and morbidity of human hepatocellular carcinoma? A commentary. J Hepatocell Carcinoma 2016;3:37-40.
44. Lee CH, Chang CJ, Lin YJ, Yen CL, Shen CH, Cheng YT, et al. Nomogram predicting extrahepatic metastasis of hepatocellular carcinoma based on commonly available clinical data. JGH Open 2018;3:38-45.
45. Shimamura T, Akamatsu N, Fujiyoshi M, Kawaguchi A, Morita S, Kawasaki S, et al. Expanded living-donor liver transplantation criteria for patients with hepatocellular carcinoma based on the Japanese nationwide survey: the 5-5-500 rule - a retrospective study. Transpl Int 2019;32:356-68.
46. Chan KM, Yu MC, Wu TJ, Lee CF, Chen TC, Lee WC, et al. Efficacy of surgical resection in management of isolated extrahepatic metastases of hepatocellular carcinoma. World J Gastroenterol 2009;15:5481-8.
47. Takemura N, Hasegawa K, Aoki T, Sakamoto Y, Sugawara Y, Makuuchi M, et al. Surgical resection of peritoneal or thoracoabdominal wall implants from hepatocellular carcinoma. Br J Surg 2014;101:1017-22.
48. Sun YF, Wang PX, Cheng JW, Gong ZJ, Huang A, Zhou KQ, et al. Postoperative

circulating tumor cells: An early predictor of extrahepatic metastases in patients with hepatocellular carcinoma undergoing curative surgical resection. Cancer Cytopathol 2020;Jun 5. https://doi.org/10.1002/cncy.22304

49. Brown ZJ, Greten TF, Heinrich B. Adjuvant treatment of hepatocellular carcinoma: prospect of immunotherapy. Hepatology 2019;70:1437-42.

50. Donadon M, Terrone A, Procopio F, Cimino M, Palmisano A, Vigano L, et al. Is R1 vascular hepatectomy for hepatocellular carcinoma oncologically adequate? Analysis of 327 consecutive patients. Surgery 2019;165:897-904.

51. Shirabe K, Aishima S, Taketomi A, Soejima Y, Uchiyama H, Kayashima H, et al. Prognostic importance of the gross classification of hepatocellular carcinoma in living donor-related liver transplantation. Br J Surg 2011;98:261-7.

Table 1. Patient characteristics

Variable	Patients (n = 1206)
Sex (male/female)	949/257
Age (years) [a]	67 (60, 72)
ALT (IU/L) [a]	41 (25, 70)
AFP (ng/mL)	
>20	524 (43.4%)
≤20	682 (56.6%)
Child–Pugh class A	1136 (94.2%)
Tumor size (cm)[a]	3.0 (2.0, 4.5)
Tumor size:	
≤3 cm	625 (51.8%)
3–5 cm	354 (29.4%)
>5 cm	227 (18.8%)
Multiple tumors	362 (30.0%)
Image-diagnosed portal invasion	358 (29.7%)
Image-diagnosed venous invasion	47 (3.9%)
Image-diagnosed non-smooth tumor margin	302 (25.0%)
Liver cirrhosis	438 (36.3%)
Intraopertive blood loss (mL) [a]	550 (190, 1271.3)
Tumor exposure	57 (4.7%)

AFP, α-fetoprotein; ALT, alanine aminotransferase

[a] Median with interquartile range.

Table 2 Final model of the multivariate logistic regression analysis for extrahepatic recurrence

	Coefficient	OR	95% CI	*P* value
AFP >200 ng/mL	0.478	1.61	0.98–2.65	0.059
Tumor size (vs ≤3 cm)				
3–5 cm	1.05	2.86	1.58–5.16	<0.001
>5 cm	1.552	4.72	2.57–8.66	<0.001
Image-diagnosed venous invasion	2.448	11.56	4.95–27.03	<0.001

AFP, α-fetoprotein; OR, odds ratio; CI, confidence interval

Table 3 Final model of the multivariate logistic regression analysis for intrahepatic recurrence within one year after surgery

	Coefficient	OR	95% CI	*P* value
Tumor exposure	0.485	1.63	0.90–2.94	0.11
Tumor size (vs ≤3 cm)				
3–5 cm	0.322	1.38	1.00–1.90	0.047
>5 cm	0.640	1.90	1.33–2.71	0.026
Image-diagnosed portal invasion	1.020	2.77	1.38–5.59	0.0004
Multiple tumor	0.943	2.57	1.94–3.40	<0.0001

OR, odds ratio CI; confidence interval

Figure legends

Figure 1. Nomogram predicting extrahepatic recurrence of hepatocellular carcinoma after hepatic resection. AFP, α-fetoprotein.

Fig.1

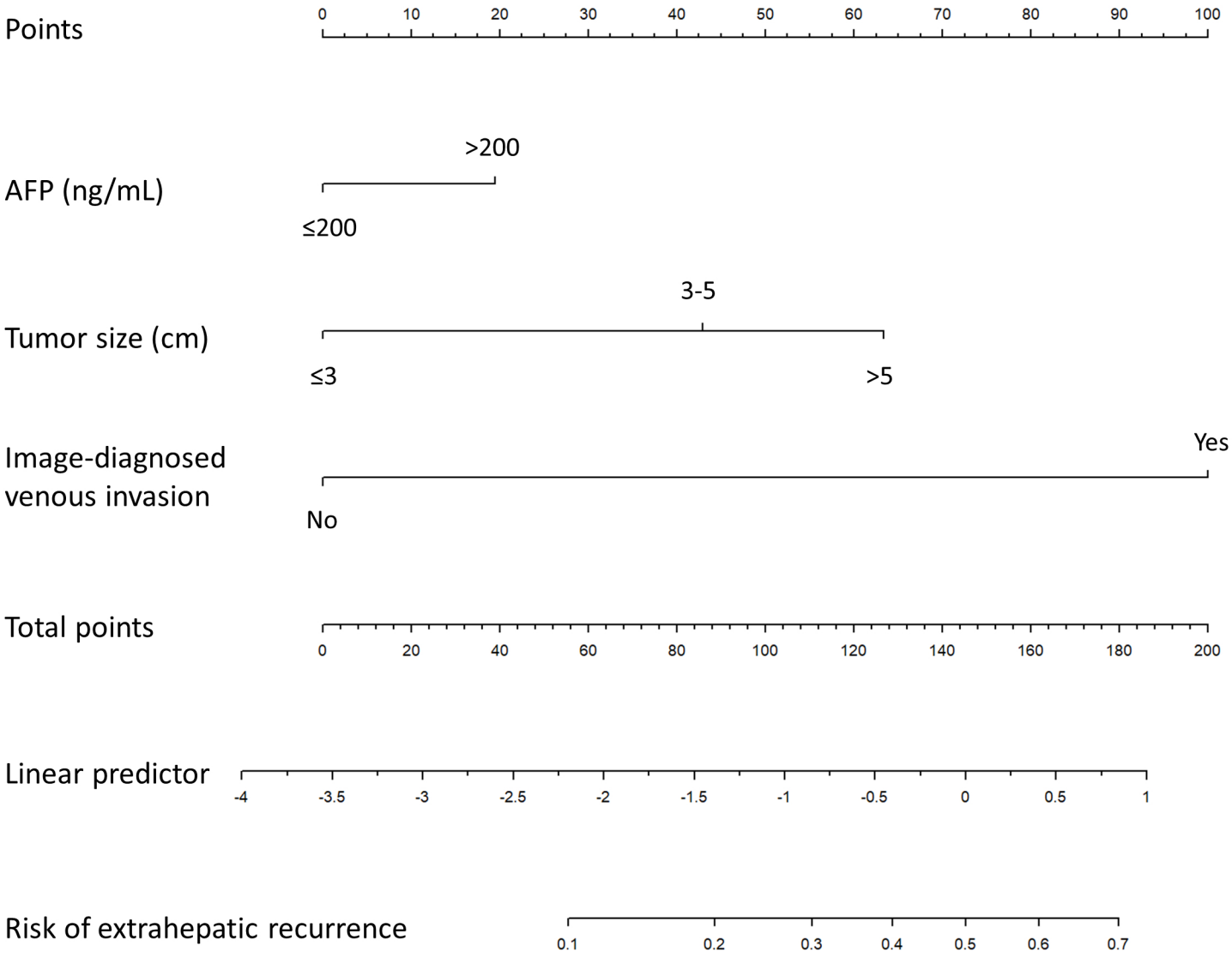

Points
0
10
20
30
40
50
60
70
80
90
100
AFP (ng/mL)
>200
≤200
Tumor size (cm)
3-5
≤3
>5
Image-diagnosed venous invasion
Yes
No
Total points
0
20
40
60
80
100
120
140
160
180
200
Linear predictor
-4
-3.5
-3
-2.5
-2
-1.5
-1
-0.5
0
0.5
1
Risk of extrahepatic recurrence
0.1
0.2
0.3
0.4
0.5
0.6
0.7

Figure 2. Model accuracy is visualized by comparing predicted versus actual probabilities of extrahepatic recurrence, showing the apparent predictive ability and bias collection for overfitting. The relative prevalence of probability levels is indicated by the vertical lines at the top of the plot.

Fig.2

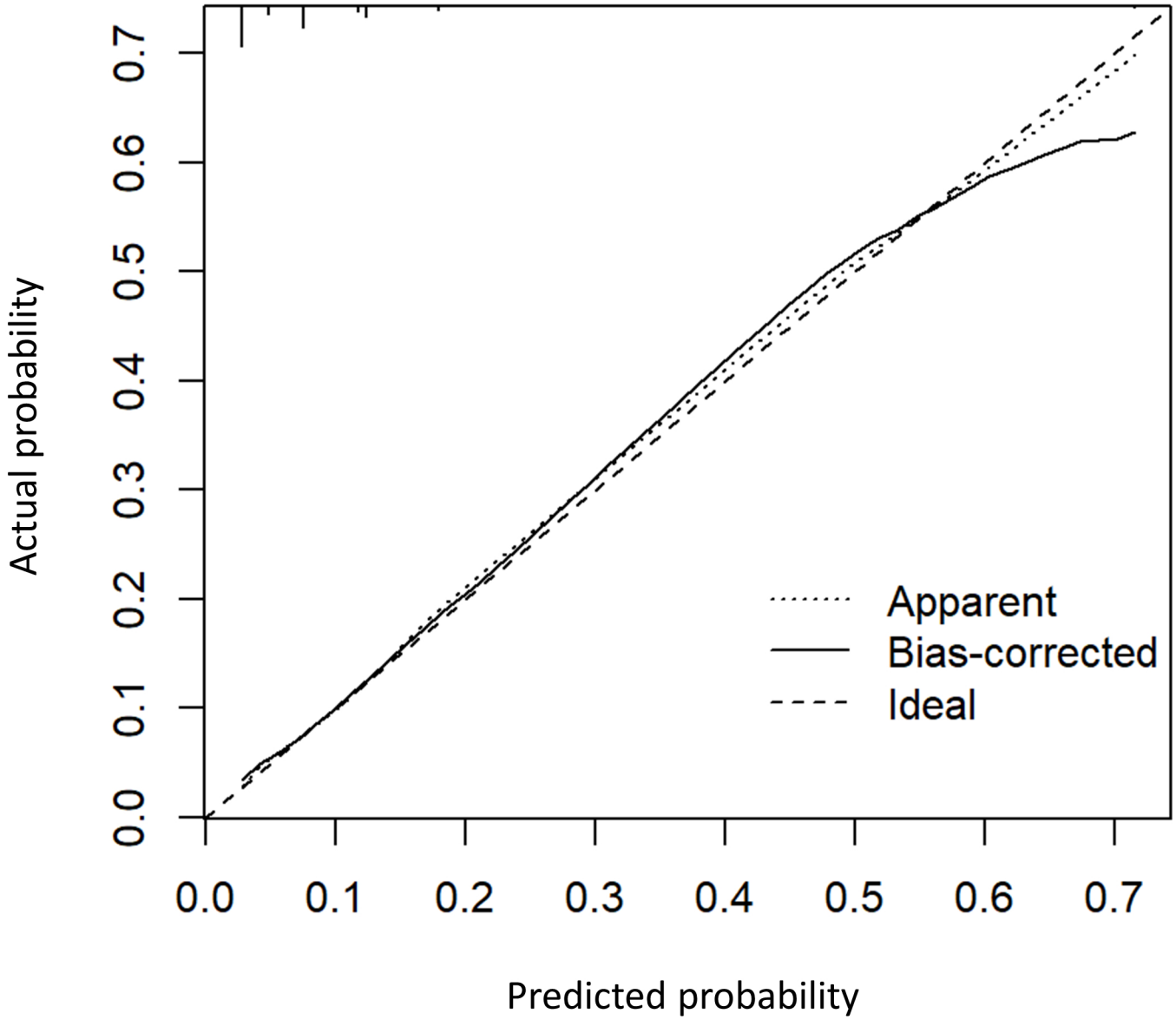

Actual probability
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
Predicted probability
Apparent
Bias-corrected
Ideal

Figure 3. The receiver operating characteristic plot based on the final multivariate model for extrahepatic recurrence demonstrated adequate predictive discrimination (area under the curve, 0.75).

Fig.3

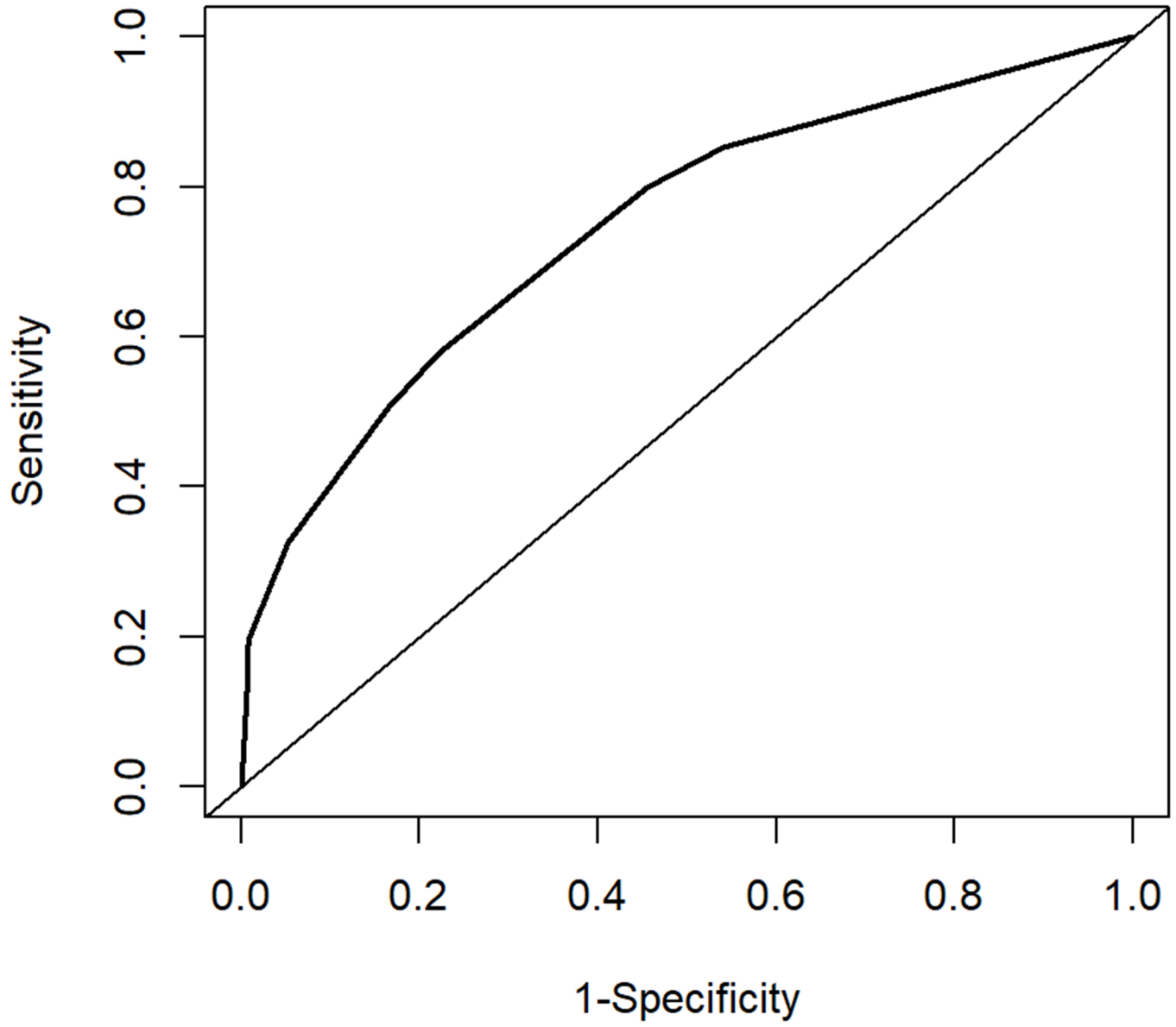


Figure 4. Nomogram predicting intrahepatic recurrence of hepatocellular carcinoma within one year after hepatic resection.

Fig.4

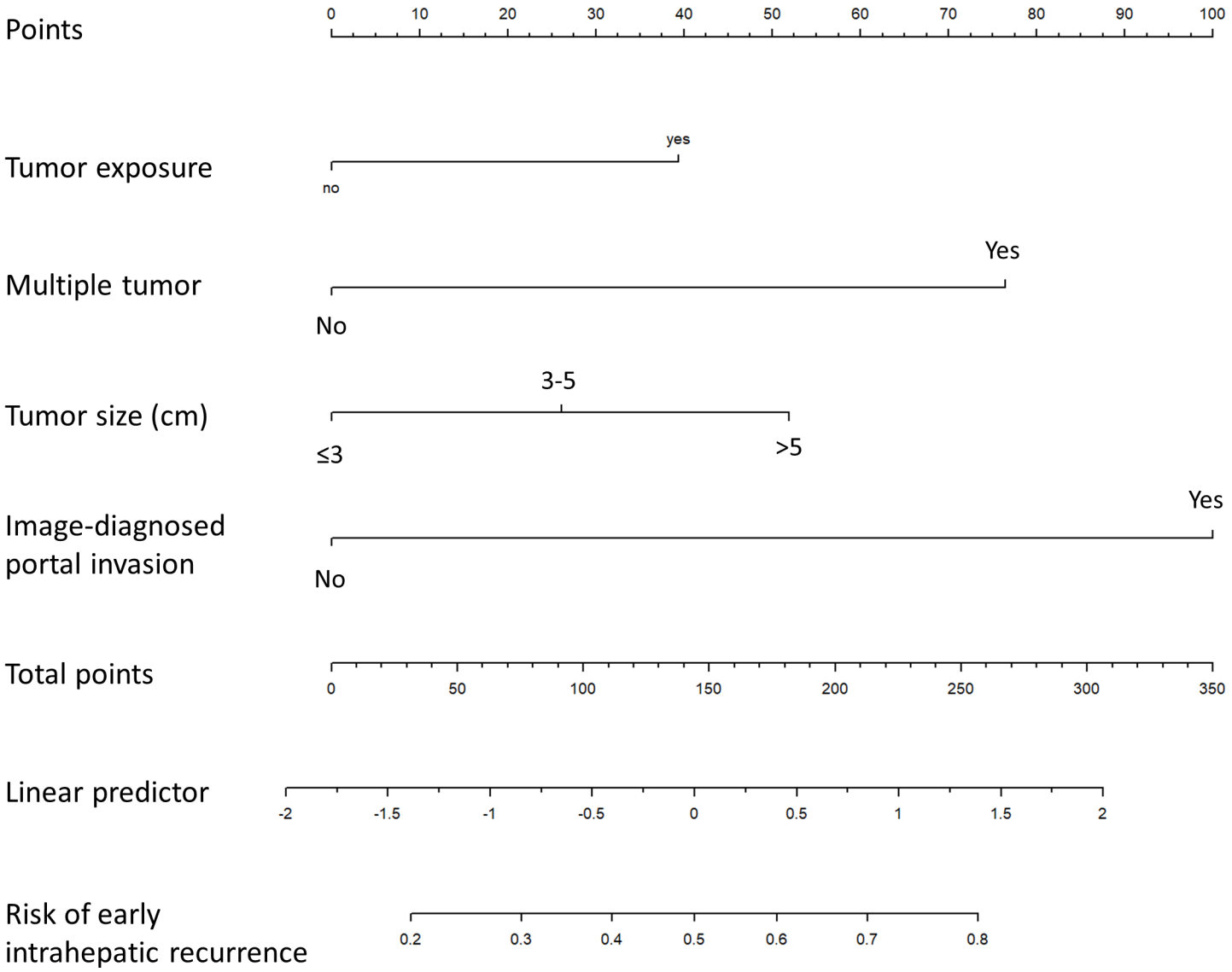

Points
0
10
20
30
40
50
60
70
80
90
100
Tumor exposure
yes
no
Multiple tumor
Yes
No
Tumor size (cm)
3-5
≤3
>5
Image-diagnosed portal invasion
Yes
No
Total points
0
50
100
150
200
250
300
350
Linear predictor
-2
-1.5
-1
-0.5
0
0.5
1
1.5
2
Risk of early intrahepatic recurrence
0.2
0.3
0.4
0.5
0.6
0.7
0.8

Figure 5. Model accuracy is visualized by comparing predicted versus actual probabilities of intrahepatic recurrence within one year after surgery, showing the apparent predictive ability and bias collection for overfitting. The relative prevalence of probability levels is indicated by the vertical lines at the top of the plot.

Fig.5

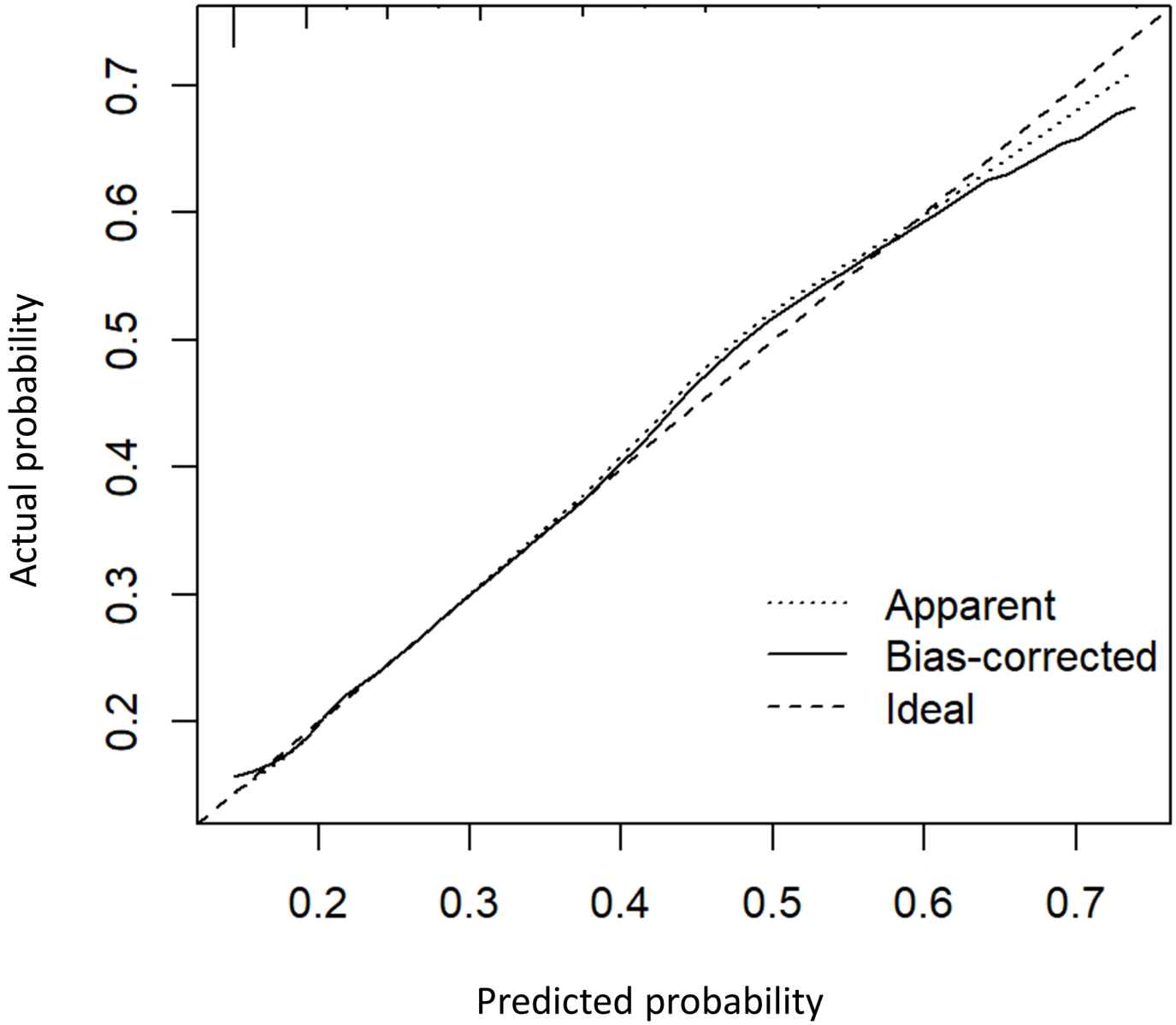
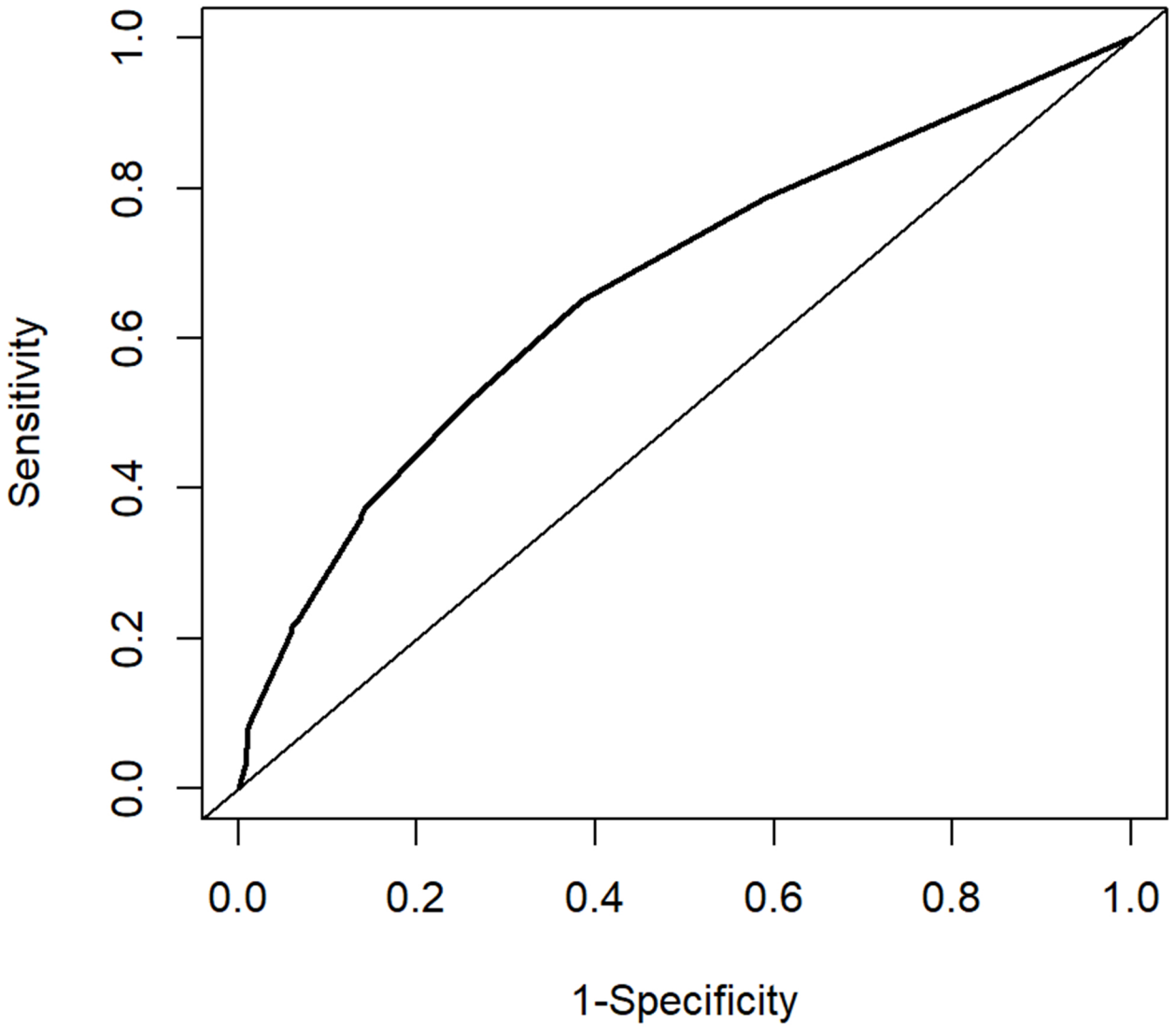

Actual probability
0.2
0.3
0.4
0.5
0.6
0.7
Predicted probability
0.2
0.3
0.4
0.5
0.6
0.7
Apparent
Bias-corrected
Ideal

Figure 6. The receiver operating characteristic plot based on the final multivariate model for intrahepatic recurrence within one year after surgery demonstrating adequate predictive discrimination (area under the curve, 0.67).

Fig.6



Supplementary Table 1. Sites of extrahepatic recurrence

Site of recurrence [a]	Patients (n = 95)
Lung	33
Bone	30
Peritoneum	16
Adrenal gland	10
Lymph node	8
Brain	4
Abdominal wall	2

[a]Including duplicates.