Clin. Lab. 2021;67:XXX-XXX

ORIGINAL ARTICLE

The Role of Cholinesterase in Differential Diagnosis between Gastric Cancer and Benign Gastric Diseases

Huiquan Gao [1, 2, #], Yanzhen Wan [3, #], Xiaoyi Fan [4], Yanyu Dong [2], Xiaona Ji [1], Wei Song [5]

[#] *Huiquan Gao and Yanzhen Wan contributed equally to this study*
[1] *First School of Clinical Medicine, Shandong University of Traditional Chinese Medicine, Jinan, Shandong, China*
[2] *Department of Oncology, The 970 Hospital of PLA, Weihai, Shandong, China*
[3] *Clinical Laboratory, Qingdao Women and Children's Hospital, Qingdao Women and Children's Hospital Affiliated to Qingdao University, Qingdao, China*
[4] *Department of Rehabilitation Medicine, Weihaiwei People's Hospital, Weihai, China*
[5] *Department of Oncology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China*

SUMMARY

Background: **Gastric cancer is the fifth most common malignancy worldwide. In early stages, no obvious symptoms are usually observed in gastric cancer patients, and it is especially hard to distinguish gastric cancer from benign gastric diseases, resulting in delayed diagnosis and poor prognosis. Common biomarkers of gastric cancer, such as CEA and CA19-9, are also elevated in benign diseases. There is an urgent need to develop a convenient and reliable biomarker for differentiating between gastric cancer and benign gastric diseases.**

Methods: **This study retrospectively analyzed the data of 126 patients, including 73 gastric cancer patients and 53 benign gastric disease patients. Patient characteristics collected for analysis included age, gender, laboratory data, and clinical staging. Unpaired *t*-test was used to check the difference of cholinesterase level between the gastric cancer group and the benign gastric disease group. Kruskal Wallis H test and Mann-Whitney U test were used to check the difference of cholinesterase level among different stage groups. Receiver operating characteristic (ROC) curve was used to assess whether cholinesterase level can be used as a biomarker for differentiating between gastric cancer and benign gastric diseases.**

Results: **Serum cholinesterase level was decreased significantly in the gastric cancer group in comparison to that of the benign gastric disease group ($p < 0.001$). In addition, cholinesterase level of stage IV patients was significantly lower than stage I patients. ROC curve analysis revealed that with a cutoff of 5,969.00 U/L, cholinesterase level showed an area under the curve of 0.819 (95% CI 0.732 - 0.905, $p < 0.001$) in differentiating between gastric cancer and benign gastric diseases. No significant difference in the levels of CEA and CA19-9 was observed between gastric cancer patients and benign gastric disease patients.**

Conclusions: **This study indicated that serum cholinesterase level could be considered as a potential biomarker for differentiating between gastric cancer and benign gastric diseases.**

(Clin. Lab. 2021;67:xx-xx. DOI: 10.7754/Clin.Lab.2020.200525)

Correspondence:
Dr. Wei Song
Department of Oncology
Shandong Provincial Hospital Affiliated to
Shandong First Medical University
Jing Wu Road 324
Jinan
250021 Shandong
China
Phone/Fax: +86 531 68777169
Email: tougao13406738582@126.com

Manuscript accepted June 18, 2020

KEY WORDS

cholinesterase, gastric cancer, biomarker, ROC curve

INTRODUCTION

Gastric cancer (GC) is the fifth most common malignancy worldwide [1], and it remains a leading cause of cancer-related mortality in China [2]. Patients with GC are mostly asymptomatic in early stages, and it is especially difficult to distinguish GC from benign gastric diseases. Hence, patients are often diagnosed as GC in the late stage with poor therapeutic effect and prognosis. Early diagnosis of GC has gained a very important social concern because it can lead to early treatment and lower mortality [3]. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) tumor markers have been widely used for the diagnosis of GC. However, the majority of studies concluded that CEA and CA19-9 were neither reliable nor accurate tools in the detection of GC in its initial stages [4]. These tumor markers were also increased in benign diseases, such as gastritis and gastric polyps. So, it is urgent to discover novel non-invasive, sufficiently sensitive and specific biomarkers for differentiating between GC and benign gastric diseases.

Serum cholinesterase (ChE) is an alpha-glycoprotein synthesized in liver and released into plasma immediately after synthesis [5]. ChE has been proposed to play a role in lipoprotein metabolism, scavenging of toxic molecules, myelin maintenance, processing of the amyloid precursor protein, neuritogenesis, synaptogenesis, thrombopoiesis, hematopoiesis, cell growth, cell adhesion, cell differentiation, and apoptosis [6]. In addition, ChE has an important role in tumorigenesis and oncogenesis and was proven to be a good indicator of tumor presence [7]. Studies suggested that reduction of serum ChE level in children was a high risk of cancer development [8,9]. Recently Kimura S et al. showed that decreased ChE level was associated with poor prognosis in several cancers with or without hepatic involvement [10]. Moreover, ChE was found to be a good biomarker of tumor response to therapy [11]. There is increasing evidence supporting the involvement of ChE in tumorigenesis, most of which demonstrated a decrease of ChE level [6].

So far, limited information is available about the role of ChE in GC. Gu et al. reported that serum ChE activity was closely related with the incidence of GC [12]. In our study, we found that ChE is drastically decreased in GC patients. In order to evaluate whether ChE could be used as a potential biomarker for differentiating between GC and benign gastric diseases, we retrospectively investigated and analyzed serum ChE levels in GC and benign gastric disease patients.

MATERIALS AND METHODS

Patients

We retrospectively analyzed the clinical and pathological records of 73 GC patients and 53 benign gastric disease patients (including 17 cases with gastritis and 36 cases with gastric polyps), hospitalized in the 970 Hospital of PLA from March 2017 to March 2018. The patients were included according to the criteria as follows, gastric adenocarcinoma was diagnosed based on endoscopic examination and confirmed by the histological examination, and benign gastric diseases (gastritis and gastric polyps) were diagnosed based on the histological examination. Exclusion criteria were as follows, patients with another type of cancer, with liver inflammation or other related liver diseases, with serious active infection or inflammatory diseases, or with organophosphorus poisoning were excluded. Patient characteristics collected for analysis included age, gender, laboratory data (ChE, CEA, and CA19-9), and clinical staging. The study has been approved by the Medical Ethics Committee of the 970 Hospital of PLA.

Biochemical analysis

All the patients fasted for 8 - 12 hours and venous blood samples were collected in vacuum blood collection tubes according to the standard procedure of blood collection. After centrifugation for 10 minutes under 3,000 rpm, serum samples were detected timely. Serum ChE level was measured by Hitachi 7600 automatic biochemical analyzer (Japan) using a serum ChE determination kit provided by Shanghai Kehua Bio-Engineering Co., Ltd (China). Butyrylthiocholine/potassium fericyanide method was used to detect serum ChE. The normal reference value was 5,000 - 12,000 U/L. CEA and CA 19-9 tumor markers were detected by Roche Cobas type 401 automatic electrochemical luminescence immunoassay system and its original kits (Roche, Switzerland). The normal reference value was 0 - 5 ng/mL for CEA and 0 - 39 U/mL for CA 19-9.

Statistical analysis

Data analysis was performed using SPSS 23. Unpaired *t*-test, Chi-square test, Spearman's rank correlation coefficient, Kruskal Wallis H test, Mann-Whitney U test, and ROC curve were used for statistical analysis, and $p < 0.05$ (2-sided) was considered to be statistically significant. Mann-Whitney U test with Bonferroni correction was applied to all pairwise comparisons, and because six rounds of pairwise comparison was made among four groups, $p < 0.008$ was considered to be statistically significant.

Table 1. The difference of ChE level in GC and benign gastric diseases.

Groups	Number of cases	Serum ChE Level (U/L) (mean ± SD)
Gastric cancer	73	5,570.33 ± 2,141.61 *
Benign gastric disease	53	8,581.533 ± 2,343.30

* - p < 0.001 compared with the benign gastric disease group. SD - standard deviation.

Table 2. Comparison of serum ChE level in different TNM stages of GC.

Staging	Number of cases	Serum ChE Level (U/L) (mean ± SD)
Stage I	15	7,213.87 ± 1,570.20
Stage II	16	6,161.75 ± 2,373.24
Stage III	10	5,960.30 ± 1,381.10
Stage IV	15	4,348.73 ± 1,723.05 *

There was a statistically significant difference among the four groups (p < 0.001). * - p < 0.001 compared with Stage I group.

Table 3. The difference of ChE level in early stage GC and benign gastric diseases.

Groups	Number of cases	Serum ChE Level (U/L) (mean ± SD)
Gastric cancer (Stage I)	15	7,213.87 ± 1,570.20 #
Benign gastric disease	53	8,581.53 ± 2,343.30

- p < 0.05 compared with the benign gastric disease group.

RESULTS

The difference of serum ChE level in GC and benign gastric diseases

In the GC group, there were 18 females and 55 males aged from 35 to 86 years old (the mean age, 62.29 ± 10.895). In the benign gastric disease group, there were 18 males and 35 females aged from 35 to 87 years old (the mean age, 60.77 ± 11.758). Unpaired *t*-test and chi-square test were used to check the difference in age and gender proportion between the two groups. No significant difference was found in age (p = 0.458). However, as for gender proportion, it differed significantly between the two groups (p < 0.001). We used Spearman's rank correlation coefficient to analyze whether serum ChE level was correlated with gender and found no correlation in the GC group (p = 0.466, r = 0.087) and the benign gastric disease group (p = 0.372, r = -0.125).

The mean value of serum ChE level was 5,570.33 U/L in the GC group, whereas in the benign gastric disease group the mean value of serum ChE was 8,581.53 U/L, with a statistically significant difference between the two groups (p < 0.001) (Table 1).

Comparison of serum ChE level in different TNM stages of GC

The clinical staging of GC was based on the 7th edition of the UICC-AJCC TNM staging criteria. Due to the retrospective nature of the study, the staging of some cases receiving no surgical treatment was not standardized. Only 56 patients in the GC group have a definite staging, including 15 cases (male 11, female 4; age 58.27 ± 7.84) of Stage I, 16 cases (male 16, female 0; age 61.81 ± 8.96) of Stage II, 10 cases (male 4, female 6; age 59.8 ± 13.15) of Stage III, and 15 cases (male 12, female 3; age 64.20 ± 9.99) of Stage IV. As ChE level in the stage II group was found not to be normally distributed, Kruskal Wallis H test was used to compare the difference among the four groups. Serum ChE level decreased from Stage I to Stage IV, with statistically significant difference among the four groups (p < 0.001) (Table 2).

Mann-Whitney U test with Bonferroni correction was

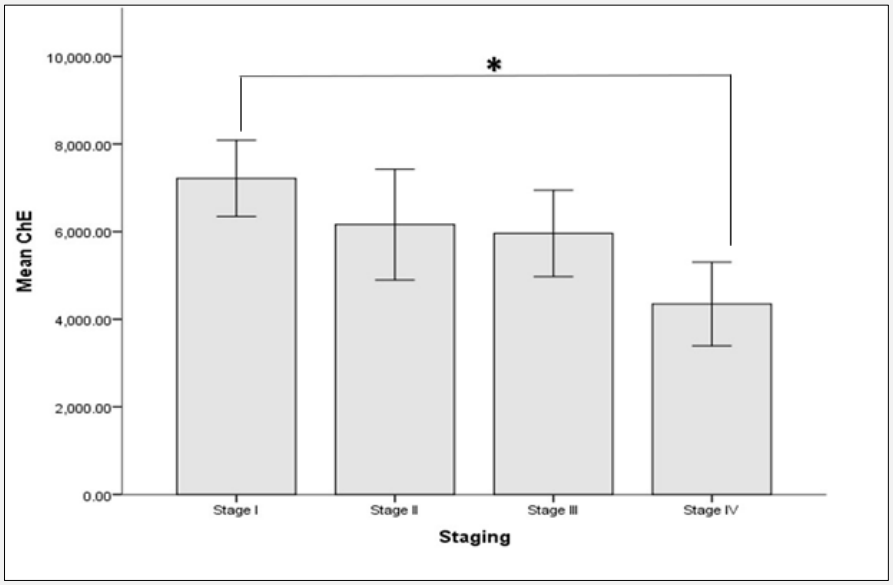

Figure 1. The difference of ChE level in different TNM stages of GC.

Data were presented as mean ± SEM (standard error of mean). Mann-Whitney U test with Bonferroni correction was used for all pairwise comparisons. Serum ChE level was significantly lower in TNM Stage IV than in Stage I group (* - $p < 0.001$). The normal reference value was 5,000 - 12,000 U/L.

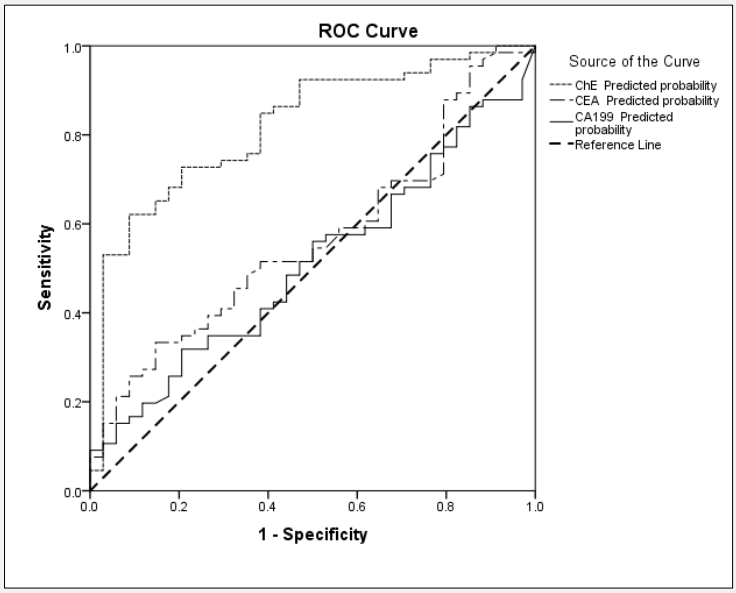

Figure 2. ROC curves for ChE, CEA, and CA199 in differentiating between GC and benign gastric diseases.

AUC for ChE, CEA, and CA19-9 was 0.819 (95% CI 0.732 - 0.905, $p < 0.001$), 0.564 (95% CI 0.449 - 0.6805, $p = 0.293$) and 0.510 (95% CI 0.395 - 0.626, $p = 0.867$), respectively.

used to analyze the difference of ChE level between two groups, and $p < 0.008$ was considered to be statistically significant. Serum ChE level was significantly lower in TNM Stage IV than in Stage I group ($p < 0.001$) (Figure 1).

The difference of serum ChE level in early stage GC and benign gastric diseases

To further investigate whether there is a difference of ChE level between early stage GC and benign gastric diseases, we compared ChE level in patients with Stage I GC and patients with benign gastric diseases. The mean serum ChE level in Stage I GC group was 7,213.87 U/L, and it was 8,581.53 U/L in the benign disease group, which was significantly higher than the former ($p = 0.037$) (Table 3).

The diagnostic value of ChE, CEA, and CA19-9 in differentiating between GC and benign gastric diseases

One hundred patients in two groups underwent simultaneous ChE, CEA, and CA19-9 detection. In the GC group, there were 66 patients (male 49, female 17; age 61.65 ± 10.72). In the benign gastric disease group, there were 34 patients (male 12, female 22; age 58.85 ± 11.51). To analyze the diagnostic value of ChE, CEA, and CA19-9 in differentiating between GC and benign gastric diseases, ROC curves were made and analyzed. As is shown in Figure 2, area under the curve (AUC) for ChE, CEA, and CA19-9 were 0.819 (95% CI 0.732 - 0.905, $p < 0.001$), 0.564 (95% CI 0.449 - 0.6805, $p = 0.293$), and 0.510 (95% CI 0.395 - 0.626, $p = 0.867$), respectively. ROC curve analysis suggested that with the optimal cutoff value of 5,969.00 U/L, ChE could produce 62.1% sensitivity, 91.2% specificity, 93.2% PPV, and 55.4% NPV in differentiating between GC and benign gastric diseases.

DISCUSSION

ChE is an enzyme which hydrolyses acetylcholine. There are two types of cholinesterase in the mammalian system, the true cholinesterase or acetylcholinesterase (AChE) and pseudocholinesterase (PChE). PChE is also known as serum cholinesterase or BChE [13]. True cholinesterase is found in the central nervous system, muscles, and in erythrocytes. BChE is an alpha-glycoprotein found in the central and peripheral nervous system, in most tissues, and in liver [14]. Serum ChE level is decreased in several conditions such as acute and chronic liver damage, cirrhosis, inflammation and organophosphate exposure [8,15,16]. Therefore, liver diseases, severe infection, and organophosphorus poisoning were excluded in this study.

There is growing evidence suggesting that ChE is involved in the regulation of cell proliferation, apoptosis, differentiation, and cell-cell interaction [17]. The non-classical roles of ChE have been implicated in modulating cancer growth [18]. Reduced circulating levels of ChE as compared with normal controls were observed in many malignancies, such as colorectal, pancreatic, bladder and prostate cancers [5,11,19-23]. Although the involvement of ChE in tumorigenesis remains unclear, findings indicated that ChE was capable of reducing cell differentiation and inhibiting signal transduction via PI3K/Akt pathway [24,25]. Another study indicated that decreased expression of the 55 kDa ChE protein might contribute to tumorigenesis [26]. Gu et al. found that the serum ChE activity in the GC group was significantly lower than that in the non-malignant tumor group [12]. Our results also demonstrated significantly lower ChE level in GC than in benign gastric diseases, which is consistent with the findings of Gu et al. However, our study is different from theirs in three aspects. First, the control group in our study includes patients with benign gastric diseases such as gastritis and gastric polyps, while the control group in their study includes patients with non-malignant tumors; Second, the GC group in our study is subdivided into four groups according to different TNM stages, while the GC group in their study is not subdivided. We found that with advancement in the clinical staging, serum ChE level decreased gradually, which was significantly lower in patients with distant metastasis than in patients in early stages. Furthermore, we compared TNM Stage I GC with benign gastric diseases and found that ChE level of Stage I GC group was significantly lower than that of benign disease group, indicating that ChE might differentiate between benign gastric diseases and the early stages of GC. Third, our study focused on the role of ChE in differential diagnosis between gastric cancer and benign gastric diseases. To further evaluate the diagnostic value of ChE in differentiating between GC and benign gastric diseases, ROC curves for ChE, CEA, and CA19-9 were generated. Results showed that ChE had the highest AUC (0.819), while CEA and CA19-9 had a low AUC (0.564 and 0.510, respectively). With the optimal cutoff value of 5,969.00 U/L, ChE produced 62.1% sensitivity, 91.2% specificity, 93.2% PPV, and 55.4% NPV, indicating that ChE might become a suitable biomarker for differentiating between GC and benign gastric diseases. Some studies reported that CEA and CA19-9 were useful markers for surveilling reoccurrence, metastasis, effectiveness of therapy and for prediction of GC [27,28]. Meanwhile, other studies found that these markers were increased in non-malignant diseases including gastritis, duodenitis, esophagitis, diverticulitis and peptic ulcer [4,29]. Multiple studies also suggested that CA19-9 and CEA were neither reliable nor accurate markers for the diagnosis of GC. Our results are in accordance with the previous studies [30-34]. The study has some limitations which are mainly inherent to its retrospective nature. For instance, male to female ratio was unequal between the two groups. Patients with GC were not stratified by different variables. The results need to be further investigated by large-scale, randomized and prospective trials.

CONCLUSION

Serum ChE level is identified as a potential simple, rapid, convenient, non-invasive and inexpensive biomarker for differentiating between GC and benign gastric diseases. This will help physicians predict the probability of GC and determine whether further invasive examinations should be performed.

Source of Funds:
This study was supported by grants from the Shandong Province Science and Technology Development Plan of Traditional Chinese Medicine (No. 2019-0313).

Declaration of Interest:
The authors declare that they have no conflicts of interest.

References:

1. Han S, Park S, An J, et al. HER2 as a potential biomarker of lymph node metastasis in undifferentiated early gastric cancer. Sci Rep 2020;10:5270 (PMID: 32210254).

2. Tang S, Cheng J, Yao Y, et al. Combination of Four Serum Exosomal MiRNAs as Novel Diagnostic Biomarkers for Early-Stage Gastric Cancer. Front Genet 2020;11:237 (PMID: 32256526).

3. Jun JK, Choi KS, Lee HY, et al. Effectiveness of the Korean National Cancer Screening Program in Reducing Gastric Cancer Mortality. Gastroenterology 2017;152:1319-28 (PMID: 28147224).

4. Kahtan Al-Bayaty M, Abdul-Rudha Abass S, Faraj Al-Marjani M. E-Cadherin Protein as a Potential Marker for Gastric Cancer and Its Association with Helicobacter Pylori- Induced Gastritis and Gastric Ulcer. Rep Biochem Mol Biol 2019;8:269-77 (PMID: 32274399).

5. Mitsunaga S, Kinoshita T, Hasebe T, et al. Low serum level of cholinesterase at recurrence of pancreatic cancer is a poor prognostic factor and relates to systemic disorder and nerve plexus invasion. Pancreas 2008;36:241-8 (PMID: 18362836).

6. Nair KK, Pramod GV, Chaudhuri K, Ashok L. Estimation of Serum Butyryl Cholinesterase in Patients with Oral Squamous Cell Carcinoma: A Cross-Sectional Study. J Clin Diagn Res 2017;11:ZC59-62 (PMID: 28893045).

7. Mikecin L, Krizmaric M, Stepan GJ, et al. Pseudocholinesterase activity in cerebrospinal fluid as a biomarker of solid central nervous system tumors in children. Croat Med J 2013;54:429-35 (PMID: 24170721).

8. Searles Nielsen S, McKean-Cowdin R, Farin FM, Holly EA, Preston-Martin S, Mueller BA. Childhood brain tumors, residential insecticide exposure, and pesticide metabolism genes. Environ Health Perspect 2010;118:144-9 (PMID: 20056567).

9. How V, Hashim Z, Ismail P, Md Said S, Omar D, Bahri Mohd Tamrin S. Exploring cancer development in adulthood: cholinesterase depression and genotoxic effect from chronic exposure to organophosphate pesticides among rural farm children. J Agromedicine 2014;19:35-43 (PMID: 24417530).

10. Kimura S, Soria F, D'Andrea D, et al. Prognostic Value of Serum Cholinesterase in Non-muscle-invasive Bladder Cancer. Clin Genitourin Cancer 2018;16:e1123-32 (PMID: 30061034).

11. Coulter DW, Boettner AD, Kortylewicz ZP, et al. Butyrylcholinesterase as a Blood Biomarker in Neuroblastoma. J Pediatr Hematol Oncol 2017;39:272-81 (PMID: 28375942).

12. Gu SZ, Zhao XH, Quan P, Li SB, Pan BR. Alterations of serum cholinesterase in patients with gastric cancer. World J Gastroenterol 2005;11:4604-6 (PMID: 16052698).

13. Patocka J, Kuca K, Jun D. Acetylcholinesterase and butyrylcholinesterase--important enzymes of human body. Acta Medica (Hradec Kralove) 2004;47:215-28 (PMID: 15841900).

14. Kumar R, Razab S, Prabhu K, Ray S, Prakash B. Serum butyrylcholinesterase and zinc in breast cancer. J Cancer Res Ther 2017;13:367-70 (PMID: 28643762).

15. Lampón N, Hermida-Cadahia EF, Riveiro A, Tutor JC. Association between butyrylcholinesterase activity and low-grade systemic inflammation. Ann Hepatol 2012;11:356-63 (PMID: 22481455).

16. Eskenazi B, Marks AR, Bradman A, et al. Organophosphate pesticide exposure and neurodevelopment in young Mexican-American children. Environ Health Perspect 2007;115:792-8 (PMID: 17520070).

17. Lazarevic-Pasti T, Leskovac A, Momic T, Petrovic S, Vasic V. Modulators of Acetylcholinesterase Activity: From Alzheimer's Disease to Anti-Cancer Drugs. Curr Med Chem 2017;24:3283-309 (PMID: 28685687).

18. Soreq H, Seidman S. Acetylcholinesterase--new roles for an old actor. Nat Rev Neurosci 2001;2:294-302 (PMID: 11283752).

19. D'Andrea D, Soria F, Abufaraj M, et al. Clinical value of cholinesterase in the prediction of biochemical recurrence after radical prostatectomy. Urol Oncol 2018;36:527-8 (PMID: 30446461).

20. Montenegro MF, Ruiz-Espejo F, Campoy FJ, et al. Acetyl- and butyrylcholinesterase activities decrease in human colon adenocarcinoma. J Mol Neurosci 2006;30:51-4 (PMID: 17192624).

21. Koie T, Ohyama C, Yamamoto H, et al. Significance of preoperative butyrylcholinesterase as an independent predictor of survival in patients with muscle-invasive bladder cancer treated with radical cystectomy. Urol Oncol 2014;32:820-5 (PMID: 24951323).

22. Battisti V, Bagatini MD, Maders LD, et al. Cholinesterase activities and biochemical determinations in patients with prostate cancer: influence of Gleason score, treatment and bone metastasis. Biomed Pharmacother 2012;66:249-55 (PMID: 22560633).

23. Koie T, Ohyama C, Hatakeyama S, et al. Significance of preoperative butyrylcholinesterase as an independent predictor of biochemical recurrence-free survival in patients with prostate cancer treated with radical prostatectomy. Int J Clin Oncol 2016;21:379-83 (PMID: 26223693).

24. Xiang AC, Xie J, Zhang XJ. Acetylcholinesterase in intestinal cell differentiation involves G2/M cell cycle arrest. Cell Mol Life Sci 2008;65:1768-79 (PMID: 18470725).

25. Bleau AM, Hambardzumyan D, Ozawa T, et al. PTEN/PI3K/Akt pathway regulates the side population phenotype and ABCG2 activity in glioma tumor stem-like cells. Cell Stem Cell 2009;4:226-35 (PMID: 19265662).

26. Xie J, Jiang H, Wan YH, et al. Induction of a 55 kDa acetylcholinesterase protein during apoptosis and its negative regulation by the Akt pathway. J Mol Cell Biol 2011;3:250-9 (PMID: 21377978).

27. Feng F, Tian Y, Xu G, et al. Diagnostic and prognostic value of CEA, CA19-9, AFP and CA125 for early gastric cancer. BMC Cancer 2017;17:737 (PMID: 29121872).

28. Tong W, Ye F, He L, et al. Serum biomarker panels for diagnosis of gastric cancer. Onco Targets Ther 2016;9:2455-63 (PMID: 27217769).

29. An X, Ding PR, Xiang XJ, et al. Carcinoembryonic antigen surge in metastatic colorectal cancer patients responding to irinotecan combination chemotherapy. Biomarkers 2010;15:243-8 (PMID: 20121626).

30. Zhou YC, Zhao HJ, Shen LZ. Preoperative serum CEA and CA19-9 in gastric cancer--a single tertiary hospital study of 1,075 cases. Asian Pac J Cancer Prev 2015;16:2685-91 (PMID: 25854347).

31. Shen M, Wang H, Wei K, Zhang J, You C. Five common tumor biomarkers and CEA for diagnosing early gastric cancer: A protocol for a network meta-analysis of diagnostic test accuracy. Medicine (Baltimore) 2018;97:e0577 (PMID: 29742692).

32. Liang Y, Wang W, Fang C, et al. Clinical significance and diagnostic value of serum CEA, CA19-9 and CA72-4 in patients with gastric cancer. Oncotarget 2016;7:49565-73 (PMID: 27385101).

33. Wada N, Kurokawa Y, Miyazaki Y, et al. The characteristics of the serum carcinoembryonic antigen and carbohydrate antigen 19-9 levels in gastric cancer cases. Surg Today 2017;47:227-32 (PMID: 27566604).

34. Yu J, Zheng W. An Alternative Method for Screening Gastric Cancer Based on Serum Levels of CEA, CA19-9, and CA72-4. J Gastrointest Cancer 2018;49:57-62 (PMID: 28028765).