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# Correlation Between von Hippel-Lindau Gene Expression and Tumor SUVmax and Survival Prognosis in Hepatocellular Carcinoma

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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**Background:** We investigated the relationship between the 18F-FDG PET/CT metabolic parameter SUVmax in primary hepatocellular carcinoma (HCC) and expression of von Hippel-Lindau (VHL), as well as its effect on HCC survival prognosis.

**Material/Methods:** We retrospectively analyzed data for 62 HCC patients who received 18F-FDG PET/CT before surgery at the First Affiliated Hospital of Bengbu Medical College from June 2013 to June 2018 (42 males, 20 females; median age 62 years). No treatment was performed prior to the examination. The relationship between preoperative 18F-FDG PET/CT metabolic parameters, clinical pathology, and disease prognosis was analyzed.

**Results:** SUVmax was significantly different in varying HCC pathological grades, and with tumor length, lymph node metastasis, portal vein tumor thrombus, and distant metastasis ($p<0.05$). SUVmax was significantly higher in the shorter patient survival group ($p<0.05$). 18F-FDG uptake was correlated with expression of glucose transporter 1 and VHL in tumor tissues (correlation coefficients 0.476 and 0.565, respectively; both $p<0.05$). Negative expression of VHL suggested poor tumor differentiation and poor prognosis, but no correlation was observed with patient age, sex, tumor length, lymph node metastasis, or distant metastasis. The survival time of patients with low VHL expression was significantly shorter than that of patients with positive VHL expression ($p=0.02$).

**Conclusions:** VHL expression in primary HCC has a significant correlation with SUVmax, and negative VHL expression predicts a worse clinical prognosis.

**MeSH Keywords:** Carcinoma, Hepatocellular • Fluorodeoxyglucose F18 • Glycolysis • von Hippel-Lindau Disease

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## Background

Glucose metabolism is abnormally active during the development of tumor cells and such cells are more dependent on the glycolysis pathway for energy supply. This biological property of glucose uptake capacity in a tumor is called the Warburg effect, which can be quantified by measuring the SUVmax of tumor tissue by using 18F-FDG PET/CT imaging.

SUVmax has great value in tumor diagnosis, staging, and prediction of prognosis. The change in SUV is due to abnormal expression of metabolic enzymes and oncogenes within the tumor, which is not fully understood. In addition, the results obtained at the cellular and clinical levels are not completely consistent and should be further explored in tissue samples. Many studies have found that the FDG uptake of primary tumors is correlated with the expression of glucose transporter 1 (GLUT1). In addition, previous studies have confirmed that FDG is closely related to the expression of various oncogenes or tumor-suppressor genes, such as KRAS proto-oncogene (*KRAS*), lactate dehydrogenase A (*LDHA*), vascular endothelial growth factor (*VEGF*), fructose-bisphosphatase 1 (*FBP1*), TP53-induced glycolysis regulatory phosphatase (*TIGAR*), and tumor protein P53 (*TP53*). These findings helped to reveal the mechanism of the Warburg effect and explore which tumor-related genes are expressed by assessing SUVmax in different tumor types, thus providing a better theoretical basis for molecular image monitoring of targeted tumor markers for personalized treatment.

The von Hippel-Lindau (*VHL*) gene is a typical tumor-suppressor gene, and its anticancer effect is mainly manifested at the level of gene transcription; it is involved in the degradation of intracellular proteins by inhibiting the Elogin ABC complex. When *VHL* is genetically mutated, its expression is inhibited, which can cause hypoxia-inducible factor 1 subunit alpha (*HIF1A*) to aggregate and activate in cells, thereby enhancing the expression of downstream target genes, promoting tumor glycolysis, tumor angiogenesis, and tumor development, and inhibiting tumor cell apoptosis. It is generally believed that the loss of VHL is an important mechanism in the occurrence and development of renal cell carcinoma. In recent years, the role of VHL in the occurrence and development of liver disease has gradually received increased attention. Volker et al. found that liver tissue severely degenerates after loss of the *VHL* gene in the liver. Liang et al. postulated that the mutation and deletion of *VHL* promotes the occurrence and development of liver cancer.

Previous studies have confirmed that the *VHL* gene can affect GLUT1 expression and inhibit glucose metabolism by regulating the HIF1A protein. However, there is no published report at the clinical level on the relationship between VHL expression and glucose metabolism. Thus, the present study retrospectively analyzed 62 cases of HCC and evaluated the correlation between GLUT1, hexokinase 2 (HK2), VHL, and SUVmax in primary liver tumors. We also analyzed the correlation between VHL expression and clinicopathological features of HCC and their relationship with patient prognosis. We expect that by analyzing the relationship between SUVmax and the expression of important regulators of glucose metabolism, we can provide additional indicators for the clinical diagnosis of HCC and selection of personalized treatment schedules.

## Material and Methods

### Subjects

We retrospectively analyzed data for 62 patients with pathologically confirmed HCC who received 18F-FDG PET/CT examination at the First Affiliated Hospital of Bengbu Medical College from January 2013 to December 2018 (42 males, 20 females; median age 62 years, range 31–82 years). Inclusion criteria were: pathologically confirmed HCC and <2 weeks interval between PET/CT examination and surgical pathological confirmation. Specimen collection and clinical data collection followed the principles of the Declaration of Helsinki.

### 18F-FDG PET/CT Examination

A Biograph 64 PET/CT instrument from Siemens Company was used. Patients fasted for 4–6 h before the examination, and their mean blood glucose was <6.3 mmol/L. A total of 5.55 MBq/kg 18F-FDG was injected intravenously (provided by Shanghai Kexin Pharmaceutical Co. Ltd., radiochemical purity >95%). After resting for 60 min and urinating, patients underwent the PET/CT examination. Patients were placed in a supine position and scanned from the base of the skull to the mid-femur, including CT scans and PET acquisition. CT scanning parameters were 120 kV and 140 mA. PET scanning parameters were: three-dimensional mode, 2 min/bed, scanning bed number according to patient height adjustment (adult routine: 6), and matrix 128×128. After the acquisition was completed, the PET image was attenuation-corrected by CT, and the PET tomography image was reconstructed by OSEM (2 iterations, 28 subsets). The PET/CT fusion image was obtained after processing using the Siemens workstation.

### Image and data analysis

Images were interpreted by 2 experienced nuclear medicine physicians. All data were imported into the IntelliSpace workstation (IntelliSpace Portal v7.0, Philips Healthcare, the Netherlands) for processing. The lesion boundary was automatically delineated by TUMOR TRACE software, and the SUVmax of the lesion was automatically calculated. According





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**Table 1.** The association between $^{18}$F-FDG uptake and clinical characteristics of HCC patients (n=62).

| Clinical variables | Patient no. | SUVmax | |
|---|---|---|---|
| | | Median | P-value |
| Age | | | |
| >60 | 32 | 4.6 | 0.15 |
| <60 | 30 | 3.1 | |
| Sex | | | |
| Male | 42 | 4.2 | 0.946 |
| Female | 20 | 3.5 | |
| Tumor differentiation | | | |
| I–II | 45 | 3.1 | 0.000 |
| III–IV | 17 | 10.5 | |
| Tumor size (cm) | | | |
| <3 cm | 26 | 2.4 | 0.000 |
| >3 cm | 36 | 5.8 | |
| Portal vein tumor thrombus | | | |
| Without | 51 | 3.3 | 0.000 |
| With | 11 | 7.9 | |
| N staging | | | |
| Without lymphatic metastasis | 49 | 3.1 | 0.000 |
| With lymphatic metastasis | 13 | 8.1 | |
| M staging | | | |
| Without distant metastasis | 49 | 3.3 | 0.007 |
| With distant metastasis | 13 | 5.4 | |
| Survival condition | | | |
| Survival | 41 | 3.3 | 0.000 |
| Death | 21 | 9.4 | |

to cross-sectional, sagittal, and coronal images, CCRCC lesions were included in the VOI using the 40% threshold method of SUVmax.

### Immunohistochemical staining (IHC)

Histochemical analysis was performed using paraffin-embedded HCC tissue with a section thickness of 4 μm and staining. Sections (4-mm slices) were obtained using a microtome and processed for staining using a Nexes auto-immunostainer (Ventana Medical Systems, USA). Primary antibodies against VHL, GLUT1, HK2, and pyruvate kinase M2 (PKM2) were obtained from Abcam (1: 400). The staining intensity fraction was interpreted and scored 0–3. A staining area score of 0 indicated 0% of cells stained; a score of 1 showed 1–9% of cells stained, 2 indicated 10–49% of cells stained, and 3 showed 50–100% of cells stained. The IHC score was determined as 0–9, which is the product of the staining intensity and the staining area. An IHC score ≥4 was considered to indicate positive expression. All IHC results were evaluated by 2 experienced observers who were blind to the condition of the patients. Where discrepancies occurred, the 2 readers reached a consensus.

### Statistical analysis

Data were analyzed using SPSS version 20.0 software. All data were analyzed using nonparametric statistical methods, and $p<0.05$ was considered statistically significant. Correlation between SUVmax and tumor biological indicators was determined by the Spearman rank method. Analysis of the relationship between VHL and patient survival time was performed by Kaplan-Meier survival curve.





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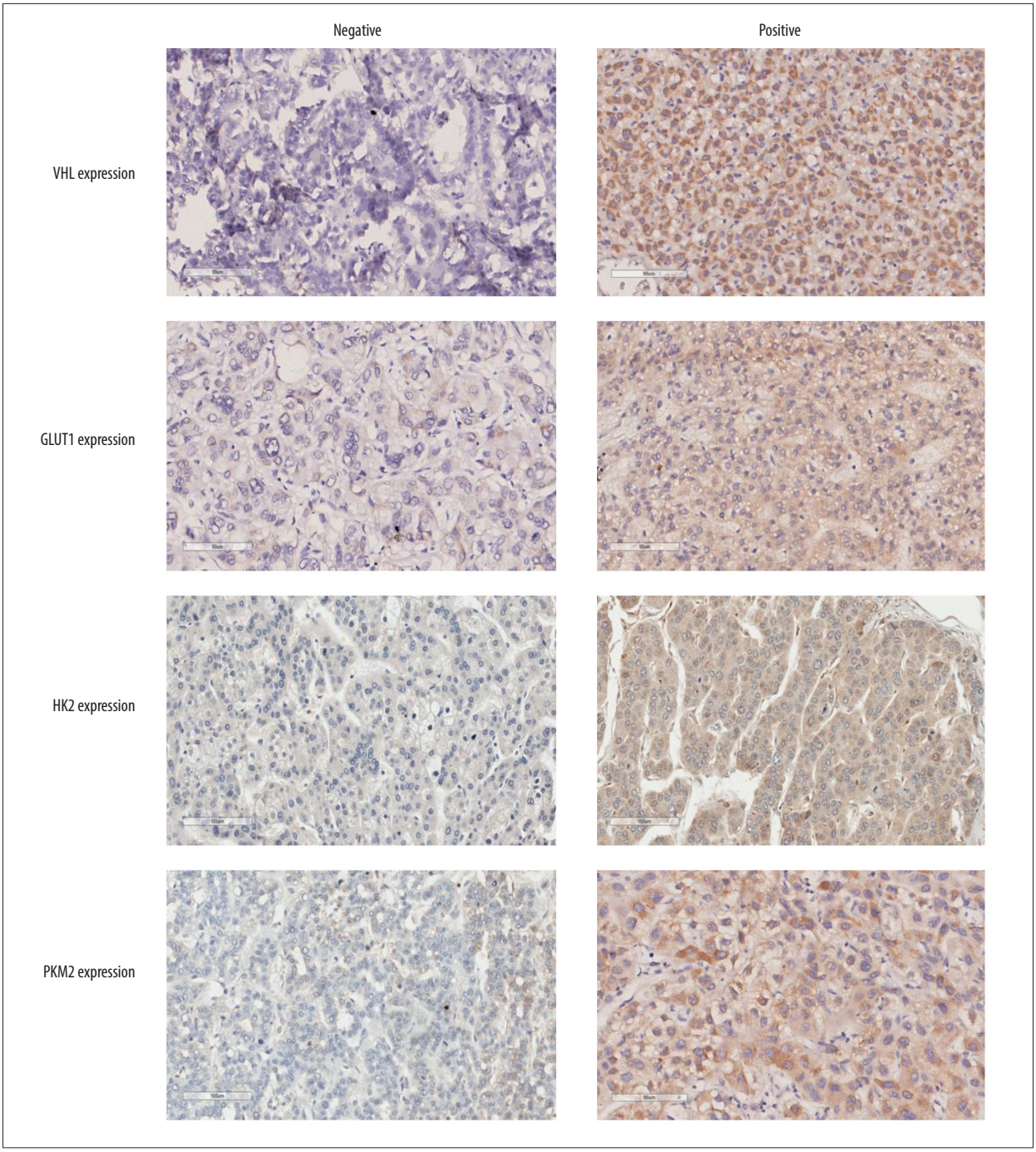


**Figure 1.** Immunohistochemistry results in HCC specimens (magnification ×200).

## Results

### Association of 18F-FDG uptake with clinical indicators and survival in HCC patients

Table 1 shows the characteristics of the HCC patients. Among the 62 patients, 42 were male and 20 were female; 32 patients were >60 years and 30 patients were <60 years (median 62 years). Patients were divided into groups by age, sex, tumor grade, tumor size, portal vein tumor thrombus, lymph node metastasis, distant metastasis, and survival (Table 1). SUVmax was significantly associated with tumor pathological grade, tumor length, lymph node metastasis, portal vein tumor thrombus, distant metastasis, and patient survival ($p<0.05$). There were no significant differences in the 18F-FDG intake index by age or sex.





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**Table 2.** Correlation analysis between 18F-FDG uptake and tumor glucose metabolizing enzyme expression.

| Factor IHC score | SUVmax | |
|---|---|---|
| | Correlation coefficient | p-Value |
| GLUT1 | 0.476 | <0.05 |
| HK2 | 0.028 | 0.83 |
| PKM2 | 0.125 | 0.18 |
| VHL | 0.565 | <0.05 |

**Table 4.** Correlation between VHL and GLUT1 expression and SUVmax based on immunohistochemical (IHC) score.

| | No. patients | VHL (IHC score) | |
|---|---|---|---|
| | | Negative | Positive |
| GLUT1 | Negative | 6.31±4.77 | 3.78±2.71 |
| | 49 | 26 | 23 |
| | Positive | 9.95±6.39 | 3.63±1.75 |
| | 13 | 10 | 3 |

**Table 3.** Relationship between 18F-FDG uptake and biological indicators of tumor glucose metabolism.

| Factor | Patient no. | SUVmax | |
|---|---|---|---|
| | | Median | p-Value |
| GLUT1 expression | | | |
| Positive | 13 | 8.49±6.23 | 0.02 |
| Negative | 49 | 5.12±4.11 | |
| HK2 expression | | | |
| Positive | 28 | 6.74±5.78 | 0.97 |
| Negative | 34 | 4.72±2.89 | |
| PKM2 expression | | | |
| Positive | 25 | 6.10±4.97 | 0.51 |
| Negative | 37 | 4.84±3.16 | |
| VHL expression | | | |
| Positive | 26 | 3.76±2.59 | P<0.01 |
| Negative | 36 | 7.32±5.43 | |

### Correlation between $^{18}$F-FDG uptake and key enzymes of glucose metabolism and VHL expression in HCC tissues

To investigate whether 18F-FDG uptake in HCC patients was associated with tumor glucose metabolism, we compared the correlation of SUVmax with GLUT1, HK2, PKM2, and VHL protein expression (Figure 1, Table 2). Expression of GLUT1 and VHL was significantly correlated with SUVmax ($p<0.05$).

The SUVmax in patients negative for VHL expression in HCC was significantly higher than that in those with positive VHL expression ($p<0.01$); the average SUVmax of patients with negative VHL expression was 7.32±5.43, whereas the average SUVmax of patients with positive VHL expression was 3.76±2.59. Cases with negative GLUT1 expression had an average SUVmax of 5.12±4.11, whereas patients positive for GLUT1 had an average SUVmax of 8.49±6.23 (Table 3). Further analysis revealed that the SUVmax value of VHL-negative and GLUT1-positive cases was the highest, with an average of 9.95±6.39. In contrast, VHL-positive and GLUT1-negative cases demonstrated the lowest SUVmax values, averaging 3.78±2.71 (Table 4).

### The expression of VHL is related to the survival of HCC patients

On comparing the relationship between VHL expression and clinical indicators of patients with HCC (Table 5), there was a significant difference in the expression of VHL between patients with varying tumor differentiation ($p=0.03$), but no difference in the expression of VHL by patient age, sex, tumor length, lymph node metastasis, or distant metastasis. On plotting survival curves, we found a significant difference between VHL expression patterns in patient survival and prognosis (Figure 2). The survival time of patients negative for VHL





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**Table 5.** Relationship between expression of VHL and clinicopathological features of HCC (n=62).

| Clinical Variables | VHL (IHC staining) | | P-value |
|---|---|---|---|
| | Negative | Positive | |
| Age | | | |
| >60 | 21 | 11 | 0.21 |
| <60 | 15 | 15 | |
| Sex | | | |
| Male | 25 | 17 | 0.06 |
| Female | 11 | 9 | |
| Tumor differentiation | | | |
| I–II | 22 | 21 | 0.03 |
| III–IV | 14 | 3 | |
| Tumor size (cm) | | | |
| <3 cm | 12 | 14 | 0.11 |
| >3 cm | 24 | 12 | |
| N staging | | | |
| Without lymphatic metastasis | 28 | 21 | 0.78 |
| With lymphatic metastasis | 8 | 5 | |
| M staging | | | |
| Without distant metastasis | 27 | 22 | 0.36 |
| With distant metastasis | 9 | 4 | |

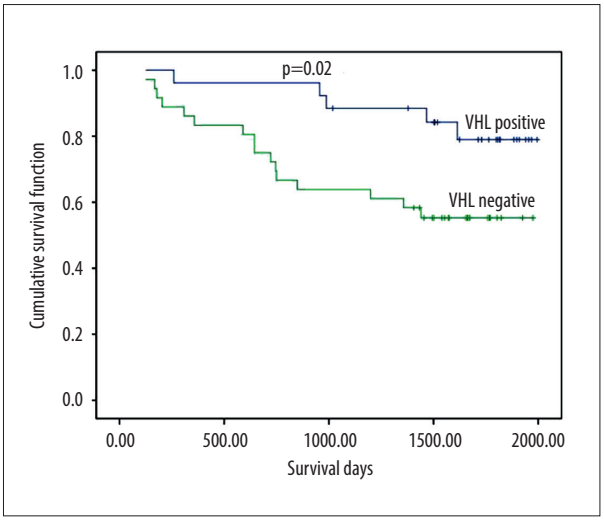


**Figure 2.** Kaplan-Meier recurrence-free survival curve according to VHL expression in HCC patients. The survival time of patients with negative VHL expression was significantly decreased compared with positive VHL expression.

expression was significantly less than that of patients positive for VHL expression (P=0.02).

## Discussion

The *VHL* gene is a tumor-suppressor gene that has an important role in inhibiting tumorigenesis. VHL is involved in biological processes associated with the development of tumors, such as transcriptional regulation, cell cycle regulation, intercellular signaling, extracellular fibronectin formation, and angiogenesis. Loss of VHL can stimulate normal cell dysplasia, leading to tumorigenesis, and is associated with reduced apoptosis and increased tumor cell survival. Jung et al. reported that tumor necrosis factor can increase the accumulation of HIF1A, which may be related to VHL.

VHL can affect the expression of GLUT1 and inhibit glucose metabolism by regulating HIF1A. However, previous research has focused on the regulation of glucose metabolism by VHL at the cellular level, and relationship between VHL expression and glucose metabolism at the clinical level remains mostly unknown. We were interested in clinically-related HCC samples, including the expression level of VHL in patients with HCC, and the relationship between tumor glycolysis and survival prognosis.





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At present, SUVmax is the most important metabolic parameter from 18F-FDG PET/CT in patient tumors that can reflect the glucose metabolism of tumors at the clinical level. High SUVmax predicts increased glucose metabolism in tumor cells and an enhanced Warburg effect. Here, we compared the expression of 3 enzymes associated with tumor metabolism and that of the tumor-suppressor VHL with tumor SUVmax. The SUVmax of FDG uptake in HCC patients was significantly correlated with the expression levels of GLUT1 and VHL, but was not correlated with additional glucose metabolism-related genes (HK2 and PKM2).

Our study showed that the expression of VHL increased with higher IHC staining scores, and the FDG uptake of tumors decreased. The expression of VHL was negatively correlated with the SUVmax of the tumor. When VHL expression is increased, glycolytic hydrolysis may be downregulated. To the best of our knowledge, this study is the first to reveal the correlation between HCC VHL expression and the Warburg effect at the clinical level. In addition, our study showed that patients with positive GLUT1 expression and negative VHL expression had increased SUVmax, whereas patients with positive GLUT1 expression and positive VHL expression had decreased SUVmax. These results indicate that tumor cells have increased glucose metabolism in HCC patients with negative VHL expression and increased glucose transporter 1-mediated expression. These findings further prove that in HCC, VHL participates in the glycolysis process, and the inhibition of VHL can result in the negative regulation of glucose metabolism and increase of tumor SUVmax.

Few previous studies have assessed the relationship between VHL expression and clinical pathological features of HCC; therefore, we further analyzed the correlation between VHL and tumor differentiation, staging, and prognosis. We found that in well-differentiated HCC, VHL expression was increased, whereas in poorly-differentiated HCC, VHL expression was decreased. In addition, we confirmed that low expression of VHL in HCC is associated with poor prognosis.

## Conclusions

GLUT1 and VHL expression in HCC are correlated with the SUVmax value as determined by PET. We are the first to report a significant correlation between the expression of VHL and SUVmax in primary HCC. Furthermore, we revealed another tumor gene marker that affects the SUVmax in HCC. We suggest that when VHL is used to predict the prognosis of cancer and targeted therapy, it should be closely combined with the PET SUVmax to form a comprehensive prediction to more accurately predict patient prognosis and screen for patients who would benefit from VHL-targeted therapy.

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