American Journal of Health Research
2024, Vol. 12, No. 2, pp. 25-36
https://doi.org/10.11648/j.ajhr.20241202.12

Research Article

Research Progress of Apoptosis Inhibitory Protein Survivin in Gastric Cancer

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Abstract

Survivin is an important member of the apoptosis inhibitory protein family, which plays an important role in suppressing apoptosis, promoting proliferation and vascular formation. The occurrence and development of tumors are related to apoptosis and imbalance of proliferation. Gastric cancer is the most common malignant tumor in the digestive system. Due to the inadequate symptoms of early symptoms, most of them have entered the middle and late stages during diagnosis. It is easy to relapse and metastasize. The mortality rate is high, which seriously endangers human health. Research have found that Survivin expresses high in gastric cancer tissue, participating in the proliferation of tumor cells, inhibiting apoptosis and the formation of blood vessels, and is of great significance to the diagnosis, judgment transfer and prognosis evaluation of gastric cancer, especially the value of combined with a number of indicators is greater. Therefore, finding an early diagnosis and judging the ideal tumor logo combination of the early diagnosis and judgment of the prognosis is important. This article reviews the biological characteristics of Survivin and its research progress in gastric cancer, so as to provide theoretical basis for the diagnosis of gastric cancer and new ideas for the successful prevention and treatment of tumors.

Keywords

Apoptosis Inhibiting Protein, Survivin, Gastric Cancer, Prognosis

1. Introduction

Gastric cancer (GC) is the most common cancer in the world, and it is also one of the common clinical digestive tract malignant tumors [1]. The latest statistics show that [2] in 2020, there are 1,93 million new cases of malignant tumors in 2020, 10 million deaths in death, of which 1.09 million new occurrences of gastric cancer and 769,000 deaths, respectively, accounting for all malignant tumors and death cases 5.64 % and 7.69%, ranked 6th among the global malignant tumors, and 3rd in mortality. In 2020, the number of new hair cancer and death cases in China is 478 508 and 373 789 cases, respectively, accounting for 43.94%and 48.62%of the world's [3]. China is a high incidence of gastric cancer. The incidence and mortality are ranked 2nd and 3rd in the cancer spectrum [4]. The 5-year survival rate is only about 30%, and the prognosis is poor, which seriously threatens the health of the people of our people. So far, the occurrence and development mechanism of the GC is still not very clear. Survivin is an important members of the Apoptosis inhibiting protein (AIP) family have functions such as regulating apoptosis and cell proliferation. Normal adult tissue is not expressed, and embryo tissue is expressed. Re-

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Received: 9 January 2024; **Accepted:** 28 February 2024; **Published:** 25 March 2024

searchers have found that Survivin is highly expressed in gastric cancer tumor tissues, participating in regulating the proliferation, apoptosis, and vascular production of tumor cells, which are related to the development and prognosis of tumor [5]. Comprehensive analysis of the relationship between Survivin and other tumor markers and gastric cancer helps the research on diagnosis and treatment and pathogenesis, which is of great significance to the prevention and treatment of tumors. This article reviews the research progress of Survivin and its research on gastric cancer.

2. Overview of Survivin

2.1. Composition and Structure of Survivin

Survivin is an anti-apoptosis gene first screened and cloned from the human gene pool in 1997 by Ambrosini et al [6] at Yale University. Survivin has the most potent inhibitor of apoptosis been found so far. It belongs to the IAPs family and is also known as survivin because of it prolongs cell survival. This gene is located on chromosome 17q25, and the expression product consisted of 142 amino acid residues with a relative molecular weight of 16.5KD [7], 4 exons and 3 introns. Survivin is the factor with the smallest molecular weight and the strongest inhibitory effect on apoptosis in the AIPs family [8]. Its protein structure includes an N-terminal baculovirus IAP repeat (BIR) with inhibitory Caspase activity and a long C-terminus α Spiral, BIR plays a crucial role in apoptosis. Survivin has a unique homodimeric structure compared to other IAP protein molecules and is present in the cytoplasm. Survivin mRNA is cleaved and found to have 9 isomers, such as Survivin-2α、Survivin-3βand Survivin-2β、Survivin-δEx3 contains 165 and 137 amino acids, respectively. Survivin-δEx3 retains most of its anti-apoptotic ability and functions similarly to Survivin, with the ability to inhibit apoptosis. Survivin-2αhas anti-apoptotic function of Survivin, Survivin-2βhas cytotoxic effects and can significantly reduce anti-apoptotic properties [9], Survivin-δEx3 and Survivin-2 have the opposite effect and have received widespread attention from foreign scholars due to its unique functions and effects. There is relatively little research on the relationship with tumors and Survivin-3. There are three isomers in human embryonic tissue: Survivin-40, Survivin-128, and Survivin-140, The latter also exists in thymus and testicular tissues, while differentiated and mature tissues do not express Survivin-40 [9]. Survivin isomers have different biological activities and play different roles in tumors.

2.2. Biological Characteristics of Survivin

2.2.1. Inhibition of Apoptosis

Apoptosis is an autonomous and orderly death regulated by cells that maintains a stable internal environment in the body. It can occur in the physiological state of individual development or in diseases. The pathways of cell apoptosis mainly include internal pathways mediated by mitochondria and external pathways mediated by death receptors. Under normal circumstances, the expression of apoptotic proteins is relatively stable. Once cells receive the stimulation of apoptotic signals, it promotes and inhibits the imbalance of expression of apoptotic gene proteins, leading to cell apoptosis [10].

Caspase is a cysteine protease with specific aspartic acid, which plays a crucial role in the process of cell apoptosis. Under normal circumstances, Caspases exist in the cytoplasm in the form of enzymes and are activated by specific binding with reactants. Caspases have the characteristics of self- activation and mutual activation. Once the apoptosis process is triggered, it exhibits a cascade amplification effect. The cascade reaction triggered by Caspases is the central link in the process of cell apoptosis and plays an important role in inducing cell apoptosis. Its cascade activation and protein dissolution occur. It is the convergence point of multiple apoptotic pathways and the ultimate pathway for executing apoptosis [11]. Most members of the Caspase family are promoters or effectors of apoptosis, playing important roles in the process of cell apoptosis [12]. The Caspase family has 14 members, which are classified according to their biological functions into inflammatory, apoptotic, and functionally unknown Caspases [13]. According to the different positions and functions upstream and downstream of the cascade reaction, the Caspase family can be divided into three categories: apoptosis initiating factors (Caspase-2, 8, 9, 10), apoptosis executing factors (Caspase-3, 6, 7), and inflammatory mediating factors (Caspase-1, 4, 5, 13, 14), which together form a cascade reaction and have an amplification effect. Caspases-3 is a key executor in regulating cell apoptosis. After activation, it can further activate Caspases-9 proenzyme, form positive feedback regulation, and accelerate the process of cell apoptosis [14]. Caspase-9 can activate downstream Caspase, initiate the cell apoptosis program, and is a key link in completing cell apoptosis [15]. It is also an important indicator reflecting the degree of cell apoptosis. Caspases-3 is one of the most important executors of apoptosis and an irreversible marker of apoptosis [16]. Its expression level can reflect the apoptosis of cells.

The process of cell apoptosis is jointly regulated by apoptosis inhibitory factors (Bcl-2, Bcl-x, Survivin, etc.) and apoptosis promoting factors (Bax, caspase, etc.) [17]. Survivin exerts a strong inhibitory effect on the cell apoptosis pathway mainly through direct protein binding and inhibition of upstream and downstream Caspase molecules. High expression of Survivin can inhibit Caspase induced cell apoptosis, bind specifically to Caspase, inhibit Caspase-3,7 activity, and block the occurrence of apoptosis. The Bcl-2 family plays an important regulatory role in the mitochondrial apoptosis pathway, and can induce cell apoptosis by activating downstream genes [18]. The endogenous pathway of cell apoptosis is regulated by the Bcl-2 family, which includes anti apoptotic genes such as Bcl-2 and pro apoptotic genes such as Bax. Bcl-2 and Bax together form a

dimeric structure, regulating the process of cell apoptosis [19]. The Bcl-2/Bax ratio directly determines cell survival. Therefore, cell apoptosis is regulated by the combined action of Caspase and many factors.

2.2.2. Participating in Cell Cycle Regulation

Survivin has a dual effect of inhibiting cell apoptosis and regulating cell cycle, and is an important factor connecting the cell cycle and apoptosis interface. Unlike other proteins in the IAPs family, Survivin expression is cell cycle dependent and highly expressed specifically in the G2/M phase [20]. Survivin is closely related to cell division, proliferation, and cell cycle regulation by inhibiting cell apoptosis. Survivin is synthesized and degraded in a cell cycle dependent manner in normal tissues, increasing in G1 phase and significantly in G2/M phase. Kobayashi et al. found that Survivin is expressed in all proliferating tissues and is widely expressed in embryonic tissues, participating in cell growth and differentiation [9]. It plays an important role in promoting the cell cycle, accelerating cell division and proliferation processes. Survivin also participates in chromosome segregation regulation and plays an important role in chromosome and cytoplasmic division [21]. The Survivin gene promotes tumor cell proliferation and differentiation by accelerating the transition of tumor cells from G1 to S phase and allowing tumor cells to evade recognition of apoptosis during G2/M phase [9].

2.2.3. Promoting Blood Vessel Formation

The formation of blood vessels is regulated by both promoting and inhibiting angiogenesis factors. In the process of angiogenesis, various pro-angiogenic factors, such as VEGF, Ang-1 and basic fibroblast growth factor (bFGF), promote the proliferation of vascular endothelial cells by up-regulating Survivin expression and play an important role in the middle of angiogenesis [10]. O 'Connor et al. used VEGF and bFGF to induce quiescent skin cells and found that Survivin expression level increased 16-fold, suggesting that Survivin may be involved in regulating tumor blood vessel formation [22]. Survivin and VEGF are closely related to angiogenesis, and VEGF can increase the Survivin expression level in vascular endothelial cells, which depend on the up-regulation of Survivin expression in angiogenesis [23]. Control of the expression or function of Survivin can affect pathologic angiogenesis. Therefore, Survivin plays an important role in angiogenesis mediated by VEGF and promotes tumor angiogenesis and tumor growth [24].

3. Expression and Prognosis of Survivin in Gastric Cancer

3.1. Expression of Survivin in Gastric Cancer

Early researchers have found that Survivin is not expressed in embryos and developing fetuses, but is widely expressed in various human malignant tumors. It is closely related to tumor cell proliferation, growth, apoptosis, and tumor formation, and can serve as an independent and sensitive marker for malignant tumors [25]. In 1998, Lu et al. were the first to use anti Survivin antibodies to perform immunohistochemical staining on 174 gastric cancer samples of different stages [26]. They found that the positive expression rate of Survivin in gastric cancer tissue was 34.5%, while adjacent normal tissues did not express it. Yu et al. reported that the positive expression rates of Survivin in 5 gastric cancer cell lines and gastric cancer tissues were 100% and 68%, respectively [27]. The positive expression rates of Survivin in adjacent gastric cancer tissues and normal gastric tissue of first-degree relatives of gastric cancer (without tumor disease) were 22% and 27%, respectively. Normal gastric mucosa did not express Survivin. Zhu et al [28] found that the positive expression rate of Smwivin in gastric cancer tissue (48.2%, 27/56) was significantly higher than that in chronic gastritis (5%, 1/20). Song et al [29] reported that the positive expression rate of Survivin in 157 stage III gastric adenocarcinoma tissues was 40.1%, mainly located in the nucleus. Da et al [30] found that the positive expression rate of Survivin in gastric cancer tissue was 70%. The poorer the tissue differentiation and the later the clinical stage, the higher the positive expression rate.

Yao Xuequan et al [31] found that the positive expression rates of Survivn in gastric cancer primary lesion, lymph node metastatic carcinoma, and normal glandular basal germinal layer cells were 49.2%, 64.0%, and 17.5%, respectively. The expression rate of cancer cells in metastatic lymph nodes was higher than that in primary lesion cancer cells. The positive expression rate of Survivin in early gastric cancer tissue was 68.5% (37/54). The difference between mild and moderate atypical hyperplasia was statistically significant ($P<0.05$) ,however, there was no statistically significant difference ($P>0.05$) compared to severe atypical hyperplasia. Survivin was not expressed in normal gastric mucosa (0/30). The positive expression rate of incomplete colorectal metaplasia was 5.00% (1/20) [32]. Suggest that Survivin may play an important role in the development of early gastric cancer. The higher the expression of Survivin,the lower the differentiation degree of early gastric cancer. Luo Xue [33] reported that the positive expression rate of Survivin in gastric cancer tissue (71.4%, 20/28) was significantly higher than that in chronic gastritis (10%, 1/10). Sun Yanxia et al [34] found that the positive expression rates of Survivin in gastric cancer, adjacent tissues, and normal gastric mucosa were 38.7%, 14.8%, and 0%, respectively, with statistically significant differences among groups ($P<0.05$). This was consistent with the report by Kania J et al [35] that normal gastric mucosa had low expression of Survivin, while gastric cancer and adjacent tissues had significantly increased expression, and the expression of cancer tissue was higher than that of adjacent tissues. Xu Tianxiang et al [36] reported that the positive expression rate of Survivin in gastric cancer tissue was (67.7%, 46/68) was significantly

higher than that of normal gastric mucosal tissue (0%, 0/30, P<0.05). Jiao Jianxin et al [37] found that the positive expression rate of Survivin in gastric cancer tissue was 68.3% (41/60), mainly located in the cytoplasm. No positive expression was found in the nucleus and adjacent tissues, which was roughly consistent with the results reported by Shintani et al [38]. Recently, Jia et al [39, 40] found that the expression level of Survivin in normal gastric mucosal tissue was extremely low, while the expression in gastric cancer and adjacent tissues was significantly increased, and the positive expression rate in gastric cancer tissue was significantly higher than that in adjacent tissues. The research results of Fang Yu et al [41] showed that the positivity rate of Survivin in gastric cancer tissue (80.23%, 69/86) was significantly higher than that in adjacent normal tissue (43.02%, 37/86), and the difference was statistically significant (P<0.001). Li Hong et al [42] analyzed the positive expression of Survivin using a microscopic imaging system and found that Survivin was not expressed in normal gastric mucosa. There was a statistically significant difference (P<0.05) between mild to moderate dysplasia and gastric cancer, while there was no statistically significant difference (P>0.05) between severe dysplasia and gastric cancer.

The above research results show that the positive expression rate of Survivin in gastric cancer tissue ranges from 34.5% to 80.23%, with some expression in adjacent tissues (22% to 43.02%) and chronic gastritis (10%), but both are significantly lower than the positive expression rate in cancer tissue. Normal gastric mucosal tissue is rarely expressed or not expressed, and quantitative analysis of immunohistochemical image absorbance parameters Survivin can be used as a marker for early diagnosis of gastric cancer. The abnormal expression of Survivin in gastric cancer tissue is closely related to gastric cancer and may be involved in the occurrence and development of gastric cancer. As a type of TM, Survivin provides objective basis for screening and diagnosis of gastric cancer.

3.2. Survivin Protein Expression and Prognosis of Gastric Cancer

Research has found that Survivin is closely related to the malignancy of tumors, and its expression level is significantly increased in infiltrating and metastatic cancer tissues [43]. Yao Xuequan et al [31] studied 120 cases of advanced gastric adenocarcinoma and found that the expression rate of Survivn was higher in poorly differentiated adenocarcinoma, those with lymph node metastasis, and those with invasion of the serosa than in well differentiated adenocarcinoma, those without lymph node metastasis, and those without invasion of the serosa. Survivn expression was significantly correlated with tumor histological type, differentiation degree, infiltration depth, and lymph node metastasis, and was also closely related to tumor angiogenesis. Its expression score was negatively correlated with apoptosis index, but not significantly correlated with proliferation index. Lee et al [44] found that Survivin was not only significantly associated with the size, depth of infiltration, lymph node metastasis, clinical staging, and prognosis of gastric cancer masses, but also with microvessel density (MVD), suggesting that Survivin may play an important role in tumor angiogenesis. Zhu et al [28] found that the positive expression rate of Survivin in gastric cancer tissue was not related to age, tumor size, depth of infiltration, clinical stage, etc., but was related to histological type. The positive expression rate of Survivin in intestinal gastric cancer was significantly higher than that in diffuse gastric cancer (P<0.05). Song et al [29] reported that the expression of Survivin in stage III gastric cancer tissue was closely related to tumor size and survival rate (P<0.05), and there was a statistically significant difference in 5-year survival rate between Survivin positive and Survivin negative individuals (P<0.05). Survivin was an independent prognostic factor for stage III gastric cancer and can serve as an important indicator for monitoring prognosis.

Li Dongxia et al [45] reported that the expression of Survivin in gastric cancer tissue was positively correlated with tissue classification, lymph node metastasis, and TNM staging (P<0.05), but not with age, gender, and degree of infiltration (P>0.05). The positive expression rate of Survivin in gastric cancer tissue increases with decreasing tissue differentiation and lymph node metastasis [30] , which indicated a significant correlation between the expression intensity of Survivin and the malignancy and development trend of tumors , It can serve as a reference indicator for poor prognosis. The expression intensity of Survivin in gastric cancer tissue was related to gastric mucosal infiltration, TNM staging, lymph node metastasis, and other factors [46]. Luo Xue et al. found that the positive expression of Survivin in gastric cancer tissue was not significantly correlated with age, depth of tumor infiltration, lymph node metastasis, clinical grade, etc., but was related to tissue classification (P<0.05). The positive expression rate of high differentiation intestinal type gastric cancer was significantly higher than that of low differentiation diffuse type gastric cancer. The high expression of Survivin may be mainly related to cellular carcinogenesis, and the resulting inhibition of apoptosis played an important role in the occurrence and development of gastric cancer. Sun Yanxia et al.. reported that the expression of Survivin in gastric cancer tissue was not related to gender, age, lymph node metastasis, and clinical stage, but was related to pathological grading and survival prognosis. The expression of Survivin in the low differentiation group was significantly higher than that in the high differentiation group (P<0.05), and the 3-year survival rate in the high expression group was significantly lower than that in the low expression group (P<0.05). This indicated that the expression of Survivin in gastric cancer tissue was related to the degree of tumor differentiation and prognosis, suggesting that Survivin played an important role in the occurrence and development of gastric cancer and can serve as an indicator for predicting prognosis. Hu Zhongdong et al [47] found that an increase in Survivin expression during

tumor infiltration and metastasis may indicate an increase in tumor malignancy, which was closely related to tumor infiltration and metastasis. Xu Tianxiang et al [36] found that the expression of Survivin in gastric cancer tissue was significantly higher than that in normal tissue, and the positive expression rate in the lymph node metastasis group was significantly higher than that in the non-lymph node metastasis group (P<0.05), indicating a close correlation between Survivin expression and lymph node metastasis. The high expression of Survivin in gastric cancer tissue was related to the malignancy and prognosis of the tumor, and had a stronger metastatic ability. There was no difference in the expression of Survivin in gastric cancer tissues of different tissue types (poorly differentiated, moderately differentiated, and signet ring cell carcinoma), but the poorer the tissue differentiation, the higher the positive expression rate [48]. The disease-free survival and median survival of patients with positive Survivin expression were significantly lower than those with negative expression. Survivin expression was associated with lymph node and distant metastasis, TNM staging, but not gender, age, tumor size and location, infiltration depth, and histological type.

The above research results indicate that Survivin positive expression is closely related to the biological characteristics and prognosis of gastric cancer, but varies in terms of tumor size, infiltration depth, lymph node metastasis, clinical staging, and histological type. The positive expression rate of Survivin in gastric cancer tissue varies greatly, which may be related to differentiation degree, TNM staging, etc.

3.3. Expression of Survivin Protein and Other Tumor Markers in Gastric Cancer and Prognosis

Research has been conducted on the joint detection of Survivin and other TM in gastric cancer tissue expression and prognosis monitoring. Lee et al [44] found that the positive expression rates of Survivin and VEGF in gastric cancer tissue were 50.0% and 69.8%, respectively, and Survivin was not associated with VEGF expression. The MVD of Survivin and VEGF positive tumors was significantly higher than that of Survivin negative tumors (P<0.001). Survivin may play an important role in the carcinogenesis process of gastric cancer by stimulating tumor angiogenesis. Sun Yuanshui et al [49] reported that the positive expression rates of VEGF-C and Survivin in gastric cancer tissues (66.0% and 57.2%) were significantly higher than those in adjacent and normal gastric tissues, and the two were positively correlated (P<0.05). VEGF-C expression was not related to tumor location and diameter, degree of differentiation, venous invasion, and distant metastasis, but was closely related to lymph node metastasis and invasion, serosal involvement, and TNM staging; Survivin expression was closely related to serosal involvement, lymphatic vessel invasion, lymph node and distant metastasis, and TNM staging. The postoperative survival rate of the VEGF-C and Survivin positive expression group was significantly lower than that of the negative group, indicating more malignant biological behavior and poorer prognosis, which can be used as a reference indicator for poor prognosis of gastric cancer.

Wang Songwen et al [46] found that the positive expression rate of Survivin in gastric cancer tissue (74.4%, 67/90) was significantly higher than that in normal gastric mucosa (0%, 0/90). The positive expression rate of Metastin (KISS-1 gene coding product) in normal gastric tissue (71.1%, 64/90) was significantly higher than that in gastric cancer tissue (35.6%, 32/90), and the intergroup difference was statistically significant (P<0.01). The high expression of Survivin in gastric cancer tissue was related to serous infiltration, TNM staging, and lymph node metastasis (P<0.05), while the expression level of Metastin was related to TNM staging and lymph node metastasis (P<0.05), and was not related to gender, age, primary site, Borrmann type, tumor size, and serous infiltration (P>0.05). Survivin and Metastin can be used as indicators to determine the biological characteristics and prognosis of gastric cancer, and have important reference value for clinical diagnosis and treatment. Song et al [29] suggested that Survivin expression was independent of p53 and Bax expression. The positive expression of Survivin was closely related to tumor size, and the difference in 5-year survival rate between Survivin negative patients was statistically significant (P<0.05). Survivin and p53 were independent prognostic factors for stage III gastric cancer, and Survivin was an important indicator for monitoring gastric cancer prognosis. Hu Zhongdong et al [47] found that the positive expression rates of Survivin and MMP-7 in gastric adenocarcinoma tissues were 75.4%, respectively (46/61) and 68.8% (42/61). Spearman rank correlation analysis showed that MMP-7 was positively correlated with Survivin expression (P<0.01), and was correlated with tumor infiltration depth, lymph node metastasis, TNM staging, differentiation degree, and 5-year survival time (P<0.05), but not with tumor size and location (P>0.05). The upregulation of the expression of both may be related to the occurrence and development of gastric cancer. Li Hong et al [42] found that the expression of Survivin and CD34 was significantly correlated with the differentiation degree, lymph node metastasis, and infiltration depth of gastric cancer (P<0.05). Survivin expression was positively correlated with MVD, and combined detection was helpful in determining the pathological grading, malignancy, and prognosis of gastric cancer.

Zhou Wei et al [50] reported that the positive expression rate of Survivin in gastric cancer tissue was 70% (35/50), and the expression rate was higher with poorer tissue differentiation and later clinical staging, while it was not expressed in normal gastric mucosal tissue. The positive expression rate of Bcl-2 in gastric cancer tissue (76%, 38/50) was significantly higher than that in normal gastric mucosa. The poorer the tissue differentiation, the higher the expression rate of Bcl-2, which was closely related to the expression of Survivin. Li Dongxia et al [45] found that the positive expression rate of

Survivin and Bcl-2 in gastric cancer tissue was 59.6%, 31/52 vs 69.2%, 36/52) were significantly higher than normal gastric mucosa (0%, 0/30 vs 16.67%), 5/30), there was a statistically significant difference between the groups (P<0.05). Fang Yu et al [41] reported that the expression of Survivin and Bcl-2 in gastric cancer tissue was positively correlated (P<0.05), both of which were highly expressed. The co positive and negative expression rates of the two were 58.14% and 13.95%, respectively. At the same time, the sensitivity, specificity, and Youden index of positive expression were significantly higher than those of single positive expression (P<0.05). Spearman analysis showed that there was no statistically significant difference in overall survival and progression free survival between individuals with simultaneous and single positive expression of Survivin and Bcl-2 in gastric cancer tissue (P>0.05). It is suggested that Survivin and Bcl-2 are closely related to the occurrence and development of gastric cancer, and high expression may exert a synergistic effect in the occurrence and development of gastric cancer, jointly inhibiting cell apoptosis. The molecular mechanism underlying the upregulation of Survivin and Bcl-2 expression was elucidated. Joint detection of Survivin and Bcl-2 expression levels provided a theoretical basis for early diagnosis, prevention, and gene therapy of gastric cancer.

Yan Yuping [51, 52] found that the positivity rate of survivin in gastric cancer tissue was significantly higher than that in adjacent tissues, while the positivity rate of caspase-3 was significantly lower than that in adjacent tissues. The positivity rate of Survivin was related to clinical staging, lymph node metastasis, and infiltration; The positive rate of caspase-3 was related to the degree of tumor differentiation, lymph node metastasis, and clinical staging. Ying Rongbiao et al [53] reported that the expression of Survivin in gastric cancer tissue was significantly negatively correlated with the expression of caspase-3, and both were significantly correlated with the depth of tumor infiltration, lymph node metastasis, and TNM staging (P<0.05). Liu Xiaomin et al [54] found that the expression of PIG II and Caspase-3 in gastric cancer tissue was positively correlated (r=0.) The positive expression rates of 859 (P<0.01) were significantly lower than those of normal gastric mucosa, intestinal metaplasia, and dysplastic tissue (P<0.01), and their expression levels were closely related to the differentiation degree, clinical stage, lymph node metastasis, and distant metastasis of gastric cancer (P<0.05). Park Haichao et al [55] reported that the positivity rate of Survivin in gastric cancer tissue (63.89%) was higher than that in normal tissue (0.0%), and the positivity rate of advanced group (III-IV) was higher than that in early group (I-II) (78.05%), while the positivity rate of Caspase-3 in gastric cancer tissue (38.89%) was lower than that in normal tissue (85.00%). The positivity rate of advanced group (21.95%) was lower than that in early group (61.29%), and the differences were statistically significant (P<0.05). It is suggested that Survivin and caspase-3 are synergistically involved in the occurrence and development of gastric cancer, and their expression was significantly correlated with biological behaviors such as tumor infiltration and metastasis. Combined detection may help to determine the malignancy of gastric cancer and evaluate its invasion and metastasis ability. It can serve as a reference indicator for the prognosis evaluation of gastric cancer and provide a reference basis for the prognosis judgment and reasonable treatment of gastric cancer. Immunohistochemical staining analysis was performed on 300 paraffin tissue samples of gastric cancer [56], and the results showed a negative correlation between Survivin and PTEN expression in gastric cancer tissue. The positive expression rates in the gastric cancer and control groups were (72.0%, 5.0%) and (34.0%, 92.5%), respectively, with statistical significance (P<0.05). The differences were related to histological type, differentiation degree, infiltration depth, distant metastasis, pathological stage, and survival rate (P<0.05 and P=0.000), The increased expression of Survivin and the decreased expression of PTEN are closely related to the occurrence, metastasis, and prognosis of gastric cancer, suggesting that the two may work together and affect each other in the invasion and metastasis of gastric cancer, and may be candidate targets for the treatment of gastric cancer.

4. Survivin mRNA Expression and Prognosis in Gastric Cancer

4.1. Survivin mRNA Expression and Prognosis in Gastric Cancer

Research has confirmed that overexpression of Survivin can accelerate the transition of the cell cycle to the S phase, inhibit G1 phase arrest, promote cell proliferation, and the occurrence and development of gastric cancer are closely related to the Survivin gene [57]. Miyachi et al. [58] used real-time fluorescence quantitative reverse transcription polymerase chain reaction (Real time RT-PCR) to detect the expression level of Survivin mRNA in gastric cancer and non-cancer tissues. They found that the expression level of Survivin mRNA in gastric cancer tissue and lymph node metastasis group was significantly higher than that in non- cancer tissue and non-metastasis group (P<0.01), with a positive expression rate of 98.1% (105/107), which was significantly correlated with lymph node metastasis, but not with histological type and infiltration depth. The increase in Survivin mRNA expression occurs in the early stage of gastric cancer, which can be used for early diagnosis of gastric cancer and to determine lymph node metastasis. Zhu et al [28] believe that the expression of Survivin mRNA is significantly correlated with the histological type of gastric cancer, and its overexpression begins in the early stages of gastric cancer. This suggests that high expression of Survivin mRNA is of great significance for the early diagnosis, lymph node metastasis, clinical staging, treatment, and prognosis of gastric cancer.

Meng et al [59] used RT-PCR technology to analyze Sur-

vivin mRNA expression level of 77 gastric cancer tissues and 7 gastric cancer cell lines (MKN-1, MKN-7, MKN-45, MKN-45P, MKN-74, AGS, and KATO-III). It was found that all cases and cell lines significantly expressed wild-type Survivin mRNA, Survivin-2βmRNA negative expression was negatively correlated with tumor staging, histological type, and depth of infiltration, Survivin-ΔEx3 mRNA was significantly positively correlated with cell apoptosis. Prompt Survivin-2βand Survivin-ΔEx3 mRNA was involved in the occurrence and development of gastric cancer, and the expression level of Survivin mRNA can serve as a biological marker for poor prognosis. Bertazza et al [60] found that the expression rates of Survivin, CK19, CEA, and VEGF genes in gastric cancer tissue (98.6%, 97.1%, 42.9%, and 38.6%) were higher than those in the control group, indicating the potential value of Survivin and CK19 genes in the diagnosis of gastric cancer. Multivariate survival analysis showed that TNM staging and Survivin mRNA levels were independent prognostic factors, while mRNA expression level of Survivin had important value for TNM staging.

4.2. Expression of Survivin mRNA in Peripheral Blood and Peritoneal Lavage Fluid and Prognosis of Gastric Cancer

In clinical practice, tumor tissue samples are most commonly used for immunohistochemical detection in Survivin, but it cannot meet the requirements of monitoring the efficacy of different treatment stages and judging the drug induced apoptosis of tumor cells. Therefore, finding sensitive and specific non-invasive detection methods is a research hotspot for monitoring tumor prognosis. Peripheral blood serves as a carrier for tumor cell metastasis, and RT-PCR technology can detect the expression level of Survivin mRNA in peripheral blood. It is a sensitive and specific non-invasive detection method that can accurately reflect the level of peripheral blood tumor cells. Therefore, detecting the expression level of Survivin mRNA in peripheral blood may become an effective indicator for monitoring tumor prognosis, and has important value in determining the recurrence, metastasis, and prognosis of gastric cancer.

The detection of Survivin mRNA in peripheral blood is easier and more valuable for the diagnosis and prognosis of gastric cancer than the collection of gastric cancer tissue specimens. Deng Jianzhong et al [61] reported that the positive expression rate of Survivin mRNA in gastric cancer tissue was 86.0% (43/50), and the expression rate in early or locally advanced stages was 68.2%, which was only related to the size of the tumor but not to age, gender, and lymph node metastasis. This was different from the results reported by Yi et al [62] that Survivin mRNA expression was related to the depth of infiltration, lymph node metastasis, and disease stage. The application of COX regression analysis [63] found that tumor stage and Survivin mRNA expression level were independent factors affecting the prognosis of gastric cancer, indicating that Survivin mRNA was involved in the occurrence and development of gastric cancer. Detecting the expression level of peripheral blood can determine the prognosis of gastric cancer. Liu Jinlong et al [64] found during follow-up that the expression of Survivin mRNA in peripheral blood of gastric cancer patients was significantly correlated with tumor size, infiltration depth, lymph node metastasis, and clinical stage, but not with tumor location and differentiation degree. The recurrence and metastasis rates of the gastric cancer group with positive Survivin mRNA were significantly higher than those of the negative group, indicating that the expression level of Survivin mRNA in peripheral blood can be used as a reference indicator for evaluating the biological behavior and prognosis of gastric cancer.

Chen Jianhua et al [65] reported that the sensitivity of peripheral blood Survivin mRNA expression in diagnosing gastric cancer was 60.4% (32/53). The specificity was 79.9%. The positive expression rate of Survivin mRNA in the group with tumors>5cm, infiltration to the serosa and lymph node metastasis was much higher than that in the group with tumors ≤ 5cm, invasion to the lower serosa and muscle layers, and no lymph node metastasis (78.3% vs 46%, 74.2% vs 3.3%, and 75.0% vs 29.4%). The RT-PCR-ELISA method for detecting Survivin mRNA in peripheral blood has strong specificity in diagnosing gastric cancer, and positive expression is significantly correlated with tumor size, infiltration depth, lymph node metastasis, and clinical staging, which had higher diagnostic value for advanced gastric cancer. Chen Guofei et al [66] found that the expression levels of Survivin mRNA and CK19 mRNA in peripheral blood of 89 gastric cancer patients were higher than those of the healthy control group, and were positively correlated with TNM staging, but not with clinical and pathological characteristics such as age, gender, and Lauren typing. The 5-year survival rate of double positive patients after surgery was lower than that of other groups. The ROC curve detection results show that Survivin mRNA and CK19 mRNA were effective indicators for diagnosing early gastric cancer. Combined detection can improve the sensitivity (92.14%) and specificity (97.75%) of diagnosis, avoiding misdiagnosis and missed diagnosis of a single indicator.

Peritoneal metastasis of gastric cancer is the most common mode of metastasis [67], and the detection of cancer cells in ascites is currently the gold standard for diagnosing peritoneal metastasis, but the sensitivity is relatively low (5%~15%) [68]. With the rapid development of molecular biology technology, the detection of molecular markers in peritoneal lavage fluid has emerged. CEA mRNA is almost exclusively present in tumor cells, and positive CEA mRNA in ascites suggests the presence of tumor cells with CEA mRNA expression. The sensitivity and specificity of RT-PCR technology in detecting CEA mRNA in peritoneal lavage fluid for diagnosing gastric cancer were 77% and 94%, respectively [69]. A meta-analysis [70] showed that the sensitivity and specificity of CEA mRNA in peritoneal lavage fluid for detecting peritoneal metastasis after gastric cancer radical surgery were 82% and

82%, respectively. Katsuragi K et al [71] found that the expression of CEA mRNA in peritoneal lavage fluid is associated with the recurrence of gastric cancer. Tan Siyi et al [72] reported that the detection of CEA mRNA in peritoneal lavage fluid was mainly used to predict the screening of peritoneal metastasis in gastric cancer. Positive cases had a high risk of recurrence and metastasis, poor prognosis, and were particularly suitable for routine testing in patients with signet ring cell carcinoma, vascular invasion, and advanced TNM. Therefore, the level of CEA mRNA in peritoneal lavage fluid can accurately predict peritoneal recurrence after radical gastrectomy for gastric cancer.

Wang et al [73] reported that the positive detection rate of Survivn mRNA in abdominal lavage fluid of gastric cancer patients was 58.3% (28/48), with a detection rate of 92% for obvious abdominal metastasis and 100% for all metastatic lymph nodes. They also pointed out that Survivn mRNA expression in abdominal lavage fluid was highly correlated with infiltration depth, tumor TNM stage, and lymph node metastasis. Survivin mRNA can be used as a molecular marker for gastric cancer peritoneal micrometastasis, Its expression level can evaluate the degree of tumor differentiation and predict lymph node metastasis. At present, there are few reports on the study of Survivn mRNA in peritoneal lavage fluid of gastric cancer patients in China. The predictive value of combined detection of CEA mRNA and Survivin mRNA in peritoneal lavage fluid for gastric cancer peritoneal metastasis needs to be confirmed.

In summary, overexpression of Survivin mRNA is an early event in gastric cancer and is significantly associated with histological types. The high expression of Survivin mRNA plays an important role in the occurrence and development of gastric cancer. It is not only used for early diagnosis of gastric cancer, but also has significant implications for lymph node metastasis, clinical staging, treatment guidance, and prognosis monitoring. Dynamic monitoring of peripheral blood and abdominal lavage fluid Survivin. The mRNA expression level has important value in predicting the prognosis of gastric cancer.

5. Serum Survivin Level and Prognosis of Gastric Cancer

The detection of TM serological indicators is simple and rapid, which not only has important value in the diagnosis of gastric cancer, but also has greater value in monitoring prognosis. Serum Survivin levels have been used for prognostic monitoring of tumors such as lung cancer, but their application in gastric cancer is relatively limited.

According to data [74], the serum levels of VEGF, Survivin, and p53 proteins in lung cancer patients were higher than those in the control group ($P<0.01$) , Three indicators were significantly correlated ,and also significantly correlated with lymph node metastasis and staging ($P<0.05$), but not with gender, age, degree of differentiation, and pathological type ($P>0.05$). Zhai Nailiang et al found that the serum Survivin levels in lung cancer patients were significantly higher than those in the normal control group [75]. The serum Survivin levels in adenocarcinoma, lymph node metastasis group, and stage III and IV patients were significantly higher than those in squamous cell carcinoma, non-lymph node metastasis, and stage I and II patients ($P<0.05$). The serum levels of VEGF, Ang-2, and Survivin in non-small cell lung cancer patients were higher than those in the control group ($P<0.01$), and the three indicators were significantly correlated with lymph node metastasis and staging ($P<0.05$), but not with age and gender ($P>0.05$). Huang Yanbo [76] found that the serum levels of Livin and Survivin were significantly increased in patients with retinoblastoma (RB), closely related to the degree of cancer tissue differentiation and clinical stage. The worse the differentiation, the higher the clinical stage, and the higher the serum levels of Livin and Survivin. The detection of serum Livin and Survivin can be used for the early diagnosis of RB. The sensitivity of the combined detection in diagnosing RB has increased to 92.5%, significantly improving the diagnostic value of RB, and can be used as an indicator for judging efficacy and prognosis. The above research results show that the combined detection of serum VEGF, Survivin, p53, Ang-2, and Livin TM can improve the diagnostic efficiency of tumors such as lung cancer and RB, and can serve as a good indicator for early diagnosis, monitoring metastasis, and staging judgment.

The serum levels of VEGF and Survivin in gastric cancer patients were higher than those in the control group ($P<0.05$), and the two were positively correlated, closely related to the degree of differentiation and lymph node metastasis ($P<0.05$). The elevated levels of serum VEGF and Survivin may play an important role in the occurrence and development of gastric cancer [77]. Fu Baiyu et al [78] found that the serum levels of p53 and Survivin were significantly increased in gastric cancer patients, while the levels of programmed cell death molecule-5 (PDCD-5) were significantly decreased ($P<0.05$). The expression levels of the three indicators were related to tumor diameter, differentiation degree, infiltration depth, TNM stage, and lymph node metastasis ($P<0.05$). Moreover, the 3-year overall survival rate and disease-free survival rate of the p53 and Survivin high expression group were significantly lower than those of the p53 and Survivin low expression group ($P<0.05$) The 3-year overall survival rate and disease-free survival rate of the high expression group of Survivin were significantly higher than those of the PDCD-5 and low expression groups of Survivin ($P<0.05$). Low expression of serum p53 and Survivin and high expression of PDCD-5 in gastric cancer patients can improve 3-year overall survival and disease-free survival, and may become prognostic markers. Therefore, the combined detection of serum VEGF, Survivin, p53, and PDCD-5 TM has important value for early diagnosis, prognostic monitoring, and guiding treatment of gastric

cancer. It not only has high sensitivity and specificity, but also had strong repeatability, simple operation, and was easy to promote and apply.

The above research results indicate that detecting the expression levels of TM such as Survivin and VEGF in gastric cancer tissue can determine its prognosis, but its application is often limited. Peripheral blood samples, especially serum samples, are easier to obtain than tumor tissue samples. Therefore, detecting peripheral blood samples of tumor patients, especially serum TM, is more convenient and may have more clinical significance.

6. Summary and Prospect

A large number of research results have confirmed that Survivin, as the factor with the strongest inhibitory effect on apoptosis, is highly expressed in gastric cancer tissue. The positive expression rate, protein level, and gene content of Survivin are significantly higher than those of the control group. It is not only related to the onset of tumors, but also closely related to the progression and prognosis of diseases. However, the research results are not the same, and large-scale prospective studies are needed. The research results indicate that Survivin is not only highly expressed in GC tissue cells, but also significantly increases in serum Survivin content, which is positively correlated with GC pathology and clinical staging. Changes in serum Survivin content have important clinical value for the diagnosis and prognosis monitoring of GC. Serological indicators have important reference value in early screening and prognostic evaluation of gastric cancer. Combined detection of multiple indicators has greater prognostic monitoring value for gastric cancer. Based on the principles of evidence-based laboratory medicine, it is imperative to screen serum Survivin, VEGF, Livin, PTEN, Caspase-3, Bcl-2 and other highly sensitive and specific indicators for the diagnosis and prognosis monitoring of gastric cancer. This will provide new indicators for the screening of gastric cancer and simple, fast, and valuable indicators for prognosis monitoring.

Abbreviations

GC: Gastric Cancer
AIP: Apoptosis Inhibiting Protein

Funding

Natural Science Funding Project Cangzhou Medical College (21Z009).

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Hou Jianzhang, Li Yong. Relationship Between the Expression of S100P in Gastric Cancer Tissue and Clinical Pathology [J]. American Journal of Clinical and Experimental Medicine, 2021, 9(3): 55-64. https://doi.org/10.11648/j.ajcem.20210903.12

[2] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics2020: GLOBO-CAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries [J]. CA Cancer J Clin, 2021, 71 (3): 209-249. https://doi.org/10.3322/caac.21660

[3] Yan Chao, Shan Fei, Li Ziyu. Analysis of Global Burden of Gastric Cancer in 2020: Focusing on the Statistics in China [J]. China Cancer, 2023, 32 (3): 161-170. https://doi.org/10.11735/j.issn.1004-0242.2023.03.A001

[4] Sun Kexin, Zheng Rongshou, Zhang Siwei, et al. Report of Cancer Incidence and Mortality in Different Areas of China, 2015 [J]. China Cancer, 2019, 28(1): 1-11. https://doi.org/10.11735/j.issn.1004-0242.2019.01.A001

[5] Zhang Shuli, Hou Jianzhang, Li Hongyan, et al. Research Progress on Apoptosis Inhibitory Protein Survivin and Its Application in Digestive Tract Tumors [J]. Ameri-can Journal of Health Research, 2023; 11(3): 84-94. https://doi.org/10.11648/j.ajhr.20231103.13

[6] Ambrosini G, Adida C, Altieri DC. A novel anti-apoptosis gene, Survivin, expressed in cancer and lymphoma [J]. Nat Med, 1997, 3(8): 917-921. https://doi.org/10.1038/nm0897-917

[7] Ma XY. Survivin, an important regulator of cell division and apoptosis: a target for new anticancer drugs [J]. Chemistry of life, 2010, 30(3): 338-344.

[8] Erridge S, Pucher PH, Markar SR, et al. Meta-analysis of determinants of survival following treatment of recurrent hepatocellular carcinoma [J]. Br J Surg, 2017, 104(11): 1433-1442. https://doi.org/10.1002/bjs.10597

[9] Gu LH, Zhou RX. Research progress of the relationship between apoptosis inhibitor protein Survivin and gastric cancer [J]. Sichuan J Anat, 2009, 17(4): 19-21.

[10] Chen KY, He HH, Ke JY, et al. Expression of Survivin gene in proliferation and apoptosis of hepatocellular carcinoma cells [J]. Hainan Med J, 2021, 32(4): 409-412. https://doi.org/10.3969/j.issn.1003-6350.2010.04.001

[11] Zhao Ruijie, Li yinqian, Wang hui, et al. Relationship of Caspase family and apoptosis [J]. Chinese Journal of Animal Science, 2010, 46(17): 73-78.

[12] Stepien A, Izdebska M, Grzanka A. The types of cell death [J]. Postepy Hig Med Dosw (Online), 2007, 61: 420-428. PMID: 17679912.

[13] Van Opdenbosch N, Lamkanfi M. Caspases in Cell Death, Inflammation and Disease [J]. Immunity, 2019, 50(6): 1352-1364. https://doi.org/10.1016/j.immuni.2019.05.020

[14] Meng J, Dang T. The Effect of CCN1 on the expression of Caspase-2 in Esophageal carcinoma cells [J]. Inner Mongolia Med J, 2022, 54(6): 641-646. https://doi.org/10.16096/J.cnki.nmgyxzz.2022.54.06.001

[15] Liu XB. Analysis of the correlation between apoptosis related protein Caspase and male condyloma acuminatum [J]. Chinese Journal of Human Sexuality, 2020, 29(11): 134-138. https://doi.org/10.3969 /j.issn.1672-1993.2020.11.040

[16] Liu D, YU ZX, Zhang HX. Cyanidin-3-o-glucoside inhibits H_2O_2-induced apoptosis by Mediating the cascaded reaction of caspase [J]. Acta Nutrimenta Sinica, 2020, 42(4): 369-373. https://doi.org/10.13325/j.cnki.acta.nutr.sin.2020.04.008

[17] Poomsawat Sopee, Punyasingh Jirapa, Vejchapipat Paisarn. Overexpression of Survivin and Caspase 3 in Oral Carcinogenesis [J]. Appl Immunohistochem Mol Morphol, 2014, 22(1): 65-71. https://doi.org/10.1097/PAI.0b013e31828a0d0c

[18] Lin XR, Qian H, Lv JW, et al. Research progress of Caspases family involved in cell apoptosis of dental pulp during the root Absorption of deciduous teeth [J]. Stomatology, 2022, 42(2): 180-183. https://doi.org/10.13591/j.cnki.kqyx.2022.02.017

[19] Kalkavan H, Green. D R. MOMP, cell suicide as a BCL-2 family business [J]. Cell Death Differ, 2017, 25(1): 1-10. https://doi.org/10.1038/cdd.2017.179

[20] Mobahat M, Narendran A, Riabowol K. Survivin as a Preferential Target for Cancer Therapy [J]. Int J Mol Sci, 2014, 15, 2494-2516. https://doi.org/10.3390/ijms15022494

[21] Yiming Zhang, Hai Huang, Huimin Zhou, et al. Activation of Nuclear Factor kB Pathway and Downstream Targets Survivin and Livin by SHARPIN Contributes to the Progression and Metastasis of Prostate Cancer [J]. Cancer, 2017, 123(5): 892-893. https://doi.org/10.1002/cncr.30497

[22] O'connor DS, Schechner JS, Adida C, et al. Control of Apoptosis during Angiogenesis by Survivin Expression in Endothelial Cells [J]. Am J Pathol, 2000, 156(2): 393-398. https://doi.org/10.1016/S0002-9440(10)64742-6

[23] Jin Ling, Ding Lina, Yu Shuo, et al. Research progress of apoptosis protein inhibitor Survivin [J]. Chin Lab Diagn, 2018, 22(6): 1100-1102.

[24] Chen HL, Xie CH, Zhong QJ, et al. Effects of Bevacizumab Combined with Chemotherapy on Serum VEGF and bFGF Levels in Patients with Advanced Non-squamous Non-small Cell Lung Cancer [J]. Drug Evaluation, 2022, 19(16): 996-999. https://doi.org/10.19939/j.cnki.1672-2809.2022.16.11

[25] Li S, Wang L, Meng Y, et al. Increased levels of LAPTM4B, VEGF and survivin are correlated with tumor progression and poor prognosis in breast cancer patients [J]. Oncotarget, 2017, 8(25): 41282-41293. https://doi.org/10.18632/oncotarget.17176

[26] Lu CD, Ahieri DC, Tanigawa N. Expression of a novel antiapoptosis Gene, Survivin, correlated with tumor cell apoptosis and p53 accumulation in gastric carcinomas [J]. Cancer Res, 1998, 58(9): 1808-1812. PMID: 9581817

[27] Yu J, Leung WK, Ebert MP, et a1. Increased expression of Survivin in gastric cancer patients and in first degree relatives [J]. Br J Cancer, 2002, 87(1): 91-97. https://doi.org/10.1038/sj.bjc.6600421

[28] Zhu XD, Lin GJ, Qian LP, et a1. Expression of Survivin in human gastric carcinoma and gastric carcinoma model of rats [J]. World J Gastro Enterol, 2003, 9(7): 1435-1438. https://doi.org/10.3748/wjg.v9.i7.1435

[29] Song KY, Jung CK, Park WS, et a1. Expression of the Antiapoptosis Gene Survivin Predicts Poor Prognosis of Stage III Gastric Adenocarcinoma [J]. Jpn J Clin Oncol, 2009, 39(5): 290-296. https://doi.org/10.1093/jjco/hyp020

[30] Da CL, Xin Y, Zhao J, et al. Signiffcance and relationship between Yes-associated protein and Survivin expression in gastric carcinoma and precancerous lesions [J]. World J Gastroenterol 2009, 15(32): 4055-4061. https://doi.org/10.3748/wjg.15.4055

[31] Yao XQ, Ku FK, Qi xP, et al. Expression of Survivin in human gastric Adenocarcinomas: correlation with proliferation and apoptosis [J]. Zhong hua Wai Ke Za Zhi, 2004, 42(3): 145-148.

[32] Sun Diwen, Chen Qi. Expression of Survivin protein in early gastric cancer and in precancerosis and its clinical significance [J]. Chin J Cancer Prev Treat, 2008, 15(16): 1215-1217. https://doi.org/10.16073/j.cnki.cjcpt.2008.16.028

[33] Luo Xue, Yao Zhongxiang. Expression and significance of Survivin in gastric carcinoma [J]. Modern medicine and hygiene, 2009, 25(3): 338-339.

[34] Sun Yanxia, Shi Zhangzhen, Lu Zhenxia, et al. The Expression of Survivin gene in gastric cancerous tissue and its clinical significance [J]. Chin J Lab Diagn, 2012, 16(5): 844-846.

[35] Kania J, Konturek SJ, Marliez K, et al. Expression of Survivin and easpase-3 in gastric cancer [J]. Dig Dis Sci, 2003, 48(2): 266-271. https://doi.org/10.1023/a:1021915124064

[36] Xu Tianxiang, Hu Jiang, Liu Yanheng. Expression of Survivin in gastric cancer and its clinical significance [J]. Inner Mongolia Med J, 2014, 46(10): 1153-1157. https://doi.org/10.16096/j.cnki.nmgyxzz.2014.10.001

[37] Jiao Jianxin, Wen Fengxia, Zhang Lingling, et al. Relationship bet-ween Survivin expression and Helicobacter pylori infection in gastric cancer [J]. China Modern Medicine, 2016, 23(4): 4-8.

[38] Shintani M, Sangawa A, Yamao N, et al. Immunohistochem ical expression of nuclear and cytoplasmic Survivin in gastrointestinal carcinoma [J]. Int J Clin ExpPathol, 2013, 6(12): 2919-2927. PMID: 24294379

[39] Jia YF, Hu RF, Li P, et al. DEC1 is required for anti-apoptotic activity of gastric cancer cells under hypoxia by promoting Survivin expression [J] Gastric Cancer, 2018, 21(4): 632-642. https://doi.org/10.1007/s10120-017-0780-z

[40] Abudoureyimu A, Muhemaitibake A. Arsenic trioxide regulates gastric cancer cell apoptosis by mediating cAMP [J]. Eur Rev Med Pharmacol Sci, 2017, 21(3): 612-617. PMID: 28239804

[41] Fang Yu, Wang Linling, Wang Haijuan, et al. Expression and clinical significance of Survivin and Bcl-2 in gastric carcinoma [J]. Anti-tumor Pharmacy, 2021, 11(4): 474-479. https://doi.org/10.3969/j.issn.2095-1264.2021.04.14

[42] Li Hong, Hui Qiyuan ,Tian Zhengliang. Quantitative Analysis of Survivin and CD34in Gastric Carcinoma and Dysplasia and Their Clinical Significance [J]. Cancer prevention and treatment research, 2010, 37(5): 544-546, 550. https://doi.org/10.3971/j.issn.1000-8578.2010.05.015

[43] Pu Z, Wang Q, Xie H, et al. Clinical pathological and prognostic significance of survivin expression in renal cell carcinoma: a metaanalysis [J]. Oncotarget, 2017, 8(12): 19825-19833. https://doi.org/10.18632/oncotarget.15082

[44] Lee GH, Joo YE, Koh YS, et al. Expression of Survivin in gastric cancer and its relationship with tumor angiogenesis [J]. Eur J Gastroenterol Hepatol, 2006, 18(9): 957-963. https://doi.org/10.1097/01.meg.0000230086.83792.56

[45] Li Dongxia, Si Yanli, Deng Xiaohui, et al. Expression of Survivin and Bcl-2 in 52 patients with gastric cancer [J]. Chongqing Medical Science, 2011, 40(22): 2206-2207, 2210. https://doi.org/10.3969/j.issn.1671-8348.2011.22.008

[46] Wang Songwen, Li Yong, Wang Jie. Expression of Survivin and Metastin in Gastric Carcinoma and its Significance [J]. Journal of Oncolog, 2010, 16(12): 961-964.

[47] Hu Zhongdong, Zhong Meizuo, Zhou Huijun. Expression and significance of MMP-7 and Survivin in gastric cancer [J]. Cancer prevention and treatment research, 2012, 39(11): 1349-1352. https://doi.org/10.3971/j.issn.1000-8578.2012.11.017

[48] He Hongmei, Xu Aiguo, Sun Xiuhua. Expression of Survivin in gastric cancer and its influence on prognosis [J]. World Latest Medical Information Digest, 2015, 159(36): 18-20. https://doi.org/10.3969/j.issn.1671-3141.2015.36.014

[49] Sun Yuanshui, Ye ZaiYuan, Zhao ZhongSheng, et al. Expression of vascular endothelial growth factor-C and survivin in gastric carcinoma and their clinical implications [J]. Chin J Gastrointest Surg, 2006, 9(3): 264-267.

[50] Zhou Wei, Dai Qigang, Deng Xing, et al. Expressions of Survivin and Bcl-2 in Gastric Carcinoma and their Significance [J]. Journal ofOncology, 2009, 15(6): 549-551.

[51] Yan Yuping,Yin Xiangli. Correlation study on expression of survivin and caspase-3with biological behavior in gastric carcinoma [J]. Journal of Clinical Medicine in Practice, 2013, 17 (13): 24-27. https://doi.org/10.7619/jcmp.201313008

[52] Wang X W. Expression of survivin and caspase-3 in gastric cancer and their correlation with clinicopathological features [J]. Chinese Journal of Gerontology, 2012, 32(20): 4405-4406. https://doi.org/10. 3969/j.issn.1005-9202. 2012.20. 023

[53] Ying Rongbiao, Feng Jun, Li Jianjun, et al. Expression of survivin and caspase-3 in gastric cancer and its clinical significance [J]. China Oncology, 2010, 20(1): 17-21.

[54] Liu Xiaomin, Li Qiaoyun, Chen Canbin, et al. Expressions and Clinicopathological Significances of PIG11 and Caspase-3 Protein in the Gastric Carcinoma [J] biomed cnjournals.com Progress in Modern Biomedicine, 2018, 18(4): 657-661. https://doi.org/10.13241/j.cnki.pmb.2018.04.012

[55] Pu Haichao, Wang Chunyan. Analysis of Survivin and Caspase-3 Expression in Gastric Cancer Patients with Different Stages [J]. Smart Healthcare, 2022, 8(7): 65-67. https://doi.org/10.19335/j.cnki.2096-1219.2022.07.021

[56] Shayimu Paerhati, Yusufu Aikeremu, Tuerdi Rousidan, et al. Expression and Clinical Correlation Analysis of Survivin and PTEN Proteins in Gastric Cancer [J]. The Practical Journal of Cancer, 2020, 35(8): 1253-1257. https://doi.org/10.3969/j.issn.1001-5930.2020.08.009

[57] Liu Z, Zhang X, Xu X, et al... RUNX3 inhibits Survivin expression and induces cell apoptosis in gastric cancer [J]. Eur J Cell Biol 2014, 93(1): 118-126. https://doi.org/10.1016/j.ejcb.2014.02.002

[58] Miyachi K, Sasaki K, Onodera S, et al. Correlation between Survivin mRNA expression and lymph node metastasis in gastric cancer [J]. Gastric Cancer, 2003, 6(4): 217-224. https://doi.org/10.1007/s10120-003-0255-2

[59] Meng H, Lu C, Mabuchi H, et al. Prognostic signiffcance and different properties of Survivin splicing variants in gastric cancer [J]. Cancer Lett 2004, 216(2): 147-155. https://doi.org/10.1016/j.canlet.2003.12.020

[60] Bertazza L, Mocellin S, Marcher A, et a1. Survivin gene levels in the peripheral blood of patients with gastric cancer independently predict survival [J]. J Transl Med, 2009, 7: 111. https://doi.org/10.1186/1479-5876-7-111

[61] Deng Jianzhong, Jin Jianhua, Lu Wenbin, et al. The expression of survivin mRNA in the peripheral blood of gastric cancer and its clinical significance [J]. China Oncology, 2010, 20(12): 903-906.

[62] Yie SM, Lou B, Ye SR, et al. Detection of Survivin-Expressing Circulating Cancer Cells (CCCs) in Peripheral Blood of Patients with Gastric and Colorectal Cancer Reveals High Risks of Relapse [J]. Annals of Surgical Oncology, 2008, 15(11): 3073-3082. https://doi.org/10.1245/s10434-008-0069-x

[63] Deng Jianzhong, Jin Jianhua, Lu Wenbin, et al. Relationship between the expression of survivin mRNA in the peripheral blood and gastric carcinoma [J]. Journal of Clinical Medicine in Practice, 2012, 12(5): 99-101.

[64] Liu Jinlong, Wu shuyan, Liu Lihong, et al. Expression of Survivin in the peripheral blood of Patients with Gastric cancer and Its Relationship with Biological Behaviors of Gastric cancer [J]. Clin J Lab Diagn, 2012, 16(1): 57-59.

[65] Chen Jianhua, Liu Jinlong. Diagnostic value of survivin expression in peripheral blood for gastric cancer [J]. Hebei Medicine, 2014, 20(2): 298-300. https://doi.org/10.3969/j.issn.1006-6233.2014. 02.049

[66] Chen Guofei, Yang Hua, JiangXingxin, et al. Expressions of Survivin mRNA and CK19 mRNA in peripheral blood of patients with gastric cancer and clinical signiffcance [J]. China Journal of Modern Medicine, 2018, 28(7): 55-60. https://doi.org/10.3969/j.issn.1005-8982.2018.07.011

[67] Bai Yurong, Lu Yidan, Sun Yangcheng, et al. Clinical efficacy of prophylactic hyperthermic intraperitoneal chemotherapy for advanced gastric cancer: a meta-analysis [J]. J Practical Oncology, 2021, 36(4): 306-313. https://doi.org/10.13267/j.cnki.syzlzz.2021.064

[68] Chae HD. Role of genetic detection in peritoneal washes with gastric carcinoma: The past, present and future [J]. World J Gastrointest Oncol, 2016, 8(3): 289-296. https://doi.org/10.4251/wjgo.v8.i3.289

[69] Kodera Y, Yamamura Y, Shimizu Y, et al. Peritoneal washing cytology: prognostic value of positive findings in patients with gastric carcinoma undergoing a potentially curative resection [J]. J Surg Oncol. 1999, 72(2): 60-64. https://doi.org/10.1002/(sici)1096-9098(199910)72:2<60::aid-jso3>3.0.co;2-1

[70] Xiao Y, Zhang J, He X, et al. Diagnostic values of carcinoembryonic antigen in predicting peritoneal recurrence after curative resection of gastric cancer: a meta-analysis [J]. Ir J Med Sci. 2014, 183(4): 557-64. https://doi.org/10.1007/s11845-013-1051-6

[71] Katsuragi K, Yashiro M, Sawada T, Prognostic impact of PCR-based identification of isolated tumour cells in the peritoneal lavage fluid of gastric cancer patients who underwent a curative R0 resection [J]. Br J Cancer, 2007, 97(4): 550-556. https://doi.org/10.1038/sj.bjc.6603909

[72] Tan Siyi, Yu Lixia, Wei Jia, et al. Clinical significance of CEA mRNA expression in peritoneal lavage fluid for patients with gastric cancer after radical surgery [J]. Chin J Cancer Biother 2020, 27(5): 541-546. https://doi.org/10.3872/j.issn.1007-385x.2020.05.011

[73] Wang ZN, Xu HM, Jiang L, et a1. Expression of Survivin mRNA in peritoneal lavage fluid from patients with gastric carcinoma [J]. Chin Med J (Engl), 2004, 117(8): 1210-1217. PMID: 15361297

[74] Wang Ying, Liang Huan. Expression of serum VEGF, Survivin and p53 in lung cancer and the ircorrelation [J]. Chinese Journal of Health Laboratory Technology, 2008, 18(8): 1573-1575.

[75] Zhai Nailiang, Liu Jinping, Gao Fuquan. Expression of serum VEGF, Ang-2 and Survivin in lung carcinoma and their correlation [J]. BMU J, 2016, 39(1): 23-26.

[76] Huang Yanbo, Xu Wenmin, Hong Zehua, et al. The application value of serum Livin combined with Survivin detection in the diagnosis of retinoblastoma [J]. China Medicine Pharmacy, 2016, 6(11): 144-147.

[77] Zhang Jun, LiuJun. Significance analysis of vascnlar endothelial growth factor and Snrvivinin Patients with gastric carcinoma [J]. Int J Lab Med, 2012, 33(6): 679-680. https://doi.org/10.3969/j.issn.1673-4130.2012.06.027

[78] Fu Baiyu, LinYi, XUu Qi, et al. Application value of combined detection of serum p53, PDCD-5 and Survivin in gastric cancer [J]. J Mol Diagn Ther, 2021, 13(4): 615-618, 622. https://doi.org/10.19930/j.cnki.jmdt.2021.04.026