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LETTER TO THE EDITOR

Prognostic role of expression of angiogenesis markers in hepatocellular carcinoma: A bioinformatics analysis

Yan-Dong Miao, Xiao-Long Tang, Jiang-Tao Wang, Deng-Hai Mi

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Abstract

The expression of angiopoietin (ANGPT) 1, ANGPT2, vascular endothelial growth factor (VEGF) A, VEGFB, VEGFC, VEGFD, and placental growth factor (PGF) is significantly higher in tumor tissues than in normal tissues in both unpaired and paired hepatocellular carcinoma (HCC) samples. ANGPT2, VEGFB, VEGFC, and PGF are primarily involved in regulating the activation of the epithelial-mesenchymal transition pathway; ANGPT1 is primarily involved in regulating the activation of the RAS/mitogen-activated protein kinase and receptor tyrosine kinase (RTK) pathways; VEGFA is engaged in regulating the RTK activation pathway; and VEGFD is mainly involved in regulating the activation of the tuberous sclerosis protein/mammalian target of rapamycin pathway. There is a significant difference in overall survival between HCC patients with high and low expression of ANGPT2, PGF, VEGFA, and VEGFD. Disease free survival (DFS) is significantly shorter in HCC patients with high ANGPT2, PGF, and VEGFA expression than in those with low ANGPT2, PGF, and VEGFA expression.

Key Words: Hepatocellular carcinoma; Angiogenesis; Marker; Bioinformatics analysis; Pathway

Core Tip: We found that the expression of angiogenesis markers was significantly higher in tumor tissues than in normal tissues in both unpaired and paired hepatocellular carcinoma (HCC) samples. These angiogenesis markers are mainly involved in regulating the activation of the EMT pathway, the RAS/mitogen-activated protein kinase and receptor tyrosine kinase pathways, and the tuberous sclerosis protein/mammalian target of rapamycin pathway. In addition, there was a significant difference in overall survival between HCC patients with high and low expression of angiopoietin-2 (ANGPT2), placental growth factor (PGF), vascular endothelial growth factor A (VEGFA), and VEGFD. Disease free survival was significantly shorter in HCC patients with high ANGPT2, PGF, and VEGFA expression than in those with low ANGPT2, PGF, and VEGFA expression.

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TO THE EDITOR

We read with read interest the article by Choi *et al*[1], in which they initially evaluated plasma levels of angiogenesis biomarkers in hepatocellular carcinoma (HCC) patients, and then assessed their roles in forecasting overall survival (OS) and progression-free survival (PFS), indicating that the plasma level of angiopoietin (ANGPT) 2 was related to tumor stage, liver function, and cancer invasiveness, and that ANGPT2 performed better in predicting OS and PFS than alpha-fetoprotein (AFP), ANGPT1, and vascular endothelial growth factor (VEGF).

We appreciate the authors' unique perspective in exploring the prognostic role of plasma levels of ANGPT1, ANGPT2, and VEGF in HCC. However, there are some errors in the original text that may cause confusion for readers. For example, the survival curve in figure 3B in the original article should have represented the survival curve between the high and low ANGPT2 expression subgroups, which the authors incorrectly labeled as ANGPT1. Second, it is well known that the VEGF family includes VEGFA, VEGFB, VEGFC, VEGFD, VEGFE, and placental growth factor (PGF)[2,3], so to which VEGF do the authors refer in the text? Usually, VEGF refers to VEGFA, but the authors should have clarified it in the text.

Moreover, it might make the results more significant if the authors could improve the outcome by demonstrating the differential expression of ANGPT1, ANGPT2, and VEGF in normal tissues and HCC tissues as a whole, for example, the analysis of HCC samples in the Cancer Genome Atlas database using bioinformatics. We found that the expression of ANGPT1, ANGPT2, VEGFA, VEGFB, VEGFC, VEGFD, and PGF was significantly higher in cancer samples than in corresponding normal samples in both unpaired and paired HCC samples (Figures 1A and B). Detailed statistical results are reported in Tables 1 and 2.

We also found that ANGPT2, VEGFB, VEGFC, and PGF are mainly involved in regulating the activation of the EMT pathway; ANGPT1 is prominently involved in regulating the activation of the RAS/mitogen-activated protein kinase and receptor tyrosine kinase (RTK) pathways; VEGFA is engaged in regulating the activation of the RTK pathway; and VEGFD is mainly involved in regulating the activation of the tuberous sclerosis protein/mammalian target of rapamycin pathway (Figure 1C). These results are consistent with those of previously reported studies[4-7]. Our findings could be a supplement to Choi *et al*'s study[1]. In the future, the roles of ANGPT1, ANGPT2, and VEGF in the development of HCC should be further explored.

Choi *et al*[1] found that OS was significantly shorter in the high ANGPT2 and high AFP subgroups than in the low ANGPT2 and AFP subgroups, respectively, though the differences in OS rates were not significant between the high and low ANGPT1 subgroups or between the high and low VEGF subgroups. Our study found that OS was significantly shorter in patients with high ANGPT2, PGF, VEGFA, or VEGFD expression than in those with low expression, respectively (Figures 2A-D; $P < 0.05$). However, there was no significant difference in survival time between patients with high and low expression of ANGPT1, VEGFB, VEGFC, and AFP (Figures 2E-H; $P > 0.05$). Prognostic data for HCC came from Liu *et al*[8].

In addition, we also analyzed the differences in disease free survival (DFS) between patients with high and low angiogenesis marker expression. We found that DFS was significantly shorter in the high ANGPT2, PGF, and VEGFA groups than in the low ANGPT2, PGF, and VEGFA groups, respectively (Figures 3A, B and C; $P < 0.05$). However, there was no significantly difference in DFS between groups with high and low expression of AFP, ANGPT1, VEGFB, VEGFC, and VEGFD (Figures 3D-H; $P > 0.05$). The above results confirm that the study performed by Choi *et al*[1] is of great value and that our discovery could be a supplement to their research.

Table 1 Detailed statistical results of differential expression analysis of angiogenesis markers in hepatocellular carcinoma

Gene	Group	Number	Minimum	Maximum	Median	IQR	Lower quartile	Upper quartile	Mean	SD	SE
ANGPT1	Normal	50	0.029	0.552	0.188	0.132	0.138	0.27	0.206	0.106	0.015
ANGPT1	Tumor	374	0	2.351	0.373	0.464	0.2	0.664	0.485	0.391	0.02
ANGPT2	Normal	50	0.043	1.351	0.278	0.33	0.195	0.525	0.394	0.289	0.041
ANGPT2	Tumor	374	0.116	3.339	0.848	0.769	0.513	1.282	0.963	0.581	0.03
VEGFA	Normal	50	1.616	3.901	2.687	0.473	2.439	2.911	2.717	0.445	0.063
VEGFA	Tumor	374	1.258	6.138	3.268	1.103	2.769	3.871	3.291	0.809	0.042
VEGFB	Normal	50	2.816	4.919	3.568	0.523	3.325	3.848	3.636	0.444	0.063
VEGFB	Tumor	374	0.978	8.003	4.532	2.234	3.223	5.458	4.292	1.521	0.079
VEGFC	Normal	50	0.408	1.901	1.019	0.453	0.787	1.239	1.057	0.355	0.05
VEGFC	Tumor	374	0.253	4.988	1.376	0.816	0.978	1.795	1.436	0.62	0.032
VEGFD	Normal	50	0.054	1.74	0.236	0.151	0.164	0.316	0.307	0.28	0.04
VEGFD	Tumor	374	0.014	6.756	0.422	0.622	0.241	0.863	0.838	1.14	0.059
PGF	Normal	50	0.182	0.992	0.471	0.204	0.37	0.575	0.501	0.188	0.027
PGF	Tumor	374	0.061	5.991	1.007	0.855	0.613	1.467	1.104	0.675	0.035
AFP	Normal	50	0.266	1.969	1.016	0.507	0.714	1.221	0.992	0.416	0.059
AFP	Tumor	374	0	13.118	1.644	2.855	0.844	3.699	2.965	3.15	0.163

ANGPT: Angiopoietin; VEGFA: Vascular endothelial growth factor; PGF: Placental growth factor; AFP: Alpha-fetoprotein; IQR: Interquartile range; SD: Standard deviation, SE: Standard error.

Table 2 Detailed statistical results of differential expression analysis of angiogenesis markers in paired samples of hepatocellular carcinoma

Gene	Group	Number	Minimum	Maximum	Median	IQR	Lower quartile	Upper quartile	Mean	SD	SE
ANGPT1	Normal	50	0.029	0.552	0.188	0.132	0.138	0.27	0.206	0.106	0.015
ANGPT1	Tumor	50	0.014	1.557	0.463	0.56	0.228	0.788	0.507	0.363	0.051
ANGPT2	Normal	50	0.043	1.351	0.278	0.33	0.195	0.525	0.394	0.289	0.041
ANGPT2	Tumor	50	0.193	2.324	1.056	0.77	0.747	1.517	1.111	0.517	0.073
VEGFA	Normal	50	1.616	3.901	2.687	0.473	2.439	2.911	2.717	0.445	0.063
VEGFA	Tumor	50	1.471	5.974	3.102	1.087	2.801	3.888	3.287	0.902	0.128
VEGFB	Normal	50	2.816	4.919	3.568	0.523	3.325	3.848	3.636	0.444	0.063
VEGFB	Tumor	50	1.164	7.789	4.833	1.993	3.323	5.317	4.328	1.575	0.223
VEGFC	Normal	50	0.408	1.901	1.019	0.453	0.787	1.239	1.057	0.355	0.05
VEGFC	Tumor	50	0.261	3.233	1.398	0.819	1.013	1.831	1.459	0.633	0.09
VEGFD	Normal	50	0.054	1.74	0.236	0.151	0.164	0.316	0.307	0.28	0.04
VEGFD	Tumor	50	0.014	5.746	0.367	0.562	0.231	0.793	0.832	1.207	0.171
PGF	Normal	50	0.182	0.992	0.471	0.204	0.37	0.575	0.501	0.188	0.027
PGF	Tumor	50	0.144	5.991	1.072	0.833	0.67	1.503	1.16	0.859	0.121
AFP	Normal	50	0.266	1.969	1.016	0.507	0.714	1.221	0.992	0.416	0.059
AFP	Tumor	50	0	5.824	1.033	1.31	0.725	2.036	1.62	1.383	0.196

ANGPT: Angiopoietin; VEGFA: Vascular endothelial growth factor; PGF: Placental growth factor; AFP: Alpha-fetoprotein; IQR: Interquartile range; SD: Standard deviation, SE: Standard error.

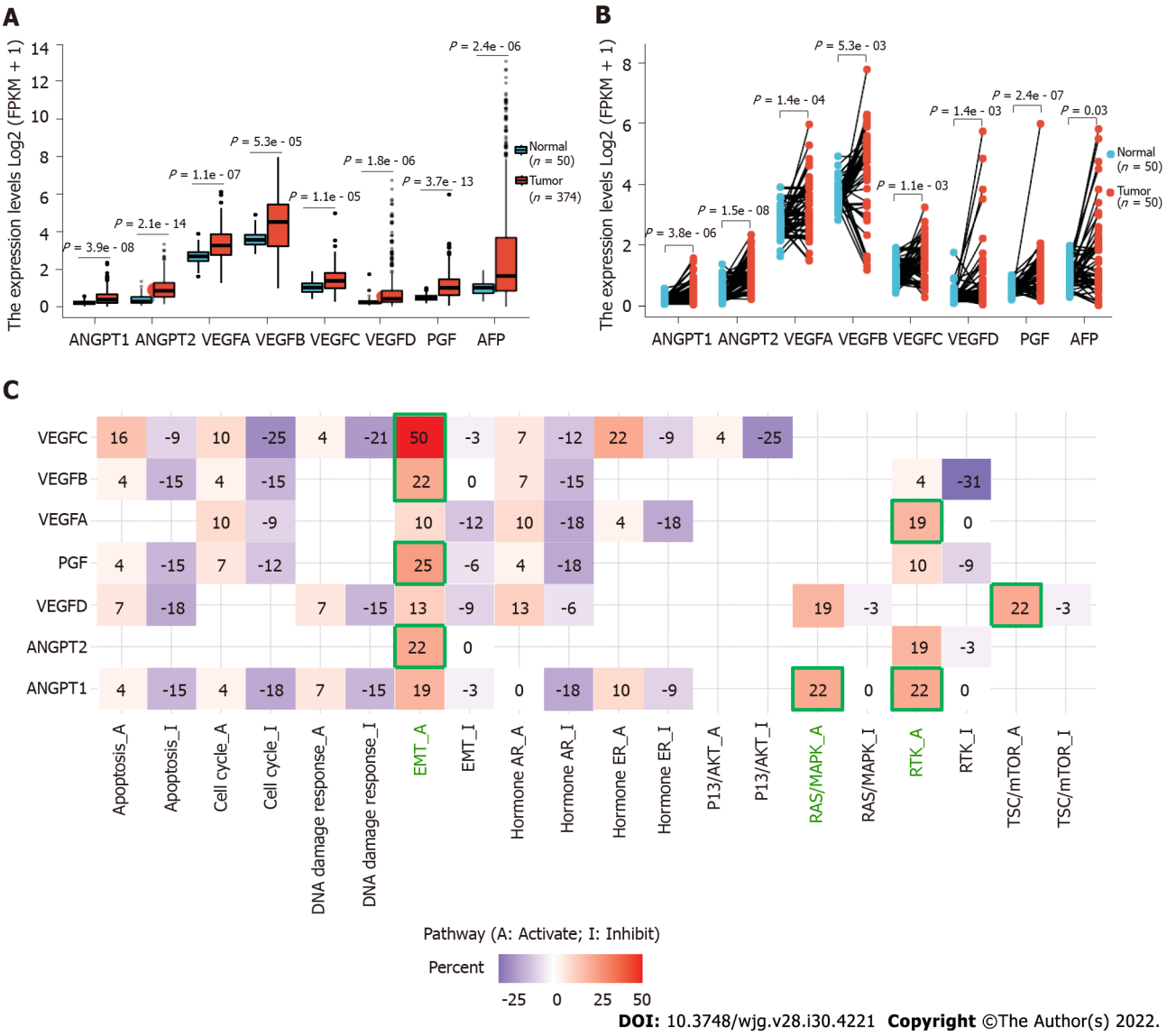

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Figure 1 Roles of angiopoietins 1 and 2, vascular endothelial growth factors A-D, and placental growth factor in development of hepatocellular carcinoma. Data source: UCSC XENA (https://xenabrowser.net/datapages/) mRNA-Seq data of TPM format for GTEx and TCGA processed uniformly *via* the Toil process[11]. Liver hepatocellular carcinoma tissue data from TCGA and corresponding normal tissue data from GTEx were used. A: Differential expression of angiopoietin (ANGPT) 1, ANGPT2, vascular endothelial growth factor (VEGF) A, VEGFB, VEGFC, VEGFD, and placental growth factor (PGF) in hepatocellular carcinoma (HCC) and normal tissue samples; B: Differential expression of ANGPT1, ANGPT2, VEGFA, VEGFB, VEGFC, VEGFD, and PGF in paired HCC and normal samples. The expression in cancer tissues is represented in orange, and that in normal tissues is displayed in blue; C: Pathway analysis for ANGPT1, ANGPT2, VEGFA, VEGFB, VEGFC, VEGFD, and PGF in HCC. ANGPT: Angiopoietin; PGF: Placental growth factor; VEGF: Vascular endothelial growth factor; AFP: Alpha-fetoprotein; EMT: Epithelial-mesenchymal transition; AR: Androgen receptor; ER: Estrogen receptor; P13K/AKT: Phosphatidylinositol 3 kinase/AKT; RAS/MAPK: RAS/mitogen-activated protein kinase; RTK: Receptor tyrosine kinase; TSC/mTOR: TSC/mammalian target of rapamycin.

Statistical analysis

We utilized R (version 4.0.3) to perform statistical analyses and display the results. The differential expression analysis of angiogenesis markers between HCC tissues and corresponding normal tissues was performed using the Wilcoxon rank-sum test, and the results are presented by using R-package "ggplot2"[9]. Survival analysis was completed through log-rank test and COX regression. Pathway analysis was performed based on the online database GSCALite (http://bioinfo.life.hust.edu.cn/web/GSCALite/)[10].

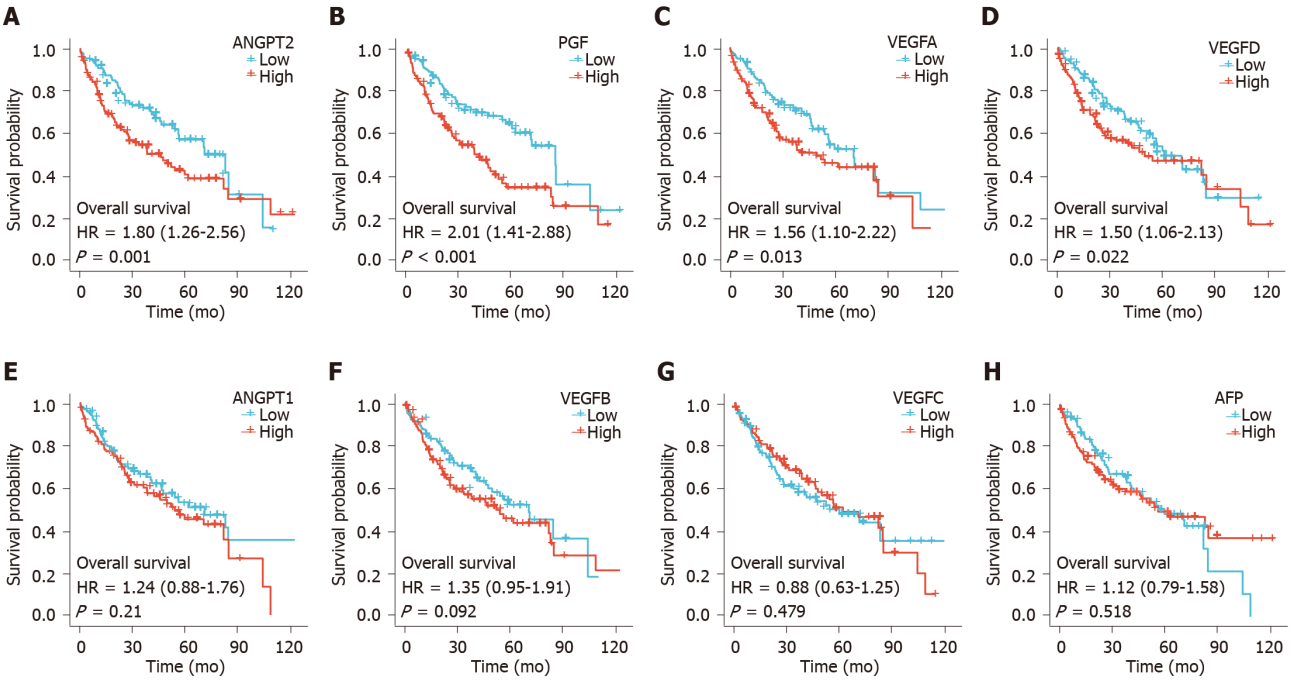

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Figure 2 Overall survival by angiogenesis marker expression in hepatocellular carcinoma. A: Angiopoietin (ANGPT) 2; B: Placental growth factor; C: Vascular endothelial growth factor (VEGF) A; D: VEGFD; E: ANGPT1; F: VEGFB; G: VEGFC; H: Alpha-fetoprotein. The red and blue lines indicate the survival curves of the high and low angiogenesis marker expression groups, respectively. ANGPT: Angiopoietin; PGF: Placental growth factor; VEGF: Vascular endothelial growth factor; AFP: Alpha-fetoprotein; HR: Hazard ratio.

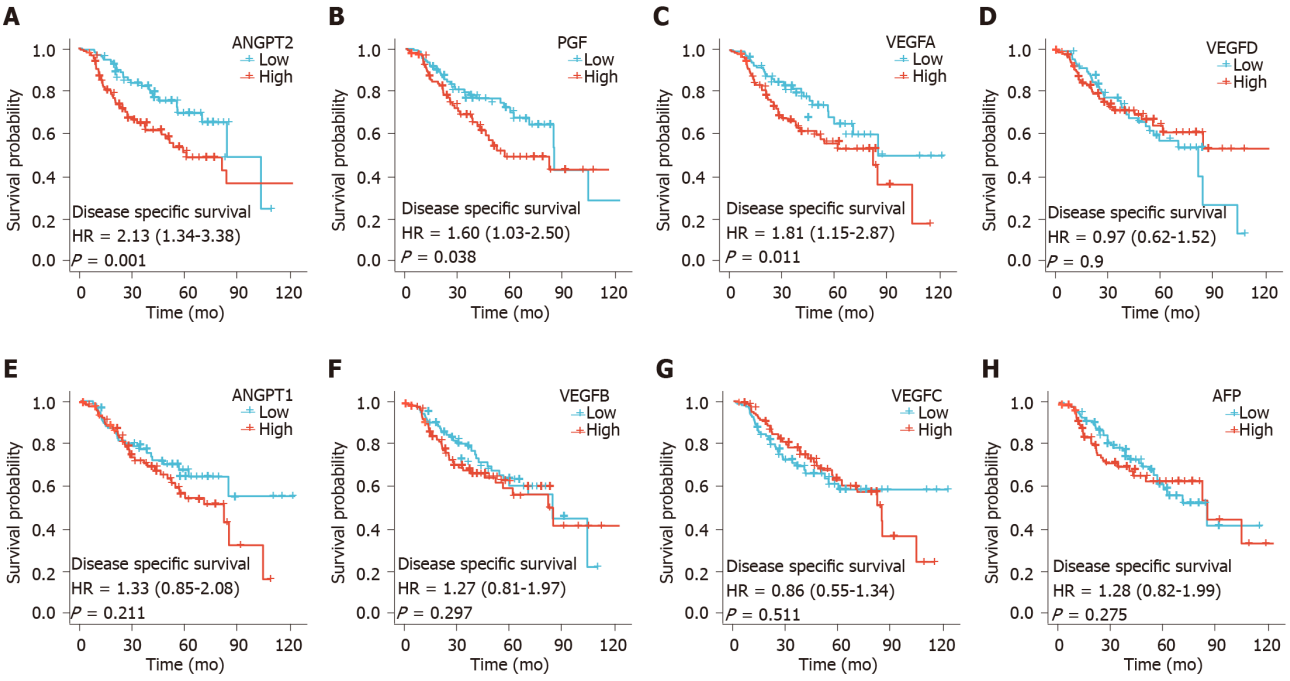

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Figure 3 Disease free survival by angiogenesis marker expression in hepatocellular carcinoma. A: Angiopoietin (ANGPT) 2; B: Placental growth factor; C: Vascular endothelial growth factor (VEGF) A; D: Alpha-fetoprotein; E: ANGPT1; F: VEGFB; G: VEGFC; H: VEGFD. The red and blue lines indicate the survival curves of the high and low angiogenesis marker expression groups, respectively. ANGPT: Angiopoietin; PGF: Placental growth factor; VEGF: Vascular endothelial growth factor; AFP: Alpha-fetoprotein; HR: Hazard ratio.

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FOOTNOTES

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