Prognostic Nomogram for Sorafenib Benefit in Hepatitis B Virus related Hepatocellular Carcinoma after Partial Hepatectomy

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Abstract

Background The prediction regarding the long-term prognosis of individuals subjected to sorafenib treatment following partial hepatectomy due to hepatitis B virus (HBV) related hepatocellular carcinoma (HCC) is rather difficult.The objective behind this work is to create an effective prognostic nomogram of sorafenib for personalized therapy of HBV-relatedHCC.

Methods 234 HBV-related HCC patients subjected or not subjected to sorafenibtreatment following partial hepatectomy at the Eastern Hepatobiliary Surgery Hospital from 2008 to 2013 were compared to investigate the association between index levels and sorafenib benefit. The optimal cut-off point of the overall survival (OS) factor level was determined by x-tile.The selection of indicators is based on clinical findings. The Cox regression model with an interaction term was employed for evaluating the predictive value. Using a multivariate Cox proportional hazards model a Nomogram was subsequently formulated to analyze 113 patients treated with sorafenib. Determination of nomogram's discriminative ability and predictive accuracy was done using the concordance index (C-index), calibration, and ROC curve.

Results Subgroup analysis revealed that Low GPC3,pERK, pAKT, serum AFP levels, without MVI, under 50 years old, male, TNM stage I/II and BCLC stage 0/A wereassociated significantly with a better OS in patients subjected to sorafenib treatment compared to those not treated with sorafenib after surgery. The independent factors for OS were found be GPC3, pERK, pAKT, serum AST and BCLC stage, following multivariate analysis of the sorafenib cohort, which was all included in the nomogram. The survival probability based on the calibration curve shows that the prediction of the nomogram was in good agreement with the actual observation. Survival was predicted to be 0.73(95% CI, 0.67 to 0.78) based on the C-index of the nomogram. The area under the ROC curve (AUC) for the nomogram to predict the survival for 1, 3, and 5-year was 0.726, 0.816, and 0.823, respectively.

Conclusion This proposed nomogram has the potential to make quite a precise prediction regarding the prognosis of HBV-related HCC patients,who underwent sorafenib therapy following partial hepatectomy.

Background

A primary liver cancer having a rather common occurrence is Hepatocellular carcinoma(HCC). Liver cancers are the 4th leading cause of cancer-related death and the 6th major source of morbidity around the globe. The World Health Organization (WHO), based on its annual projections, estimates that over a million people will die of liver cancer in 2030[1]. Several randomized studies that test adjuvant treatments, such aschemotherapy,interferon (IFN), internal radiation, chemoembolization, retinoids, and immune therapies, have not yet proven beneficial or led to uncertain outcomes, hence are notrecommended to be practiced clinically [2, 3]. In the past decade, the treatment of advanced HCC has improved significantly[4].

Sorafenib is the first approved drug for the systemic therapy of advanced-stage HCC. All other therapies have only recently exhibited clinical efficacy. Food and Drug Administration (FDA), USA, has approved

Lenvatinib,as first [5] or regorafenib [6], nivolumab [7], cabozantinib [8], and ramucirumab as second-line treatments. Being a multi-kinase inhibitor, Sorafenib targets themitogen-activated protein kinase/extracellular signal-regulatedkinase (MAPK/ERK) pathway, the vascular endothelial growth factor receptors-1/2/3 (VEGFR1/2/3), and c-KIT, among other targets, that provide a median survival advantage of nearly 3months and reduce the risk of mortality by 31% in patients with an advanced stage of HCC[4].

Sorafenib acts by VEGFsignalingdriven angiogenesis andcell proliferation inhibited byMAPK/ERK [9].In addition, sorafenib is known to impact both endothelial as well as tumor cells [9].Although numerous investigations have been brought forward, the reliable predictive biomarkers of sorafenib responses(including targets of sorafenib such as VEGF or MAPK/ERK) in HCC patients are not ascertained as yet. Althoughsorafenib has been found to be beneficial for all patient subgroups, phase 3 Asia-Pacific HCC and SHARP trials based on latest meta-analysis of individual data revealed that sorafenib has significantly greater benefits for patients with HCV etiology and exclusive liver disease [10, 11]. In terms of biomarkers, the correlation analysis ofSHARP trial showed that sorafenib treatment had a non-significant trend to improve survival in tumors with low plasma concentration of hepatocyte growth factor (HGF) and highc-Kit [12].A great volume of efforts has been invested in the biomarkers screening for predictingthe responses of sorafenib as well as prognosis of patients. Nevertheless, not a singlebiomarker has been identified for the clear prediction of sorafenib efficacy to date. In this scenario, investigating the association between clinicopathological index or biomarkers and sorafenib advantage in HCCneeds a characteristic prognostic model for the prediction in the patient's selection in order to improve therapeutic efficacy.

Glypican-3 (GPC3) is a glycoprotein of oncofetal type, adhering to the cellular membrane through the glycophosphatidylinositol anchor.In an adult healthy liver, no GPC3 expression was obvious. Contrastingly, GPC3 was overexpressed in HCC. The GPC3 protein and geneexpression in serum and tumor tissues ofHCCs was higher compared to non-malignant healthy livers [13, 14]. The prognostic value of serum GPC3 level and tumorcellGPC3immunoreactivity as a biomarker in patients with HCChas already been well established.In addition, being a novel target molecule for therapeutic agents, GPC3 has also attracted much attention, and its clinical trials are progressing[15]. So far, there haven't been any investigationsfor exploringthe association betweenthe GPC3 expression and the prognosis of HCCpatients subjected to sorafenib treatment. In liver cancer cells MAPK/ERK and PI3K/Akt are two of the major prooncogenic signaling pathways. These two signaling pathways are often hyperactivated and dysregulated in HCC and have a regulatory role in survival, cell differentiation, and proliferation [16–22]. Triggering of singling pathways of MAPK and PI3K-AKT-mTOR had a poor outcome, and pERK (phosphorylated extracellular signal-regulated kinase) and pAKT (phosphorylation of protein kinase B) are the most common surrogate of AKT and MAPK pathway activation [4]. In this study, serum AST is included in many HCC prediction systems [23, 24], and it is an independent risk factor predicting prognosis. Previous investigations involving HCC patients subjected to sorafenib treatment have focused on an advanced stage of the disease, however, this study also included the early stage of HCC. In this study, we screened thesorafenib biomarker and clinicopathological index in HCC patients related to the hepatitis B virus and treated with sorafenib following partial hepatectomy. We then used a multivariate

Cox proportional hazards model to establish a nomogram to carry out an analysis of the 113 patients treated with sorafenib.

For most cancer types, nomograms have been developed [25–27].In fact, for many cancers, the use of nomograms is more beneficial than traditional staging systems, therefore nomogramsareoften put forth as an alternative or as entirely newstandards [28–31]. To the best of our understanding, this is the very first endeavor toconstruct a nomogram for prognosis based on theclinicopathologic and biomarker data of 113 patients of hepatitis B virus-related HCC treated with sorafenib after partial hepatectomy, in order to determine whether or not the model can predictpatient survival accurately.

Methods

Patients and Treatment

To investigatethe different aspects related to the advantages of sorafenib in HCC patients, 233 patients who went through surgery between April 2008 and February 2013 at Eastern Hepatobiliary SurgeryHospital (EHBH) were made a part of this study. Of them, 113 patientshad been given sorafenib therapy following partial hepatectomy and were referred to asthe sorafenib group. The rest of the patients who did not receive sorafenib was the control group.The inclusion criteria were defined as (1) Preoperatively the liver function wasChild-Pugh A/B and the diagnosis was HCC; (2) Received sorafenib treatment within a month following surgery and continued until death or more than one year; (3)hepatitis B core antibody (HBcAb)and/or Hepatitis B surface antigen (HBsAg) are positive whereas hepatitis C antibody is negative; (4) The HCC patients hadnot been exposed to any pre-surgical treatmentsuch aschemoembolization, high-intensity focused ultrasound or radiofrequency ablation.Their detailedclinicopathological features are described in Fig.1.Slidesfrom each surgically resected tissuewere prepared using hematoxylin and eosin (H&E)-stained and examined by two accomplished hematopathologists(Hui Dong and WenMing Cong). The primary HCC specimens were collected from patients formicroarrays construction and Immunohistochemistry (IHC) staining. Fig. S1 shows the flow diagrams of patients.

Follow-Up

During the first-year post-surgery, follow up of the patients was done once every 2-3 months and later every 3-6 months. Assessments of liver function and serum tumor markers were carried out at every follow-up.

When recurrence or metastasis is suspected, every 6 months or soonermagneticresonanceimaging (MRI) or contrast-enhanced CT was performed. Metastasis or recurrence of HCCis the presence of a newly detectable tumor withor without elevated serum tumor markers and confirmed on both radiologic images. The time duration between surgery and last follow-up exam or the death was termed as overall survival (OS). Calculation of TTR was carried out from the date of surgery to the diagnosis of metastasis or recurrence.

Tissue microarrays, IHC, and scoring

233 specimens were selected, and the representative core of each specimen was utilized to construct tissue microarrays. IHC was carried out and samples weremeasured according to previous reports [32, 33]. The system for imaging included a CCD camera by Leica, DFC420, linked to Leica DM IRE2 microscope obtained from Leica Microsystems Imaging Solutions, Cambridge, UK. The representative fieldsimages were taken from individual core under 200×magnification employing Leica QW in Plus v3 software. Counting and measurement of the photographs IOD were done employing software of Image-Pro plus V6.0 (Media Cybernetics, Bethesda, MD, USA) and the parameters used were IOD and Area sum. Dilution of the Primary antibodies was done as follows: a rabbit monoclonal [SP86] to Glypican 3 (ab95363; Abcam, Hong Kong; 1:100 dilution, cytomembrane staining), a monoclonal rabbit antibody against Erk1/2 (137F5)(4695; Cell Signaling Technology, Danvers, MA, USA; 1:100 dilution, cytoplasmic staining), a rabbit monoclonal antibody against AKT1 (D9R8K)(75692, Cell Signaling Technology, Danvers, MA, USA; 1:200 dilution, cytoplasmic staining).

Statistical Analysis

Identification of risk factors was done via statistical analyses carried out using SPSS V22.0 software (IBM, Chicago, IL). Grouping of the categorical variables was completed in the light of clinical findings, and prior to modeling, decisions were made for the groups. A comparison of the continuous variables was done using the Mann-Whitney testfor variables with the abnormal distribution. Optimalcessation points for the OS were calculated using the X-Tile statistical package (version3.6.1, Yale University, New Haven, CT, USA). X-tile plot shows the presence of significant HCC subpopulations, and a two-dimensional projection of eachpossible subpopulation was used to show the robustness ofthe relationship between an outcome and a biomarker [34].The extent of quantitative factors such as, -AST, serum ALT -ALP, -Cre, GPC3, pERK, pAKT were assessed by creating X-tile plots. Kaplan-Meier method was utilized to draw the survival curve while log-rank test was used for drawing the comparison. Multivariate analyses were carried out employing the Cox regression analysis.The estimated values were employed for time-dependent ROC(receiver operating characteristic) analysis. A nomogram was created based entirely on the outcomes of multivariate analysis, using rmS6.0-0 packages in R version 4.0.1(http://www.r-project.org/). Finally, using the backward step-down selection process bath on the Akaike information criterion, a model selection process was implemented [35].Concordance index (C-index) was employed to estimate Nomogram's performance and a comparison of the nomogramspredicted versus with the Kaplan-Meiermethod-based survival probabilities was used for nomograms performance evaluation.These activities were initiated using Bootstraps with 1,000 resample. The accuracy of the prognostic prediction increased with an increase in the value of C-index [23].*P* values under 0.05 were taken as statistically significant.

Results

Clinicopathologic Characteristics of Patients

In the sorafenib cohort, 113 individuals with HBV-related HCC were included who were subjected to sorafenib therapy after partial hepatectomy. For the control cohort, we studied 120 consecutive HBV-related HCC patientswho did not receive sorafenib therapy after partialhepatectomy. Fig. 1 enlists the clinicopathologic traitsof patients in the sorafenib and control cohorts. For the sorafenib cohort, the mean follow-up time was found to be 48.6 months, with a range extending from 12.8 to 126.5 months, the mean TTR came out to be 14.4 months (having a range extending from 1.3 to 98.7 months) whereas the mean OS was 35.7 months (ranging between 0.9 to 119.6 months). The mean follow-up time in the control cohort was 47.5 months (range, 4.9-111.5 months) whereas the mean TTR and mean OS was 12.7 months (range, 1.0 to 110.1 months) and 32.3 months (range, 3.1 to 111.5 months) respectively.

Relationship between indicators and prognosis in patients treated with sorafenib after surgery

To investigate the clinicopathologic characteristics in HCC patients and biomarkers expression in HCC specimens, and their relationship with the outcome of the patient, pathologic features, serological indicator, HCC staging systems, and biomarkers were selected based on the clinical findings.IHC staining was employed for the detection of the expression of biomarkers including GPC3, pERK and pAKT in postoperative HCC specimens of 233 patients who were/were not subjected to secondary sorafenib therapy, followed by quantification and scoring. Fig. 2 shows the Representative images ofexpressed biomarkers in HCC specimens. Further, in order to define the optimal limit of those biomarkers and serological indicator levels, we used X-Tile to extend across all of the biomarker's expression and serological indicator value as the cutoff point for dividing the patients and estimating the magnitude of benefit of sorafenib against control in the high- or low-level groups. Patients were also groupedaccording to the pathologic features and HCC staging systems. According to sorafenibtreatment status, subgroupanalysis revealed that low levels of GPC3 (p=0.002), pERK (p<0.001) and pAKT (p=0.001) were related to OS, andsurvival advantages of sorafenib treatment have also been witnessed in HCC in male patients (p=0.025), Age<50years (p=0.018), the lack ofMVI (p=0.013), AFP <400μg/L (p=0.015), , ALT<44 U/L (p=0.007), ALP<97U/L (p=0.006), AST<40U/L (p=0.003) , BCLC stage 0/A (p=0.0056), TNM stage□/□ (p=0.011) or Child-Pugh stage A (p=0.009) (Fig.1). Consistent results were obtained using the Kaplan-Meier analysis of OS (Fig. S2). In addition, a significantinteractionwas also detected between treatment and these factors (Table 1). At the same time, the data also verified the significance of these factors in predicting the TTR advantages of sorafenib in HCC patients (Fig.S3).

Independent Prognostic Factors in the Sorafenib Cohort

HCC Precision therapy is heavily reliant on the optimal combination of clinical variablesand biomarkers to stratify patients[36, 37]. Therefore, Cox regression was performed according to the significant prognostic factors selected by the subgroupanalysis. Table 1illustrates the results of the univariate analysis as well as multivariate analysis. Univariate analysis of OS exhibits thatlow levels of GPC3, pERK, pAKT, serum AFP, without MVI, under 50 years old, male, TNM stage I or II, and BCLC stage 0/A had a significant association with an improved OS in sorafenib. Multivariate analyses demonstrated that serum AST, BCLC staging system, GPC3, pERK, and pAKT came out as independent risk factors associated with

OS.Diminished levels of GPC3 (*P*<0.001 Fig. 3A), pERK (*P*<0.001 as seen in Fig. 3B), pAKT (*P*<0.00 as seen in Fig. 3C), serum AST (*P*<0.001 as illustrated in Fig. 3E) and BCLC stage B/C (*P*<0.001, Fig. 3D) predicted better OS of patients in the sorafenib category.

Constructing and validating the prognostic predictionnomogram

The prognostic nomogram for the integration of all independentsignificant factorsfor OS in the sorafenib cohort can be seen in Fig.4.the nomogramwas evaluated in terms of its description power by using ROCcurves and C-index values. For OS prediction theC-index was found to be 0.73; 95% CI ranging from 0.67-0.78. Figs 5A, 5C, and 5E show that thecalibration plot for 1, 3- or 5-year survival probability following surgical reflected that the prediction of nomogramis in optimal agreement with real-time observations (The 1-, 3-, and 5-year AUCs of the nomogram in the sorafenib cohort were 0. 726, 0.816, and 0.823, respectively (Figs 5B, 5D and 5F). In addition, the nomogram can rather exactly classify patients into three prognostic subcategories havingrespective scores of ≤28, 28-122,>122. The respective 5-year rates of OS of the three subgroupswere 46.9%, 17.5%, and 0%in the sorafenib cohort(*P*<0.001, Fig. 3F). The respective mean OS of nomogram stage, stage, and stagein sorafenib cohort was found to be 56.0, 36.0, and 16.0 months, but the respective OS of three subgroups were 41.2, 29.5, 24.5 moths in control cohort. The nomogram also showed the prognostic value in the control group (*p*=0.003, Fig. S4F). In comparison to control group, the sorafenib group was found to have better OS in stage (*p*<0.001, Fig. S5A) and stage (*p*=0.017, Fig. S5B), but no significant difference was observed in stage III group (*p*=0.226, Fig. S5C).

Comparing the Accuracy of prediction between Nomogram and Single Independent Factor

The predictive potential for the prognosis of the nomogram and independent factor was comparedfor HCC patients exposed to sorafenib therapyfollowing partialhepatectomy or the absence of it.Among these independent risk factors, only GPC3(Fig.S4A) and BCLC system(Fig.S4D) showed the prognostic value in the control cohort. The C-index forOS predictionin sorafenib cohort, were 0.59 for BCLC staging system, 0.61 for serum AST, 0.62 for GPC3, 0.63 for pERK, 0.58 for pAKT, which were considerably less than the C-index established using the nomogram (0.73; P <0.001).

Discussion

Survival benefits of sorafenib are limited, and some HCC patients later succumbed to diseaseprogression after responding initially to sorafenib [38, 39].It is noteworthy in particular, that as HCC is a highly heterogeneous malignancy, different individuals suffering from it might show variable responses to sorafenib thus resulting in an increasedneed for biomarkers regarding the selection of patients as well as prediction of response.Recently, the understanding of the underlying mechanism that influencesthe responses of HCC towards sorafenib has increased[37].Llovetet al.generated a newly 146-gene signature able to recognize 30% of patients who benefitted from sorafenib [4]. A recent study reportedFLT3 may be able to predict sorafenib benefit in HCC patients.Numerous other works have reported that amplifying VEGFA, FGF3/FGF4 or FGF19 may potentially predict HCC responseto sorafenib [40, 41].However, for

sorafenib, no effective biomarkers of response have been identified [4]. This work revolves around developing a nomogram to accurately make predictions regarding patient survivalin HCC, for an individual exposed to sorafenib treatment after hepatic resection.

The significance of prognosis of tumor cellsserum GPC3 levelsand GPC3immunoreactivity in patients with HCChas been defined[42].EMT has been found to influence HCC resistance to sorafenib. Among various characteristics of EMT, an important hallmark is E-cadherin inhibition. Inhibition of E-cadherin leads todegeneration of the surrounding extracellular matrixdue to the migration of primary malignant cells from their primary site and finally their migration into the blood vessels and eventual takeover of secondary organs [43].Wu et al.and Qi et al. showed that E-cadherin and GPC3 expression are correlatednegatively in HepG2 cells [44, 45].Additionally, the level of E-cadherin was lowin GPC3 overexpression HCC tumor tissues[45].In GPC3-silenced HepG2 cells, a decrease in Slug and Snailand other EMT-related proteins and migration-related proteins (matrix metalloproteinase 2 and 9) was observed [44].In summary, these results indicate that EMT is promoted by GPC3 overexpression in HCC cells[13]. The level of GPC3 was also showed in this nomogram. Our results showed that a low level of GPC3 patients hasa better OS than high in the sorafenib cohort. The low level of GPC3 is significantly related to an improved OS inpatients subjected to sorafenib adjuvant therapy compared to those not treated with sorafenib.

pERK is a proxy for the sorafenib inhibitory of the RAS/MAPK pathwayin vitro and solid tumors [9]. Several studies have proposed pERK as a candidate biomarker associated with prognosis following treatment with sorafenib, despite conflicting outcomes [46–48]. Thelack of a validated system of scoring forpERKimmunestaining, and the variation among cohorts,endpoints, and detection techniques could be the reason behind these inconsistencies [4]. The pERK level was included in the OS nomogram. Our results showed that a low level of pERK significantly correlated with an improved OS in patients exposed to sorafenib adjuvant therapy patients compared to those not treated with sorafenib. Decreased levels of pERK in patients led to better OS compared to those with high levels of pERK in the sorafenib cohort, but this was not found in the control group (Fig.S4).

The pAKT level was included in the OS nomogram. Our results showed that sorafenib adjuvant therapy patients have better OS compared with not treated with sorafenib in a low level of pAKT cohort, and low levels of pAKT patients have better OS than high in sorafenib cohort. This result is supported by previous reports. Many studies have revealed that in sorafenib-resistant HCC cells, the Akt pathway is highly activated,[49–52] and inhibition of Akt can potentially reverse this opposition by shifting autophagy from a role in cellular protection to amechanism promoting death [49]. In addition, the response towards sorafenib is impaired in HCC due toirregular p-AKT activation [53, 54].EMT has been observed to impact sorafenibresistance to HCC [53], and hyperactivity of PI3K/AKT signalingas a major originating reason[54, 55]. In this trial, we arrived at the result that patients with low pAKT expression in the Sorafenib cohort had a better prognosis, but for the control group, this trend was nonexistent. Simultaneously, among the patients with low pAKT level,patients who received sorafenib therapy after surgery had a better OS than those who did not.

The serum AST and BCLC systems were also shown in this nomogram. Serum AST is included in many HCC prediction systems [23, 24]. Our results showed that low serum AST has a better OS as compared to high serum AST in the sorafenib cohort, but this trend was not found in the control group(Fig.S4). In patients with low serum AST, those treated with sorafenib after surgery had a better OS than those who were not treated with sorafenib. Previous studies have focused on the advanced stage of BCLC in HCC patients, and this study found that sorafenib adjuvant therapy after surgery in the initial stage of BCLC had a better OS in comparisonto those not treated with sorafenib.

Our proposed nomogram can thus quite predict the prognosis of HCC patients treated with sorafenib post-surgery quite accurately. The prediction accuracy of the nomogram was better than that of a single independent factor. We also found that treatment with sorafenib after surgery in nomogram stage I patients had a significant benefit, while nomogram stage II patients had a partial benefit, but nomogram stage III patients had no significant benefit. Thus, our nomogram can be employed to predict patient prognosis in patients with HCC exposed to sorafenib therapy after surgery, to select appropriate candidates for potentially successful adjuvant therapy, and patients were stratified in a randomized controlled trial design based on accurate prognostic stratification. At the same time, the model has the potential to facilitate active communication between patients and doctors about postoperative sequential treatment and prognostic analysis [56].

This study suffers from some inevitable limitations. First, only a single Chinese institution was used for the establishment of a nomogram. Secondly, the patients in the cohort had abackground of HBV infection, HCV infection patients were not included. Since HCV infection was an important factor or HCC cancerization, especially in Western countries, it is not clearwhether this nomogram is suitable for patients with a Western background.Third, this study only hasa primary cohort but no validation cohort, which is still a limitation and to a certain extent, might affect the results as well. Finally, whether or not the proposed nomogram applies to individual patients receiving another adjuvant therapy other than sorafenib still remains to be ascertained.

Conclusion

To conclude, our proposed nomogram can be used to choose appropriate candidates for potential and effective sorafenib adjuvant therapy after surgery. There is still an immense need for additional studies to establish whether or not it applies to other patient cohorts.

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate transaminase
AUC	The area under the ROC curve

C-index	Concordance index
FDA	Food and Drug Administration
GPC3	Glypican-3
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HE	Hematoxylin-eosin
HGF	Hepatocyte growth factor
IFN	Interferon
IHC	Immunohistochemistry
MAPK/ERK	Mitogen-activated protein kinase/extracellular signal-regulatedkinase
MRI	Magneticresonanceimaging
OS	Overall survival
pAKT	Phosphorylated AKT
pERK	Phosphorylated ERK
ROC	Receiver operating characteristic
TBIL	Total bilirubin
TNM	Tumor-node-metastasis classification system
TTR	Time to recurrence
VEGFR	Vascular endothelial growth factor receptors
WHO	World Health Organization

Declarations

Ethics Approval and Consent Statement

The research protocol was approved by the Ethics Committee Shanghai Eastern Hepatobiliary Surgery Hospital. All the patients provide written informed consent.

Consent for Publication

All authors have seen the manuscript and approved to submit to your journal.

Availability of data and materials

All data analysed during this study are included in this manuscript.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Study concept design: W-MC, HDand WD; Immunohistochemistry stain: WD, HY, and Z-HX; Acquisition of data, interpretation of data: WD, HY, YF, KY, Y-QZ, LH, Y-CZ and Z-YC; All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Table

Due to technical limitations Table 1 is available as a download in the Supplementary Files.

Figures

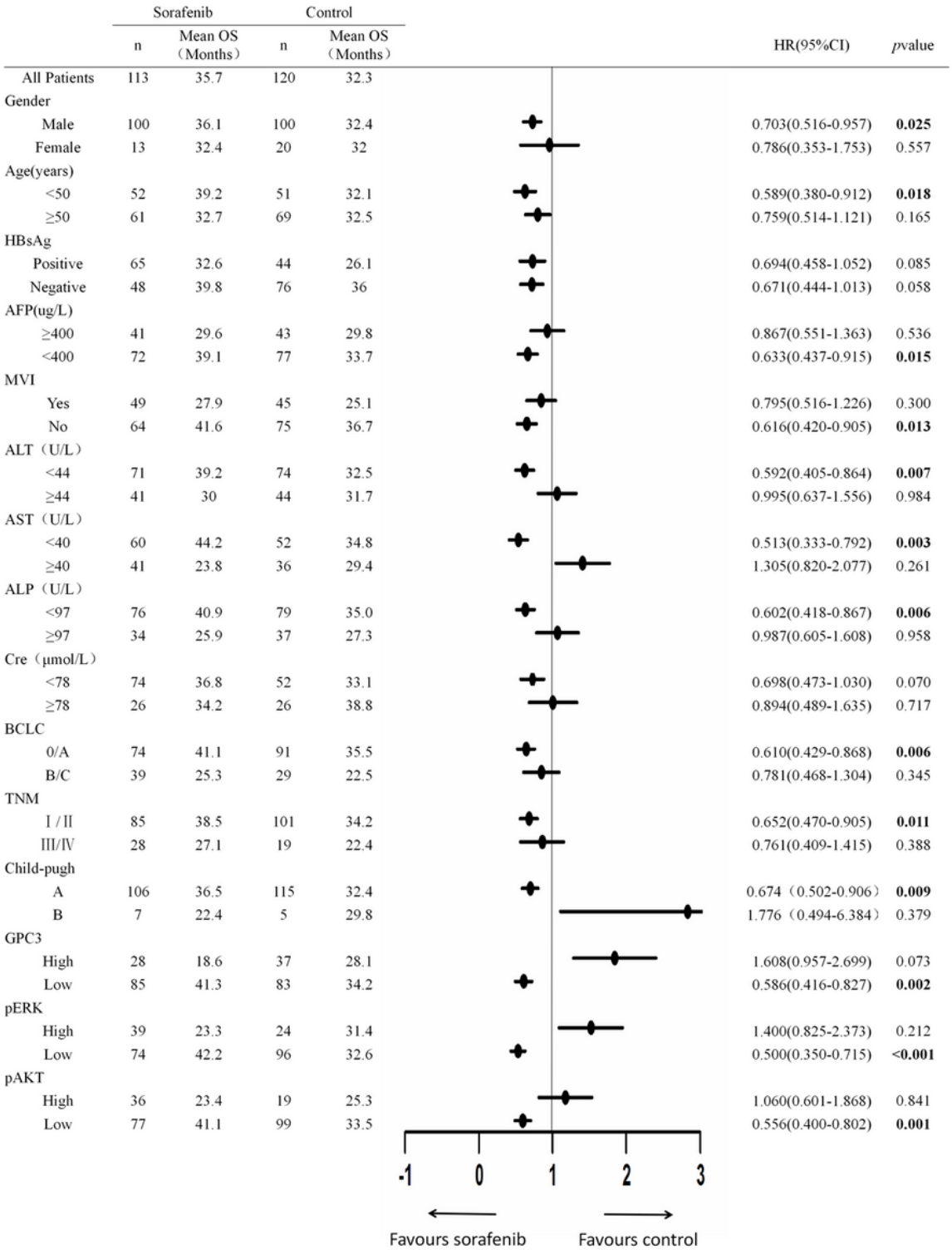

Figure 1

The Baseline Characteristics of Subgroup. * The p value of interactions between treatment and biomark levels or clinical variables were also shown.

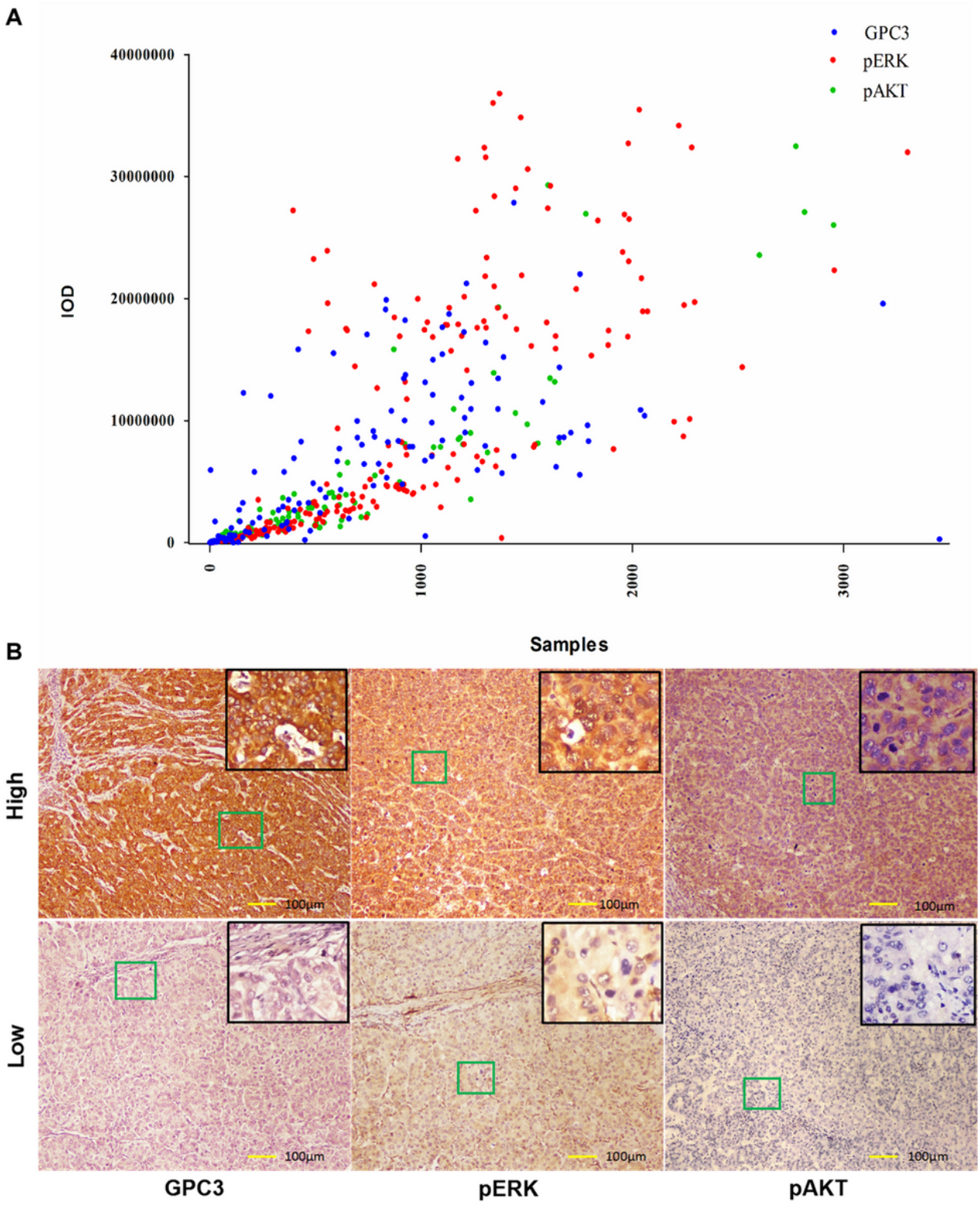

Figure 2

Expression of GPC3, pERK and pAKT in Hepatitis B Virus related HCC. a. Immunohistochemical expression of GPC3, pERK and pAKT in HBV-related HCC. A scatter plot of samples and IOD for each marker was obtained. b. Representative images of IHC staining of GPC3, pERK and pAKT from indicated patients were shown. Scale bar=100 μm.

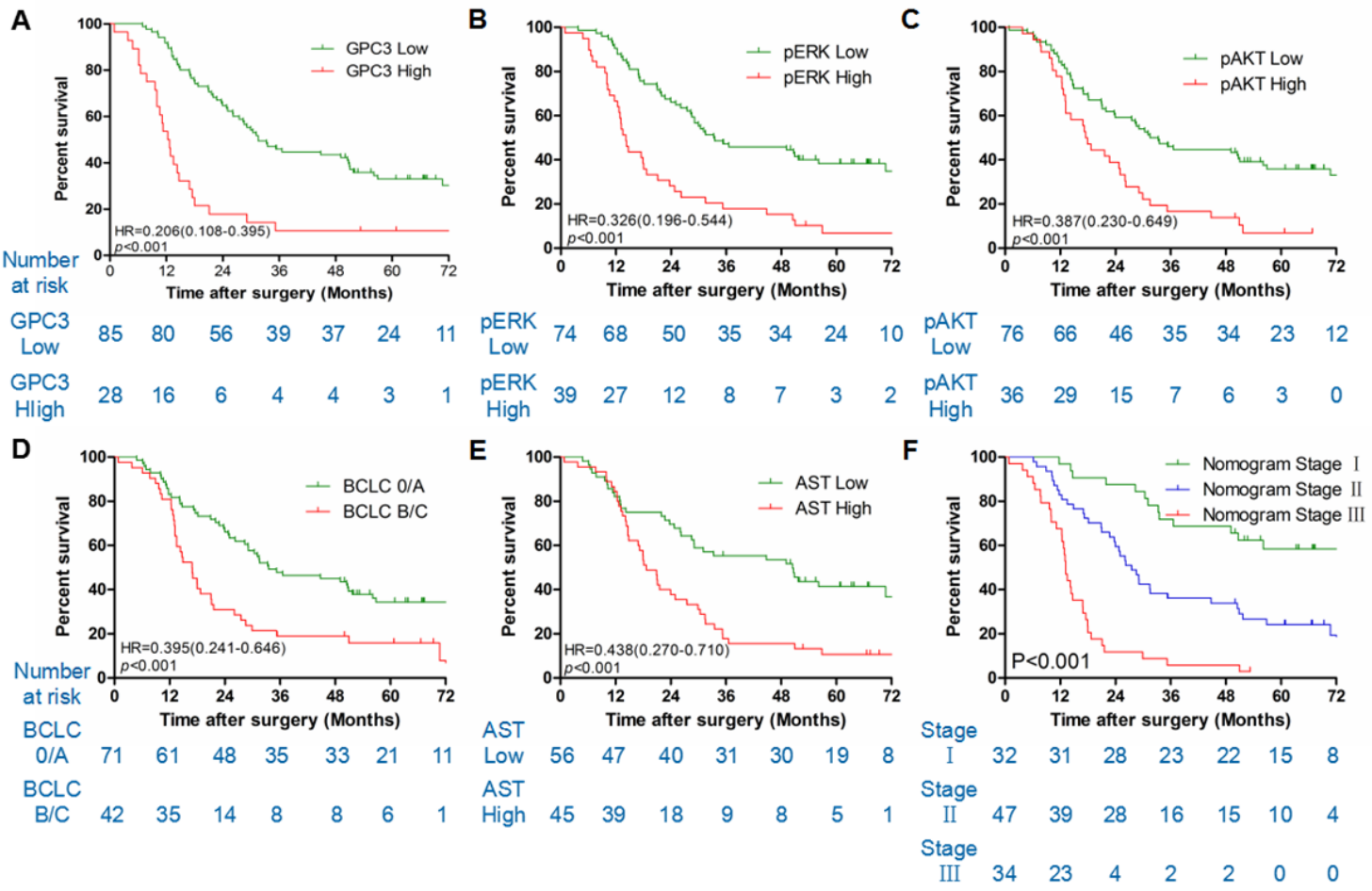

Figure 3

Kaplan-Meier survival curves of OS in the sorafenib cohort. GPC3(a), pERK(b), pAKT(c), BCLC staging system(d), serum AST(e) and nomogram stage(f) of sorfenib cohort.

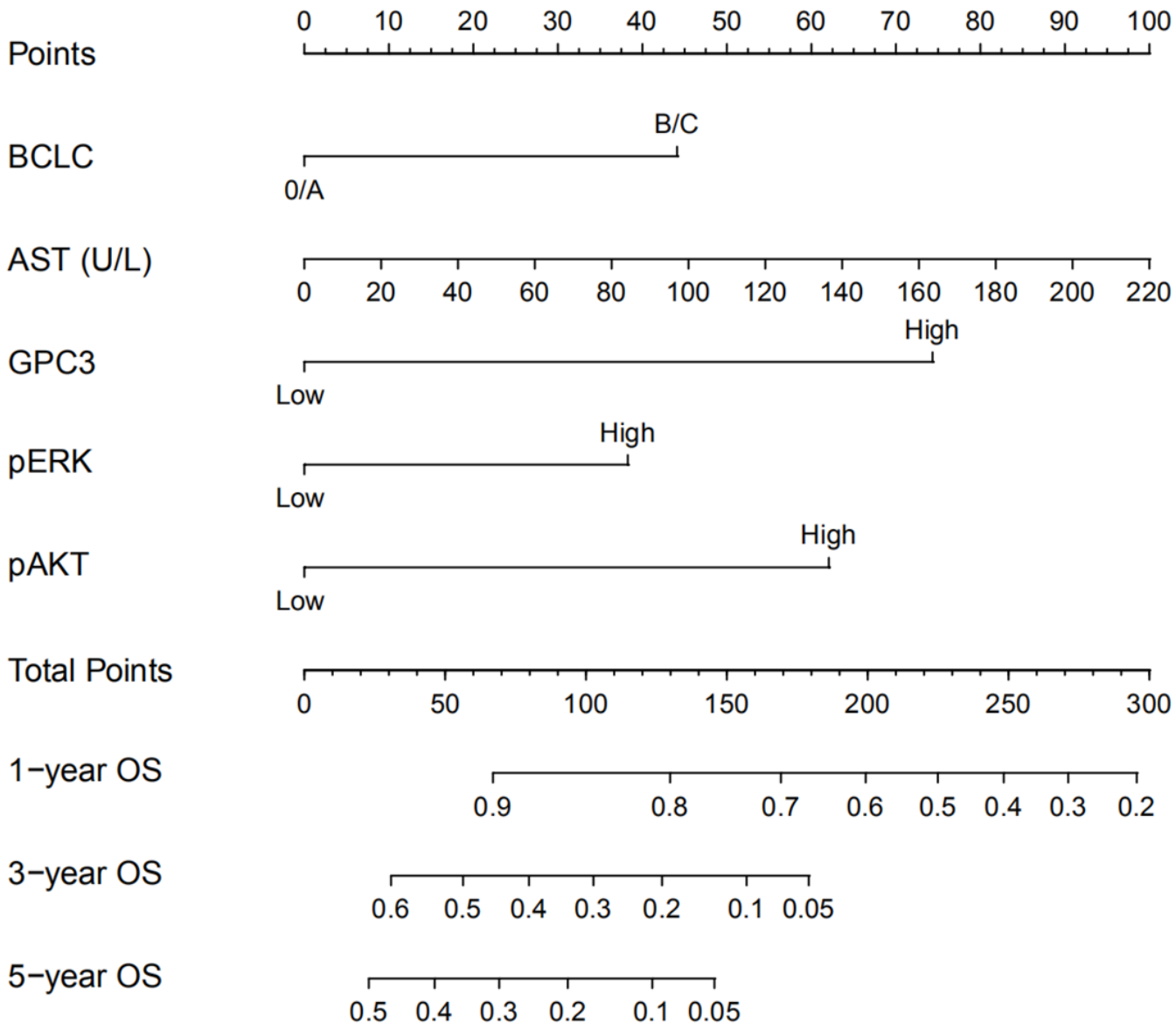

Figure 4

Nomogram for predicting OS of patients who received sorafenib after liver resection for Hepatitis B Virus related HCC. To use the nomogram, an individual patient's value is located on each variable axis and a line is drawn upwards to determine the number of points received for each variable value. The sum of these numbers is located on the total points axis and a line is drawn downwards to the survival axes to determine the likelihood of 1-, 3- or 5-year survival rate.

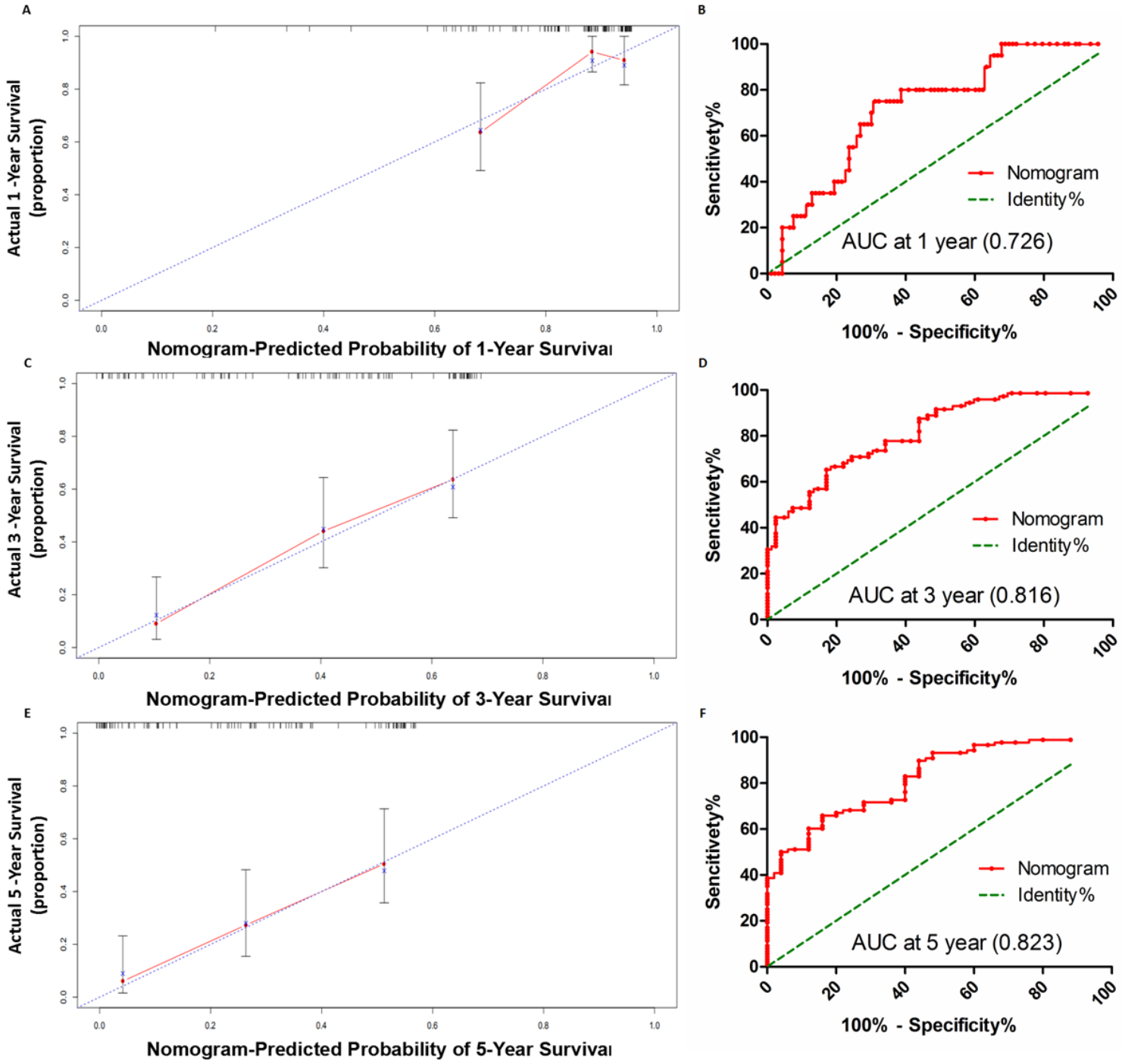

Figure 5

The calibration curve for predicting patients OS at 1-year(a), 3-year(c) and 5-year(e) in the sorafenib cohort; The AUC values of ROC predicted 1-year(b), 3-year(d) and 5-year(f) OS rates of Nomogram in the sorafenib cohort.

Supplementary Files

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