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The prognostic values of insulin-like growth factor binding protein in breast cancer

Jiao Wang, MD[a], Xin-Xin Luo, MS[b], Yun-Liang Tang, MD[c], Ji-Xion Xu, MD, PhD[a], Zhen-Guo Zeng, MD, PhD[d,*]

Abstract

Insulin-like growth factor binding proteins (IGFBPs) are a family of proteins binding to insulin-like growth factors, generally consisting 6 high-affinity IGFBPs, namely IGFBP1 through IGFBP6. IGFBP family members have been indicated to be involved in the development and progression of tumors and may be useful prognostic biomarkers in various malignancies. However, the prognostic role of individual IGFBPs, especially at the mRNA level in breast cancer patients remains elusive.

We accessed the prognostic roles of IGFBPs family (IGFBP1-6) in breast cancer through the "Kaplan–Meier plotter" online database and OncoLnc database.

Our results showed that the high expression of IGFBP1 mRNA was associated with favorable relapsed free survival (RFS) in all breast cancer patients. The high expression of IGFBP2 mRNA was associated with favorable overall survival (OS) and RFS in all breast cancer patients. The high expression of IGFBP3 mRNA was significantly correlated to worsen RFS in all breast cancer patients. The high expression of IGFBP4 mRNA was associated with favorable OS, RFS, distant metastasis-free survival, and post-progression survival in all breast cancer patients.

Our results indicated that expression of IGFBPs mRNA may have prognostic values in breast cancer patients, and have a benefit for developing tools to predict the prognosis more accurately.

Abbreviations: CI = confidence intervals, DMFS = distant metastasis-free survival, ER = estrogen receptor, HR = hazard ratio, IGFBP = insulin-like growth factor binding proteins, IGFs = insulin-like growth factors, KM plotter = Kaplan–Meier plotter, OS = overall survival, PAPP-A = pregnancy-associated plasma protein-A, PPS = post-progression survival, RFS = favorable relapsed free survival.

Keywords: breast cancer, hazard ratio (HR), IGFBP, KM plotter, prognosis

1. Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-associated mortality among females worldwide.[1] Despite remarkable progress achieved in the diagnosis and treatment of breast cancer in recent years, the prognosis of patients with breast cancer still remains very poor.[2] Therefore, the identification of key molecules involved in breast cancer is urgent and highly demanded for improving the clinical prognosis.

Insulin-like growth factor binding proteins (IGFBPs) are a family of proteins binding to insulin-like growth factors (IGFs), generally consisting 6 high-affinity IGFBPs, namely IGFBP1 through IGFBP6. IGFBP family members have been indicated to be involved in the development and progression of tumors and may be useful prognostic biomarkers in various malignancies. Recent studies validated IGFBPs' role in the diagnosis and prognosis prediction in some solid tumor including rectal carcinoma, ovarian cancer, pancreatic cancer, and so on.[3] However, the prognostic role of individual IGFBPs, especially at the mRNA level, in breast cancer remains ill-defined.

The "Kaplan–Meier plotter" (KM plotter), handled by a PostgreSQL server, is established using gene expression data and survival information from Gene Expression Omnibus (GEO; www.ncbi.nlm.nih.gov/geo/) database, which has been widely used to analyze the clinical impact of individual genes on overall survival (OS), relapsed free survival (RFS), distant metastasis-free survival (DMFS), and post-progression survival (PPS) of breast cancer patients.[4] Up till now, a number of genes have been reported by using KM plotter in gastric cancer,[5–7] ovarian cancer,[8–10] and lung cancer.[10–14] In the present study, we investigated the prognostic role of individual IGFBPs in breast cancer patients by using KM plotter database.

2. Materials and methods

The correlation between mRNA expression of individual IGFBPs and survival was performed on KM plotter database. Currently, KM plotter database is capable to evaluate the effect of 22,277 genes on prognostic in lung cancer, ovarian cancer, breast cancer,

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[a] Department of Endocrinology and Metabolism, The First Affiliated Hospital of Nanchang University, [b] Department of Pharmacy, Jiangxi Provincial People's Hospital, [c] Department of Rehabilitation Medicine, [d] Department of Critical Care Medicine, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China.

[*] Correspondence: Zhen-Guo Zeng, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China (e-mail: tylncu@163.com).

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and gastric cancer data. All breast cancer patients in the database were identified from the GEO (http://www.ncbi.nlm.nih.gov/geo/) datasets.[4] The clinical data include ER, PR, HER2 status, lymph node status, differentiation grade, intrinsic subtype, TP53 status, and Pietenpol subtype. The expression of IGFBP family members, namely IGFBP1, IGFBP2, IGFBP3, IGFBP4, IGFBP5, and IGFBP6 in breast cancer patients was respectively analyzed by in the KM plotter database (http://kmplot.com/analysis/index.php?p=service&cancer=breast). The Kaplan–Meier survival plots were obtained from the KM plotter database. Another database OncoLnc was also used to validate some results from KM plotter database. OncoLnc contains survival data for 8647 patients from 21 cancer studies performed by The Cancer Genome Atlas (TCGA), along with RNA-SEQ expression for mRNAs and miRNAs from TCGA, and lncRNA expression from MiTranscriptome beta.[15] To validate the prognostic value of individual *IGFBP* genes in breast cancer patients, the samples were collected and divided into low expression or high expression group according to the median mRNA level. Hazard ratio (HR), 95% confidence intervals (CI), and log-rank *P* were calculated and presented on the main plots. A *P*-value of $\leq .05$ was considered statistically significant.

All the data of this paper was obtained from the open-access KM plotter database, we did not get these data from patients directly, nor intervene these patients. So the ethical approval was not necessary.

3. Results

First, OS of enrolled breast cancer patients associated with 6 IGFBPs (IGFBP1-6) was exhibited in Figure 1. Next, we evaluated the prognostic value of IGFBP1, IGFBP2, IGFBP3, IGFBP4, IGFBP5, IGFBP6 mRNA expression respectively in breast cancer patients.

The valid Affymetrix ID is 205302_at (IGFBP1). Figure 2 showed the results of OS, RFS, DMFS, and PPS in breast cancer patients. Specifically, the high expression of IGFBP1 mRNA was not correlated to OS (HR 0.87 [0.7–1.07], $P=.19$), DMFS (HR 1.02 [0.84–1.24], $P=.85$), and PPS (HR 0.92 [0.73–1.18], $P=.53$) for breast cancer patients followed for 20 years. Significantly, we found that the high expression of IGFBP1 mRNA was correlated to favorable RFS for breast cancer patients (HR 0.82 [0.73–0.91], $P=.00027$).

Similarly, the valid Affymetrix ID is 202718_at (IGFBP2). The high expression of IGFBP2 mRNA was significantly correlated to favorable OS (HR 0.71 [0.57–0.88], $P=.0014$) and RFS (HR 0.8 [0.72–0.9], $P=7.8e{-}05$) for breast cancer patients. Statistically, the high expression of IGFBP2 mRNA was not correlated to DMFS (HR 0.83 [0.69–1.01], $P=.062$) and PPS (HR 0.79 [0.62–1.01], $P=.064$) in breast cancer patients (Fig. 3).

The valid Affymetrix ID is 210095_s_at (IGFBP3).The high expression of IGFBP3 mRNA was significantly correlated to worsen RFS (HR 1.12 [1–1.25], $P=.045$) for all breast cancer

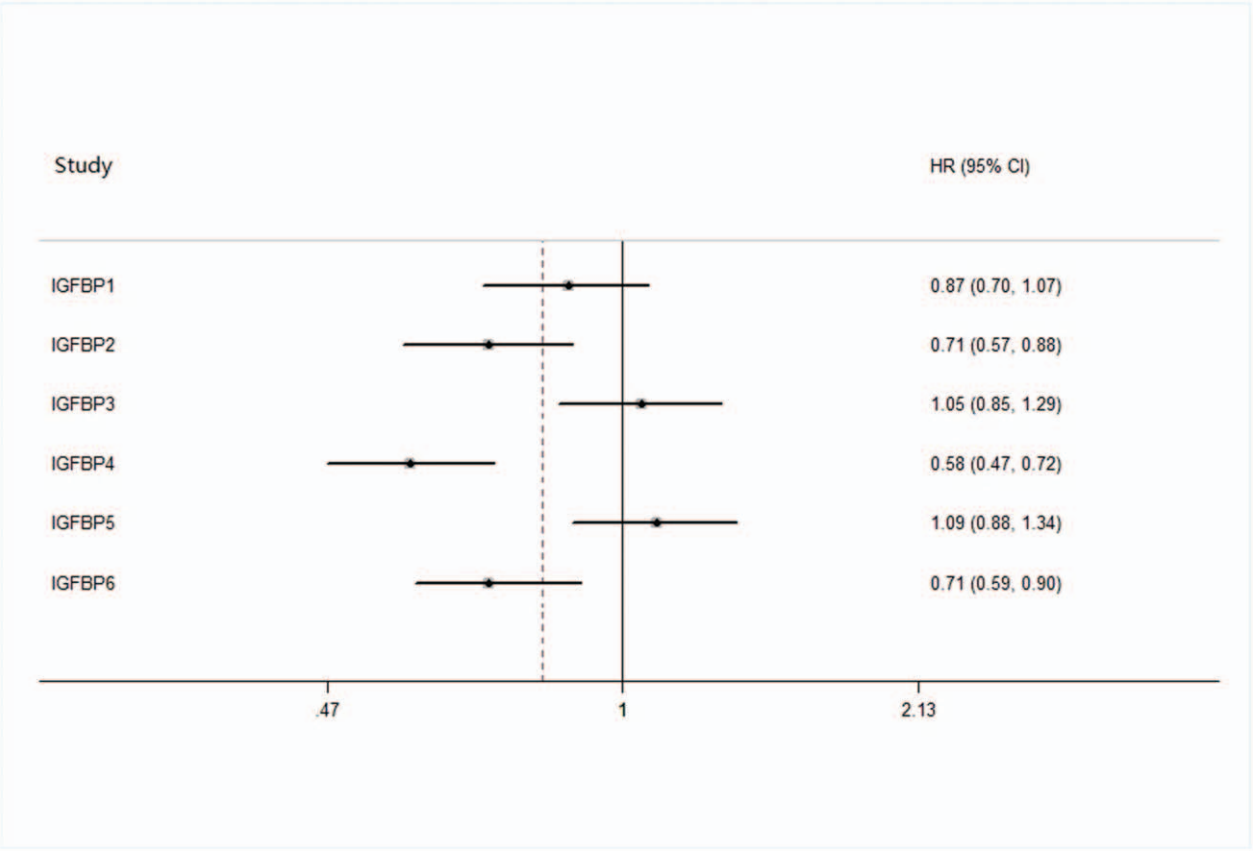

Figure 1. The prognostic HRs value of individual IGFBPs members in all breast cancer in www.kmplot.com. HRs = hazard ratios, IGFBPs = insulin-like growth factor binding proteins.

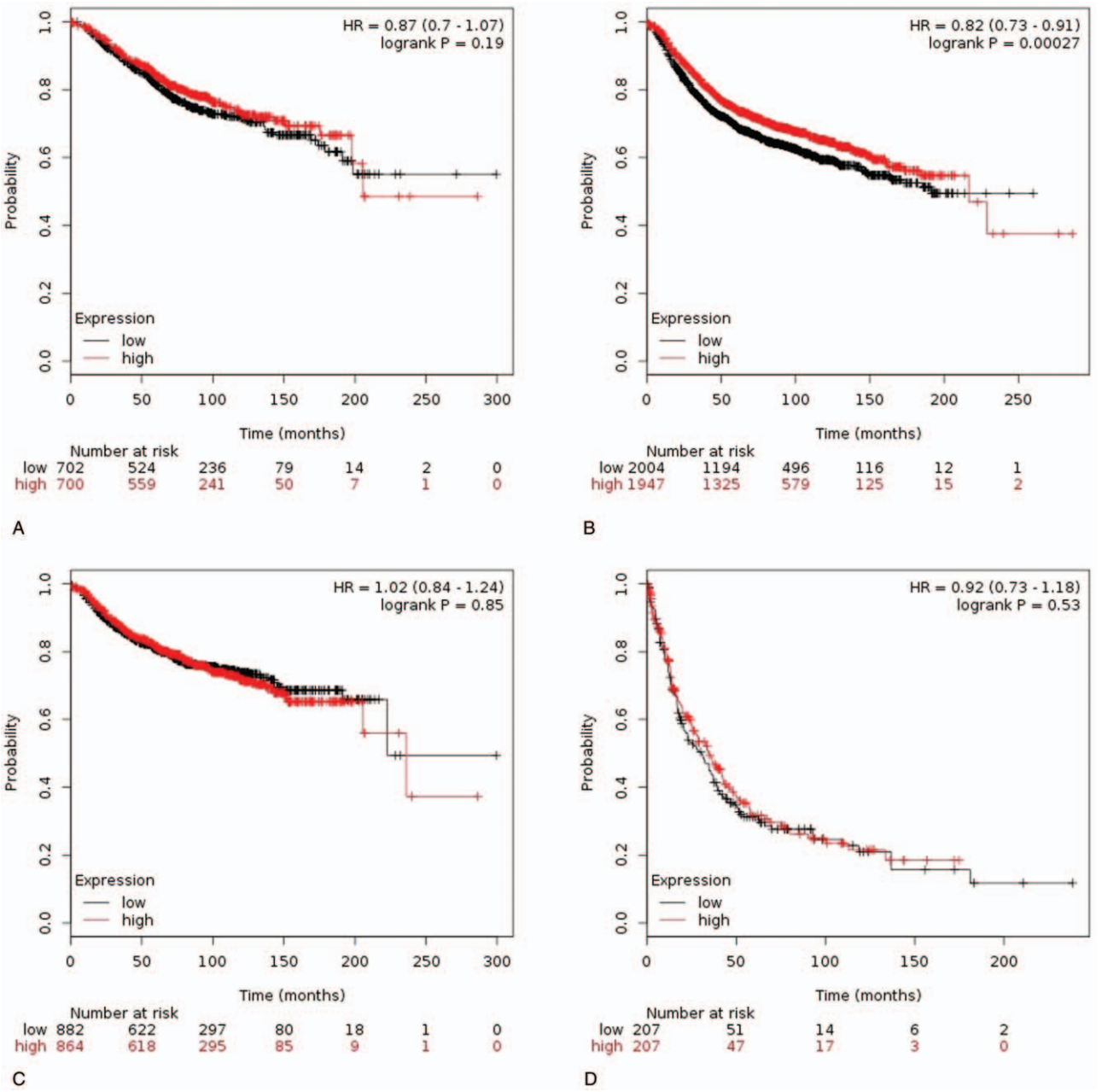

Figure 2. For IGFBP1, its Affymetrix ID is 205302_at. (A) OS curves are plotted for breast cancer patients (n = 1402). (B) RFS curves are plotted for breast cancer patients (n = 3951). (C) DMFS curves are plotted for breast cancer patients (n = 1746). (D) PPS curves are plotted for breast cancer patients (n = 414). DMFS = distant metastasis-free survival, IGFBP = insulin-like growth factor binding proteins, OS = overall survival, PPS = post-progression survival, RFS = relapsed free survival.

patients. Statistically, the high expression of IGFBP3 mRNA was not correlated to OS (HR 0.83 1.05 [0.85–1.29], $P = .68$), DMFS (HR 1.18 [0.97–1.43], $P = .094$), and PPS (HR 1.03 [0.81–1.31], $P = .81$) in breast cancer patients (Fig. 4).

Figure 5 demonstrates the prognostic value of IGFBP4 in the database. The valid Affymetrix ID is 201508_at (IGFBP4). Collectively, the high expression of IGFBP4 mRNA was significantly correlated to favorable OS (HR 0.58 [0.47–0.72], $P = 6.5e{-}07$), RFS, (HR 0.66 [0.59–0.74], $P = 1.4e{-}13$), DMFS (HR 0.64 [0.53–0.78], $P = 5.9e{-}06$), and PPS (HR 0.65 [0.51–0.83], $P = .00042$) for breast cancer patients.

Figure 6 demonstrates the prognostic value of IGFBP5 in the database. The valid Affymetrix ID is 211959_at (IGFBP5). The high expression of IGFBP5 mRNA was not correlated to OS (HR 1.09 [0.88–1.34], $P = .45$), RFS (HR 1.01 [0.91–1.13], $P = .87$), and PPS (HR 1.04 [0.81–1.32], $P = .77$) in breast cancer. The high expression of IGFBP5 mRNA was correlated to worsen DMFS (HR 1.24 [1.02–1.51], $P = .028$) for all breast cancer patients.

Figure 7 demonstrates the prognostic value of IGFBP6 in the database. The valid Affymetrix ID is 203851_at (IGFBP6). The high expression of IGFBP6 mRNA was significantly correlated to favorable OS (HR 0.73 [0.59–0.9], $P = .0035$) and RFS (HR 0.67

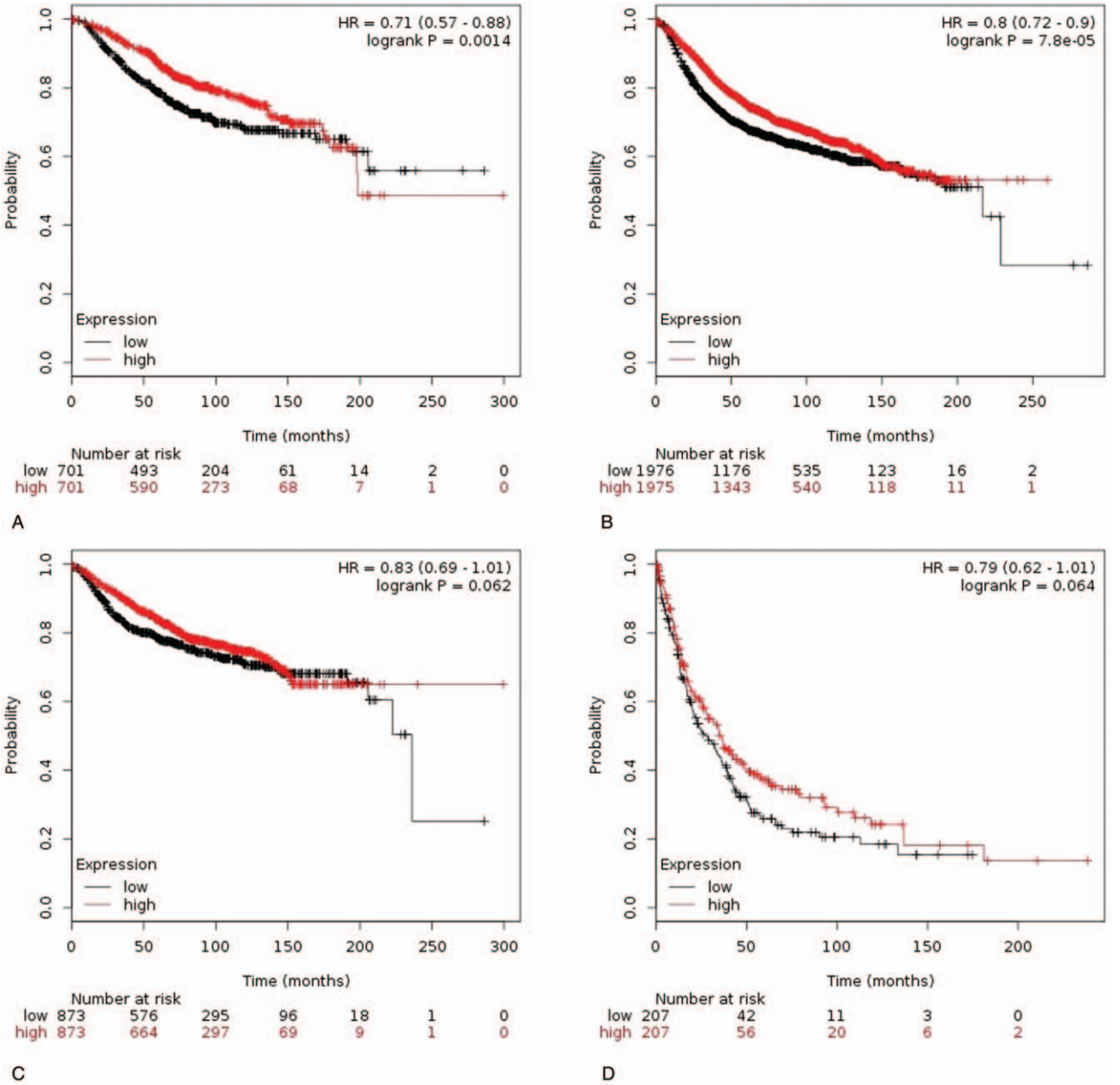

Figure 3. For IGFBP2, its Affymetrix ID is 202718_at. (A) OS curves are plotted for breast cancer patients (n = 1402). (B) RFS curves are plotted for breast cancer patients (n = 3951). (C) DMFS curves are plotted for breast cancer patients (n = 1746). (D) PPS curves are plotted for breast cancer patients (n = 414). DMFS = distant metastasis-free survival, IGFBP = insulin-like growth factor binding proteins, OS = overall survival, PPS = post-progression survival, RFS = relapsed free survival.

[0.6–0.75], $P = 1.3e{-}12$), and PPS (HR 0.72 (0.56–0.91), $P = .0069$), while it was not correlated to DMFS (HR 0.86 [0.71–1.04], $P = .12$) in all breast cancer patients.

Furthermore, we also employed another database OncoLnc to validate the prognostic roles of IGFBP2, IGFBP4, and IGFBP6 mRNA expression (Fig. 8), which were shown to have prognostic value for breast cancer patients in KM plotter database. It was found that the high expression of IGFBP4 ($P = .0472$) and IGFBP6 ($P = .0058$) mRNA were correlated to favorable OS. Inconsistent with the aforementioned result, the high expression of IGFBP2 mRNA was not correlated to favorable OS ($P = .74$).

We then access the correlation of individual IGFBPs mRNA expression with other clinicopathological features, we examined the correlation of OS with ER (Table 1), differentiation grade (Table 2), lymph node status (Table 3), and TP53 status (Table 4) in breast cancer patients. As shown in Table 1, The high expression of IGFBP4 mRNA was significantly associated with favorable OS in estrogen receptor (ER) positive breast cancer, HR 0.7 (0.49–1), $P = .049$, while significant relevance was not observed for other IGFBPs. From Table 2, the high expression of IGFBP4 and IGFBP6 mRNA was significantly associated with favorable OS in grade II breast cancer patients, (HR 0.48 [0.31–0.75], $P = .00088$; HR 0.45 [0.29–0.7], $P = .00027$ respectively),

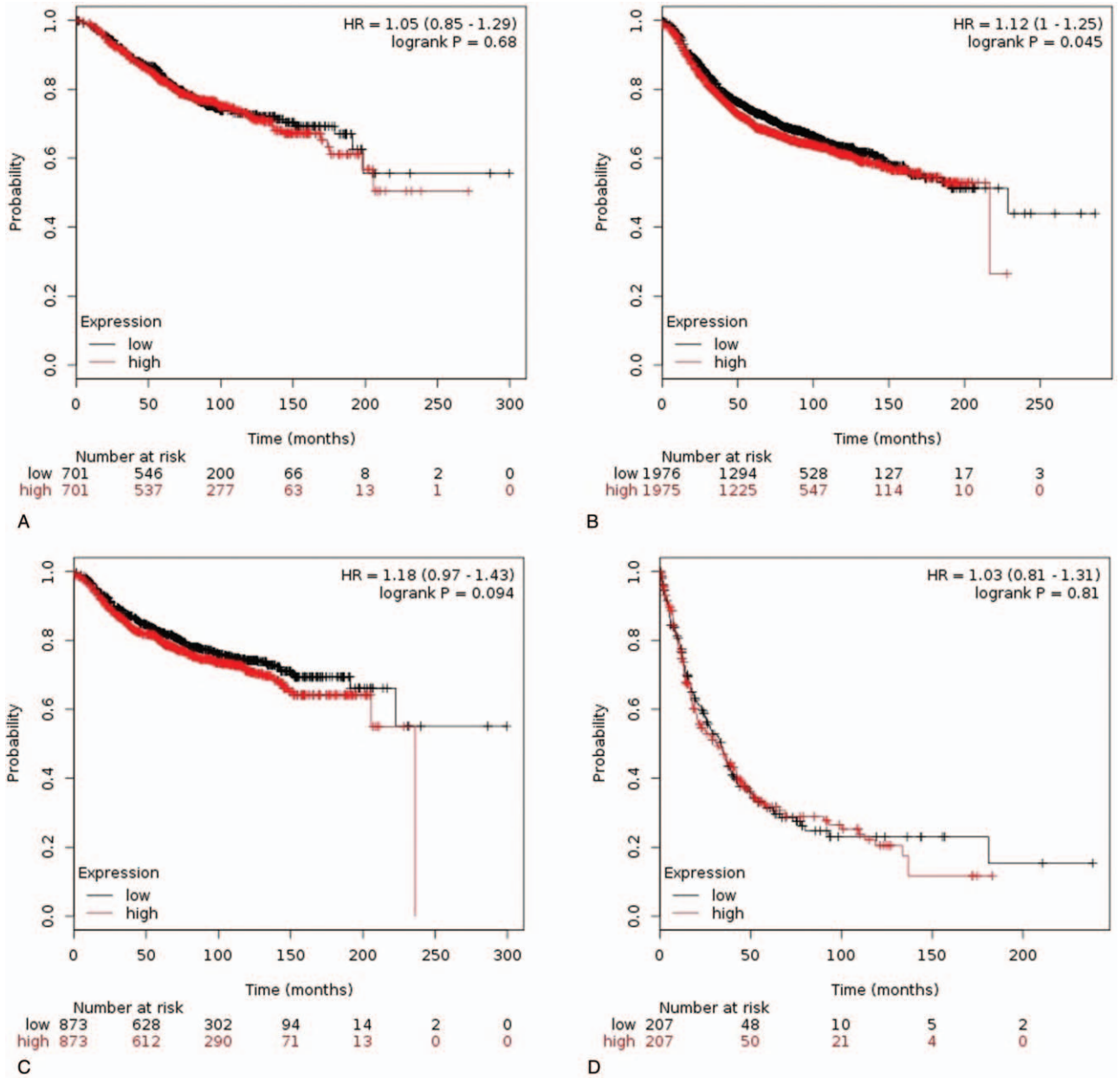

Figure 4. For IGFBP3, its Affymetrix ID is 210095_s_at. (A) OS curves are plotted for breast cancer patients (n = 1402). (B) RFS curves are plotted for breast cancer patients (n = 3951). (C) DMFS curves are plotted for breast cancer patients (n = 1746). (D) PPS curves are plotted for breast cancer patients (n = 414). DMFS = distant metastasis-free survival, IGFBP = insulin-like growth factor binding proteins, OS = overall survival, PPS = post-progression survival, RFS = relapsed free survival.

while other IGFBPs mRNA expression was not related to pathological grades of breast cancer patients. Just the high expression of IGFBP4 mRNA was significantly associated with favorable OS (HR 0.66 [0.46–0.96], $P = .03$) in breast cancer patients with lymph node positive. From Table 4, all of the IGFBPs mRNA expression was not significantly correlation of TP53 status in breast cancer patients.

4. Discussion

IGFBP1, secreted by hepatoma and other cell types in various phosphorylated forms, mainly functions in the intracellular and pericellular compartments to regulate cell growth and survival.[3] It interacts with several other proteins in addition to ligands IGFs and plays an important role on the development and progression of several cancer types.[3,16–18] Previous studies have investigated the association between circulating IGFBP1 levels and breast cancer. Kaaks et al reported that reduced levels of IGFBP1 were associated with increased breast cancer risk, possibly by the anti-tumor effects of IGFBP1.[19] IGFBP1 appears to modulate the anti-apoptotic effects of IGF-1 through IGF-dependent and -independent mechanisms in human breast cancer.[20] In addition, IGFBP1 has an influence on survival, which mechanically depends on inhibiting breast cancer cell motility and the known favorable effect of insulin.[21,22] However, Krajcik et al's study showed IGFBP1 level was not associated with the incidence

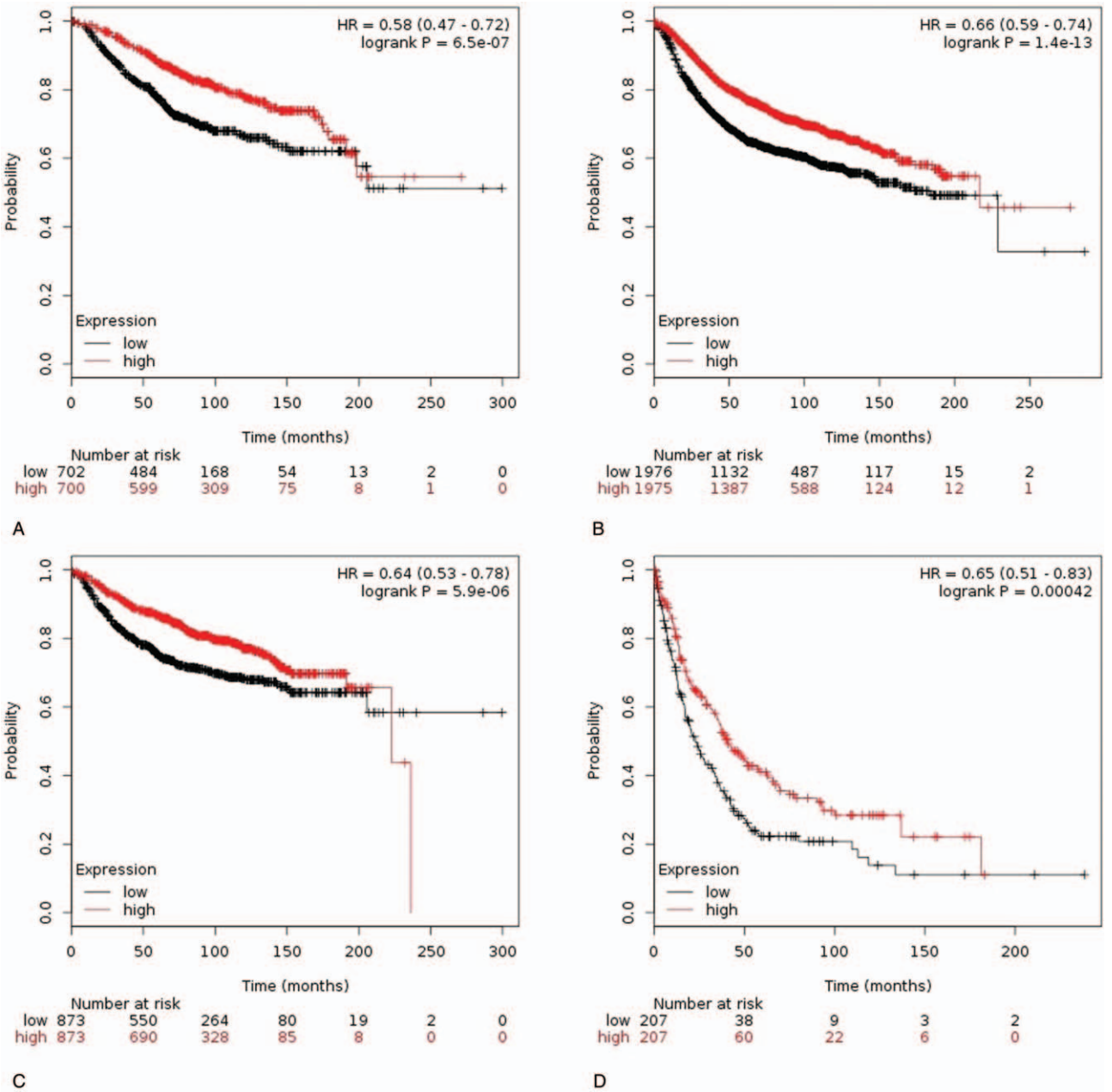

Figure 5. For IGFBP4, its Affymetrix ID is 201508_at. (A) OS curves are plotted for breast cancer patients (n = 1402). (B) RFS curves are plotted for breast cancer patients (n = 3951). (C) DMFS curves are plotted for breast cancer patients (n = 1746). (D) PPS curves are plotted for breast cancer patients (n = 414). DMFS = distant metastasis-free survival, IGFBP = insulin-like growth factor binding proteins, OS = overall survival, PPS = post-progression survival, RFS = relapsed free survival.

of breast cancer in either pre- or postmenopausal women.[23] In the present study, we found that the high expression of IGFBP1 mRNA was significantly correlated to favorable RFS for all breast cancer patients. This heterogeneity might be related to variability in clinicopathological features of breast cancer patients.

IGFBP2 is one of the most abundant IGFBPs in serum.[24] Recently, accumulating evidence strongly indicates that high expression of IGFBP2 is associated with various tumor types, such as colon cancer,[25] lung cancer,[26] ovarian cancer,[27] and prostate cancer.[28] In breast cancer patients, the concentration of IGFBP2 in serum and in breast cancer tissue is significantly elevated.[29,30] Moreover, IGFBP2 was an independent and positive predictor of OS in breast cancer.[31] Decreased IGFBP2 level attenuated the associated aggressive phenotype of breast cancer cells both in vitro and in vivo. Perks et als study showed that IGFBP2 has effect on *PTEN*, one of the most frequently mutated tumor suppressor genes in human breast cancer cells.[32] Consistent with the previous studies, the results in KM plotter also indicate IGFBP2 has a positive role in breast cancer as evidenced by favorable survival. However, high expression of IGFBP2 mRNA was not correlated to favorable OS in OncoLnc, it may be due to the smaller sample size. Moreover, the exact antineoplastic mechanism needs further to be explored.

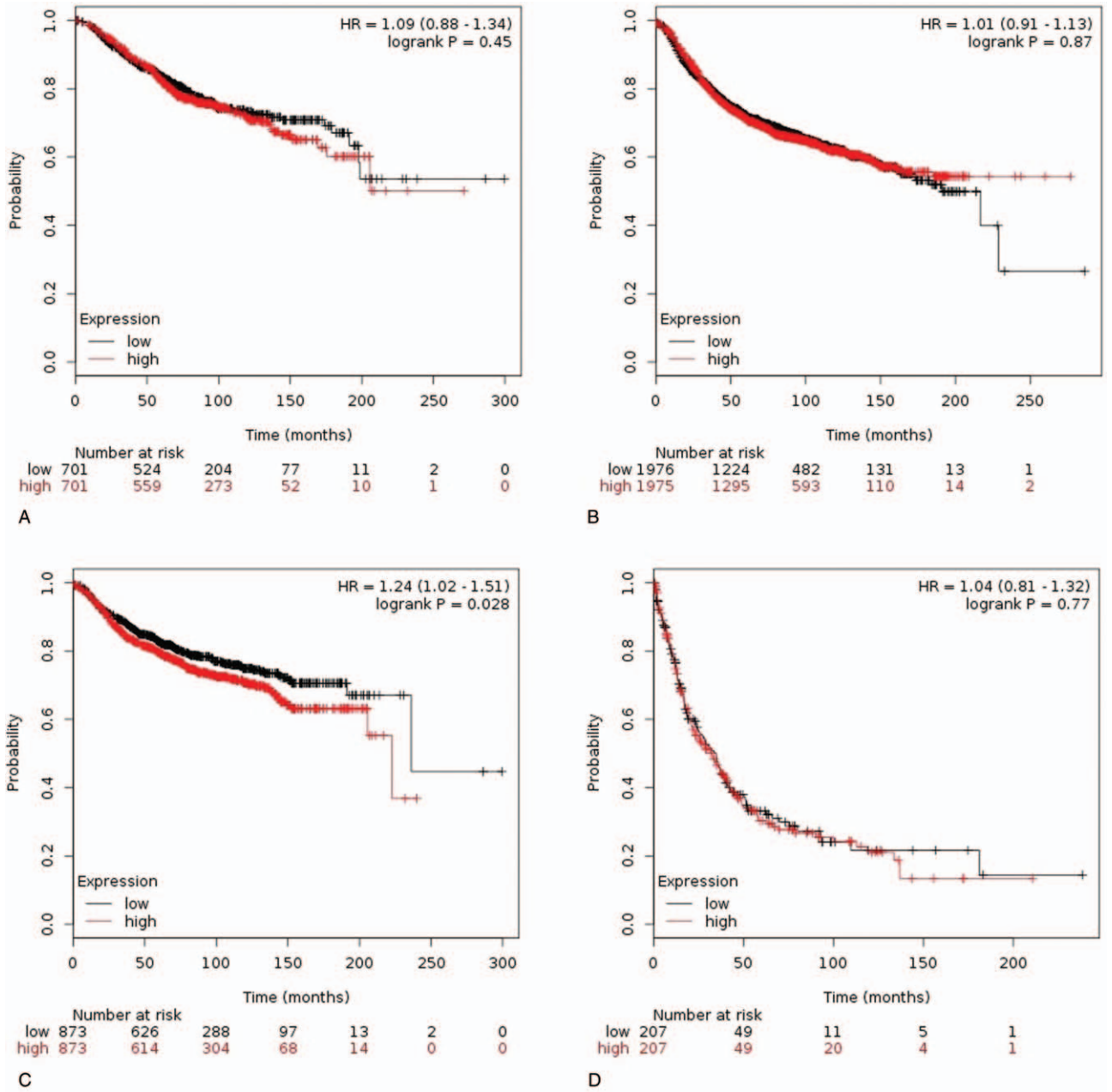

Figure 6. For IGFBP5, its Affymetrix ID is 211959_at. (A) OS curves are plotted for breast cancer patients (n = 1402). (B) RFS curves are plotted for breast cancer patients (n = 3951). (C) DMFS curves are plotted for breast cancer patients (n = 1746). (D) PPS curves are plotted for breast cancer patients (n = 414). DMFS = distant metastasis-free survival, IGFBP = insulin-like growth factor binding proteins, OS = overall survival, PPS = post-progression survival, RFS = relapsed free survival.

In terms of IGFBP3, there is no consistent evidence for an association between serum IGFBP3 levels and the prognosis of breast cancer. Several studies indicated that the risk of death was increased in breast cancer patients with higher IGFBP3 levels,[33–37] and this relevance was independent of other prognostic markers.[33] However, serum IGFBP3 concentration was not prognostic role for outcome in breast cancer has also been reported.[38,39] On the contrary, Mu et als study suggested that serum IGFBP3 level was associated with favorable survival in breast cancer patients.[40] Specifically, our study exhibits that the high expression of IGFBP3 mRNA was significantly correlated to worsen RFS, but not to OS, DMFS, and PPS. The possible explanation for these results may be the variation of enrolled subjects' disease state, such as differentiation grade, lymph node status, or TP53 status.

In accordance with the present results, IGFBP4 expression is positively correlated with ER status in mammary tumors.[41,42] In vitro, IGFBP4 inhibited estradiol-triggered growth of MCF-7 cells through Akt/PKB signaling pathway.[43] In breast cancer population, the high expression of IGFBP4 was correlated to favorable prognosis for ER-positive patients, which may serve as an independent prognostic marker in breast cancer.[44] Recently, pregnancy-associated plasma protein-A (PAPP-A) holds a great attention for IGF system. PAPP-A is a metalloproteinase that is

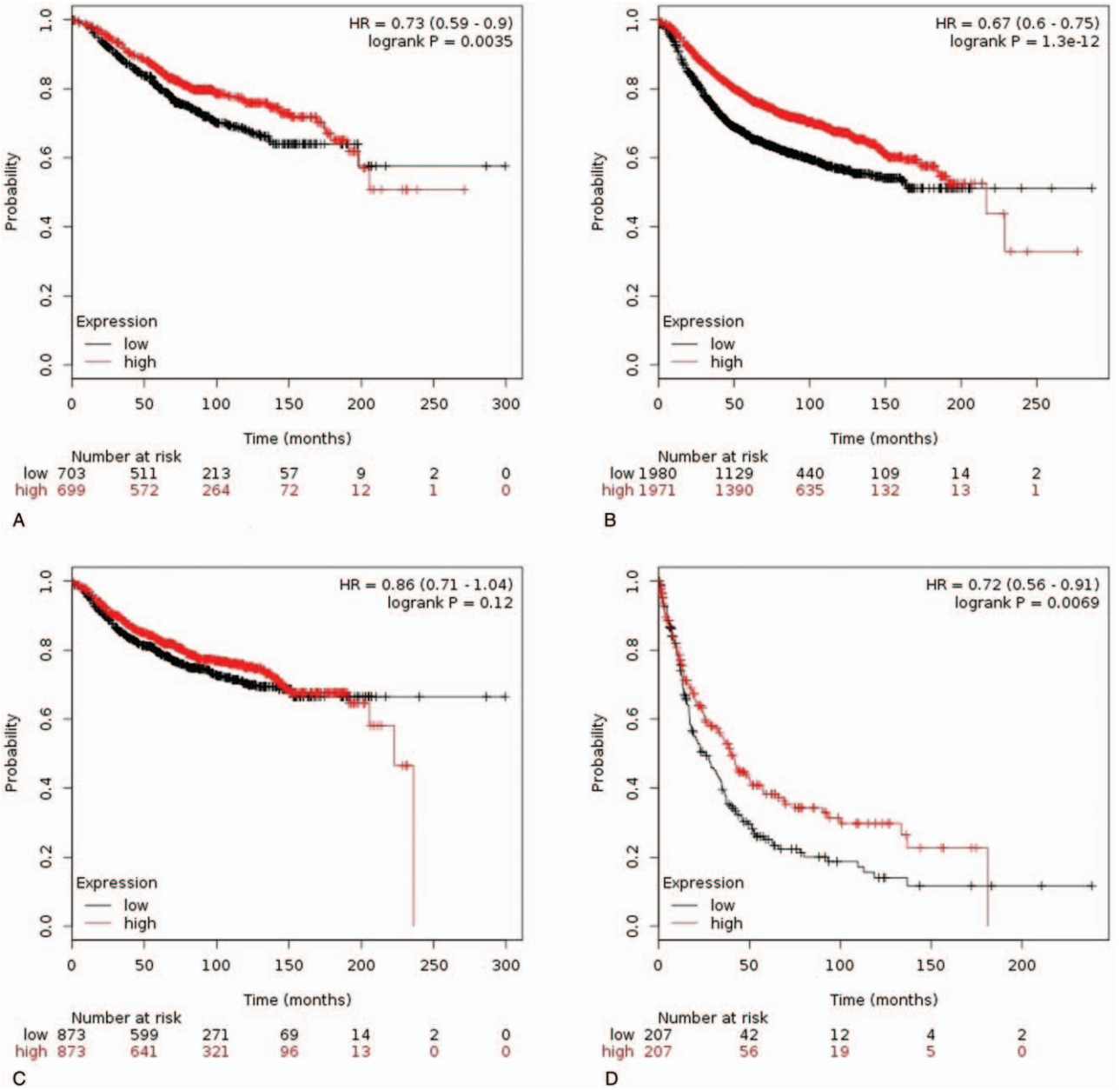

Figure 7. For IGFBP6, its Affymetrix ID is 203851_at. (A) OS curves are plotted for breast cancer patients (n = 1402). (B) RFS curves are plotted for breast cancer patients (n = 3951). (C) DMFS curves are plotted for breast cancer patients (n = 1746). (D) PPS curves are plotted for breast cancer patients (n = 414). DMFS = distant metastasis-free survival, IGFBP = insulin-like growth factor binding proteins, OS = overall survival, PPS = post-progression survival, RFS = relapsed free survival.

able to specifically cleave IGFBP4, resulting in reduced affinity for IGFs. Consequently, serum PAPP-A level may be associated with prognosis of breast cancer patients.

IGFBP5 is the most evolutionarily conserved member in a family of 6 high-affinity IGFBPs.[45,46] it plays a certain role in apoptosis and proliferation in breast cancer cell,[47] possibly mediated by IGF-independent, cytostatic and cytotoxic effects. Mita et al reported that low expression of IGFBP-5 was associated with better-prognosis for ER-positive breast cancer patients.[44] Similarly, overexpression of IGFBP5 was associated with poor survival in breast cancer patients with positive lymph nodes and negative ER, which is consistent with our results.[48] In addition, Hermani's study showed IGFBP5 strongly decreased estradiol-triggered growth of breast cancer cells.[43] Taking together, IGFBP5 may considered to be a positive prognostic marker in breast cancer.

The role of IGFBP6 has been widely investigated in other solid tumors; however, it remains unexplored in breast cancer. It is established that IGFBP6 level is lower in tumor tissue than normal cells, implying an anti-tumor effect on cancer patients.[42] In the present study, we found the high expression of IGFBP6 mRNA was significantly correlated to favorable OS, RFS, and PPS for all breast cancer. These paradoxical results may be explained by heterogeneity in cancer.

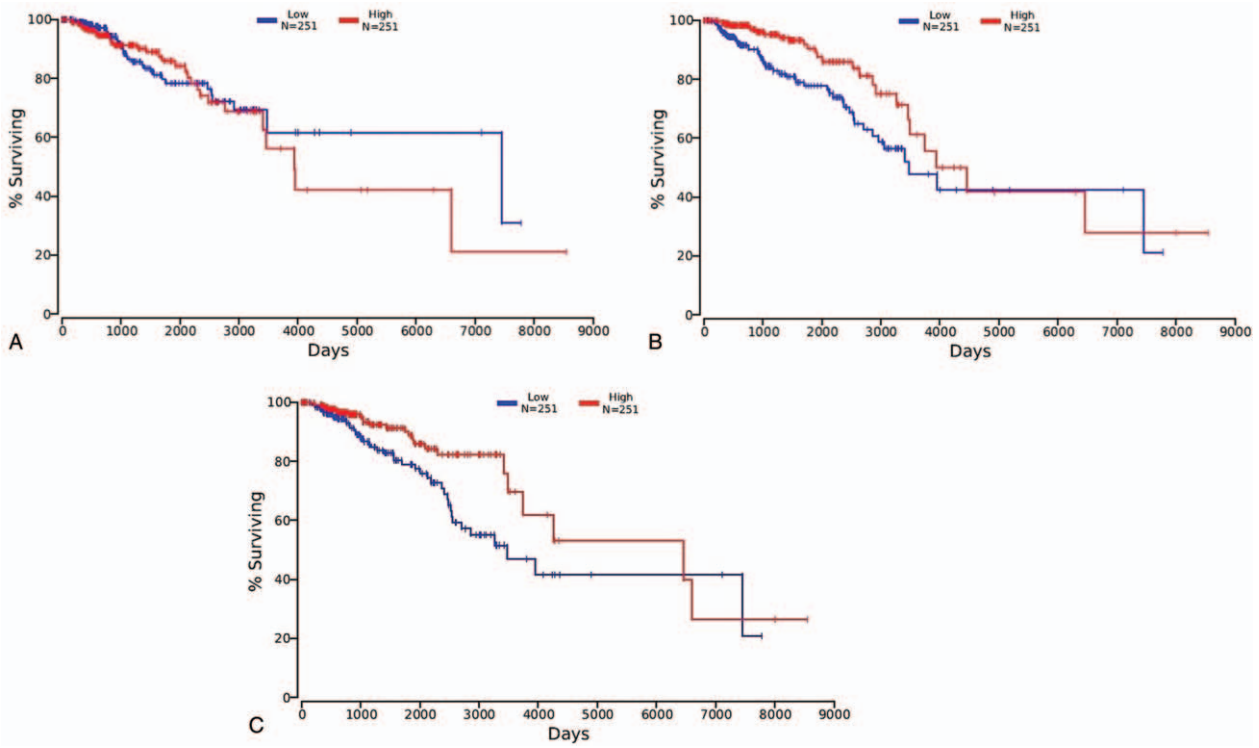

Figure 8. OncoLnc database validate OS in breast cancer patients with high and low expression of IGFBP2 (A), IGFBP4 (B), IGFBP6 (C). IGFBP = insulin-like growth factor binding proteins, OS = overall survival.

It is noteworthy that the high expression of IGFBP4 mRNA was significantly associated with favorable OS for ER positive breast cancer patients in our study. The cross talk between IGFBP and estrogen-signaling pathway plays a certain role in human breast cancer. On one hand, IGF is able to trigger the proliferative signal in breast cancer cells in concert with estrogen.[49] On the other hand, estrogen can also modulate IGFBPs gene expression and the ER status of human breast cancer cells.[50] Furthermore, IGFBPs inhibit estrogen-dependent growth of MCF-7 breast cancer cells.[17]

The IGF signaling pathway has been associated with both initiation and progression of breast cancer. The majority of biological effects of IGF signaling are mediated by IGF receptors. IGFBPs, have greater affinity for binding to the IGFs than the IGF receptors, were originally characterized as passive reservoirs of circulating IGFs. IGFBPs have many actions beyond their endocrine role in IGFs transport. They also function in the pericellular and intracellular compartments to regulate cell growth and survival via interacting with lots of proteins, in addition to IGFs. Intranuclear roles of IGFBPs in transcriptional regulation, induction of apoptosis and DNA damage repair point to their intimate involvement in tumor development and progression.[3] Two parts of IGFBPs may interact with each other to regulate cell proliferation, differentiation, and apoptosis. However, the possible relationship between circulating and tumor IGFBPs is still not very clear. Moreover, the interaction of IGFBPs with breast cancer can be either inhibitory or stimulatory.

Table 1

Correlation of IGFBP mRNA with different ER status of breast cancer patients.

IGFBP family	ER	Cases	HR	95% CI	*P*-value
IGFBP1	Positive	548	0.93	0.65–1.32	.68
	Negative	251	0.71	0.45–1.13	.14
IGFBP2	Positive	548	1.2	0.84–1.71	.31
	Negative	251	0.82	0.52–1.29	.39
IGFBP3	Positive	548	0.99	0.7–1.41	.96
	Negative	251	0.77	0.49–1.21	.25
IGFBP4	Positive	548	0.7	0.49–1	.049
	Negative	251	0.69	0.44–1.1	.12
IGFBP5	Positive	548	1.13	0.8–1.61	.49
	Negative	251	1.12	0.71–1.76	.63
IGFBP6	Positive	548	0.73	0.51–1.04	.082
	Negative	251	1.05	0.67–1.65	.83

CI = confidence interval, ER = estrogen receptor, HR = hazard ratio, IGFBP = insulin-like growth factor binding proteins.

Table 2

Correlation of IGFBP mRNA expression with different pathological grade status of breast patients.

IGFBP family	Pathological grade	Cases	HR	95% CI	*P*-value
IGFBP1	I	161	0.66	0.26–1.7	.39
	II	387	1.15	0.75–1.76	.53
	III	503	0.89	0.64–1.24	.49
IGFBP2	I	161	2.27	0.86–5.96	.088
	II	387	0.9	0.57–1.37	.61
	III	503	0.93	0.67–1.29	.68
IGFBP3	I	161	1.07	0.43–2.65	.89
	II	387	0.85	0.56–1.31	.47
	III	503	0.96	0.69–1.33	.81
IGFBP4	I	161	0.85	0.35–2.04	.71
	II	387	0.48	0.31–0.75	.00088
	III	503	1.05	0.76–1.46	.75
IGFBP5	I	161	0.79	0.32–1.93	.6
	II	387	1.2	0.78–1.85	.4
	III	503	1.29	0.93–1.79	.13
IGFBP6	I	161	1.77	0.71–4.45	.22
	II	387	0.45	0.29–0.7	.00027
	III	503	1.08	0.78–1.5	.64

CI = confidence interval, HR = hazard ratio, IGFBP = insulin-like growth factor binding proteins.

Table 3

Correlation of IGFBP mRNA with different lymph node status of breast cancer patients.

IGFBP family	Lymph node status	Cases	HR	95% CI	*P*-value
IGFBP1	Positive	313	0.73	0.5–1.08	.12
	Negative	594	0.96	0.66–1.39	.81
IGFBP2	Positive	313	0.89	0.6–1.31	.56
	Negative	594	0.88	0.61–1.27	.5
IGFBP3	Positive	313	0.78	0.53–1.16	.22
	Negative	594	1.12	0.77–1.62	.55
IGFBP4	Positive	313	0.81	0.55–1.19	.28
	Negative	594	0.66	0.46–0.96	.03
IGFBP5	Positive	313	1.27	0.85–1.88	.24
	Negative	594	0.84	0.58–1.21	.34
IGFBP6	Positive	313	0.91	0.62–1.34	.62
	Negative	594	0.84	0.58–1.22	.36

CI = confidence interval, HR = hazard ratio, IGFBP = insulin-like growth factor binding proteins.

Table 4

Correlation of IGFBP mRNA with different TP53 status of breast cancer patients.

IGFBP family	TP53	Cases	HR	95% CI	*P*-value
IGFBP1	Mutated	111	1.34	0.6–3.01	.47
	Wild	187	0.65	0.33–1.25	.19
IGFBP2	Mutated	111	1.52	0.69–3.35	.29
	Wild	187	1.43	0.74–2.75	.29
IGFBP3	Mutated	111	1.11	0.52–2.38	.78
	Wild	187	0.82	0.43–1.56	.54
IGFBP4	Mutated	111	1.39	0.63–3.07	.42
	Wild	187	0.54	0.28–1.05	.063
IGFBP5	Mutated	111	1.38	0.62–3.05	.42
	Wild	187	1.27	0.66–2.43	.48
IGFBP6	Mutated	111	0.85	0.39–1.88	.69
	Wild	187	0.69	0.36–1.33	.26

CI = confidence interval, HR = hazard ratio, IGFBP = insulin-like growth factor binding proteins.

In summary, by using the KM plotter database, we demonstrated that the high expression of IGFBP1 mRNA was associated with favorable RFS in all breast cancer patients. The high expression of IGFBP2 mRNA was associated with favorable OS and RFS in all breast cancer patients. The high expression of IGFBP3 mRNA was significantly correlated to worsen RFS in all breast cancer patients. The high expression of IGFBP4 mRNA was associated with favorable OS, RFS, DMFS, and PPS in all breast cancer patients. Moreover, the high expression of IGFBP4 mRNA was also significantly associated with favorable OS in ER-positive, grade II, and lymph node-positive breast cancer patients. The high expression of IGFBP5 mRNA was significantly correlated to worsen DMFS in all breast cancer patients. The high expression of IGFBP6 mRNA was associated with favorable OS, RFS, and PPS in all breast cancer patients. In addition, the high expression of IGFBP6 mRNA was also associated with favorable OS in grade II breast cancer patients. These results may be benefit for better understanding of the heterogeneity and complexity in the molecular biology of breast cancer, paving a way for developing tools to predict the prognosis more accurately and design the customized treatment strategies for breast cancer patients.

Author contributions

Data curation: Jiao Wang.
Methodology: Ji-Xion Xu.
Supervision: Yun-Liang Tang.
Writing – original draft: Xin-Xin Luo.
Writing – review and editing: Jiao Wang, Zhen-Guo Zeng.

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