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Benefit of Serum-Thymidine Kinase 1 Concentration for Risk Assessment from Gastric Neoplasms Progression to Carcinomas: A Systematic Review and Meta-analysis

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Keywords:

Serum thymidine kinase 1 concentration (STK1p); Gastric carcinoma(GC); Meta-analysis; Neoplasms; Tumor-free; Chicken anti-human TK1 polyclonal antibodies (TK1-IgY-pAb)

1. Abstract

1.1. Background: Human Thymidine kinase 1 (hTK1), a key enzyme involved in the DNA synthesis during S-phase of the cell cycle and upregulation of cell proliferation, thus it is reliable tumor proliferating biomarker for assessment of tumor proliferation rate in serum and in tissue in oncology. This meta-analysis is investigation whether the serum TK1 concentration（STK1p）based on hTK1-IgY-polyclonal-antibody can provide a benefit for risk assessment from gastric neoplasm progression to gastric carcinoma (GC) as well as for evaluation of treatment effect in GC.

1.2. Methods: Relevant studies were identified from the following electronic databases: PubMed, Embase, Chinese National Knowledge Infrastructure, Wanfang, the Chongqing VIP Chinese Science and Technology Periodical Database and Chinese Biomedical Literature Database from May 1, 2008, until November 30, 2021. Study quality was evaluated by the modified Newcastle-Ottawa Scale. Pooled estimates of weighted mean difference (MD), sensitivity analyses and publication bias were evaluated using Review manager and STATA software. RESULTS: Twenty-seven studies included to 1,909 GCs and 1,229 neoplasms (superficial gastritis, chronic gastritis, atrophic and gastric ulcers) and 2,260 tumor-frees. The results showed that STK1p levels increased significantly in the following manner (P<.0.006): tumor-free < superficial gastritis < chronic gastritis < atrophic gastritis < gastric ulcer < GC. The STK1p value of the GCs one-month-post-surgery decline significantly by 66% compared to pre-surgery.

1.3. Conclusion: STK1p value has the potential to be an early risk warning indicator for early gastric neoplasms progression to GCs and to be a helpful index for monitoring the response to surgery.

1.4. Core Tip: In spite of improvements in diagnosis and treatment the long-term survival rate for a large number of GCs is still dismal. Hence, it is important to explore serum biomarkers for early prediction of risk gastric neoplasms into GCs. In this meta-analysis, the STK1p as a prognostic biomarker was investigated showed significantly higher in GCs compere to different neoplasm and tumor-free people and was significantly reduced one-month post-surgery. It demonstrates that STK1p as tumor proliferating serum-biomarker, can be not only used for early risk gastric neoplasm progression and evaluation of treatment effect in GC patients, but also for a variety of other tumor types in clinical setting.

2. Introduction

It is reported that, in 2020, there were 1,089,103 new cases of gastric carcinomas (GCs) worldwide, with 768,793 of death [1]. GC is the fifth most common malignant neoplasm in the world and the third most common cause of cancer-related death in China [2]. Ad-

vanced gastric carcinoma is associated with poor outcomes with a 5-year survival rate of only 30%. In areas with high incidence of gastric carcinoma, gastroscopy is recommended for individuals over the age of 40. Some are still in advanced diagnosis [3]. When detection of early GCs and treatment in time the survival can be improved up to 90% [4]. Therefore, an in-depth understanding of the pathogenesis of GCs and exploration of highly sensitive and specific early diagnostic approaches, offering patients a better chance of early treatment and cure, are very crucial [5]. The gastric pathological lesions include non-neoplasms, neoplasms and GCs The gastric neoplasms are a higher risk for progression into GCs which is one of leading cause of death [6]. The process of precancerous condition from gene mutations in normal person's cell to abnormal person's cell proliferation will take around 10–30 years, before finally becoming a malignant tumour [7]. Similarly, before the occurrence of GCs, a gradual and prolonged precancerous process takes place, consisting of groups of neoplasms with sequential pathogenesis stages: superficial gastritis (SG) → chronic gastritis (CG) → atrophic gastritis (AG) → gastric ulcer (GU), and finally intraepithelial neoplasia and invasive GC [8-10]. The non-neoplasms with familial adenomatous polyposis (FAP) are considered as a favourable prognosis, a few deaths occur [11], and however, about 21% of non-invasive neoplasms may progress to invasive carcinomas [12]. It is known that cancer is groups of uncontrolled, cell proliferative, and chronic diseases [7]. Thus, early detection of gastric neoplasms through appropriate optimal biomarkers combined with endoscopic images and follow-up individual treatments are important for good outcomes. There are series of growth factors, which can be associated with clinical presentation of early neoplasms process in GCs. However, none of the growth factors, such as HGF, VEGF, FGF, and IGF-1, insulin-like 1 growth factor and granulocyte-colony stimulating factor (G-CSF), are suitable as diagnostic biomarkers for detecting or differentiating different types of gastric malignancies [13]. Thymidine kinase 1 (TK1) is a key enzyme involved in the pyrimidine salvage pathway playing an important role in DNA synthesis during S-phase of the cell cycle [7,14-17]. The TK1 upregulation expression is highly dependent on tumor cell proliferation [7,15,17- 20] and can be used for assessment of tumor cell proliferation rate by serological methods, as well as histochemical staining in clinical setting [7]. Although the TK1 concentration in serum (STK1p) is low, a reliable quantitation of STK1p with high sensitivity and specificity based on chicken anti-human TK1-polyclonal-antibody (TK1-IgY-pAb) [18] has been achieved by using a commercial enhanced chemiluminescence dot blot immunoassay kit (ECL-dot blot, Sino-Swed TongKang Biotech Ltd Ltd., Shenzhen, China). The STK1p level correlates significantly to tumor growth rate and increases to different levels in patients with malignancies depending on growth rate, tumor types, stages and individual situation. The STK1p level has also been reviewed for early tumor risk progression in health screening [19,20], monitoring the effect of therapies, relapse and survival in which not only haematological tumours, but also solid tumours [7], including GCs [21,22]. Meta-analyses of lung [23] breast [24], hepatocellular [25], and colorectal cancers [26] conformed that the STK1p increased significantly from tumor-free to benign/precancerous and then carcinomas. However, the variations of the STK1p among neoplasms in the process to GCs formation still remained unclear. So far, there are a number of publications using STK1p to monitor the treatment of GCs based on the ECL-dot blot. However, most of the STK1p publications are based on a limited number of cases, which may reduce the reliability of the conclusions. This meta-analysis study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Our hypothesis is the meta-analysis of STK1p based on TK1-IgY-pAb shall provide benefit of for Risk Assessment from Gastric Neoplasm Progression to Carcinoma as well as for evaluation of treatment effect in GC patients.

3. Materials and Methods

3.1. Literature Search

A thorough search of relevant articles was performed from PubMed, Embase, Chinese National Knowledge Infrastructure, Wanfang, the Chongqing VIP Chinese Science and Technology Periodical Database and Chinese Biomedical Literature Database from May 1, 2008, until November 30, 2021. The following medical subject headings terms were used to search: "Thymidine kinase 1" or "TK1"; "gastric" or "gastric polyps" or "gastrointestinal" or "stomach"; ''tumor'' or "carcinoma" or "neoplasm" or "malignancy". The search was limited to human studies, but not to language.

3.2. Inclusion and Exclusion Criteria

The studies were reviewed, screened, and selected by two independent reviewers strictly following the inclusion and exclusion criteria. The inclusion criteria include: (1) STK1p was analysed by the ECL dot blot assay based on the chicken anti-human TK1 polyclonal antibodies (TK1-IgY-pAb) [18]; (2) the kit used in the study was manufactured by Sino-Swed TongKang Biotech Ltd., Shenzhen, China; (3) the diagnosis of tumor-free, gastric neoplasms and GCs follows the international standard test; (5) control groups were included in the study. The exclusion criteria were: (1) insufficient data; (2) immunohistochemistry of TK1 and TK activity studies; (3) studies containing unqualified data; (4) review articles.

3.3. Data Extraction

The quality of studies was assessed using the Newcastle-Ottawa Scale (NOS) by two reviewers independently. Studies with NOS scores greater than 5 were included in this meta-analysis. The full text and the additional information of each study were carefully reviewed. After that, the following data were extracted from each study: first author's name, publication year, article's title, published journal, study population characteristics, and relevant data for meta-analysis. The meta-analysis followed the PRISMA guidelines.

3.4. Statistical Methods

Review Manager 5.4 statistical software provided by Networks of Cochrane Review Groups was used to examine the heterogeneity of the literatures and calculate the weighted mean difference (MD) and 95% confidence interval (CI). As described in previous study [26], according to the test results, the fixed-effects model was used when the I2 was lower than 50% and the P value of the heterogeneity was >0.05. Otherwise, we used the random-effects model to calculate. Moreover, funnel plots were used to evaluate the sensitivity. Finally, Egger's tests were conducted with STATA version 12.0 software (College Station, TX: Stata Corp LP) to examine publication bias with the significance level. The 2-tailed was used for the comparison of STK1p values among the different groups (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). The $P<0.05$ was considered as statistically significant difference.

4. Results

4.1. Literature Search and Study Characteristics

Figure 1 illustrates the process of article retrieval and study selection. Initially, 139 publications were identified from various databases. After titles and abstracts were reviewed, 68 articles were remained for full-text review since 71 articles were excluded due to unrelated to the research topic. Then, 41 of the 68 articles were further excluded: 22 articles because the experimental methods failed to meet the inclusion criteria, 15 articles because they lacked sufficient data, and 4 articles because they were review papers. Finally, 27 articles were eligible and included in the final meta-analysis [27-53]. The main clinical features of the included studies were extracted and listed in Table 1. A total of 1,909 GC patients, 1,229 neoplasms (superficial gastritis, chronic gastritis, atrophic gastritis, and gastric ulcer) patients and 2,260 tumor-free persons from 27 studies were included in our meta-analysis. All GC patients were confirmed by pathological examination. After surgery the STK1p values of 251 patients were followed up for one month.

Table 1: Summary of clinical data from each included publication

Author and issuing time	Location	*Tumor-free (n)	Neoplasm (n)	GCS (n)	M (n)	F (n)	Age (years)	GCS TNM	Clinical stage (n)				Surgery treatment	
									I	II	III	IV	Pre- (n)	Post- (n)
Chen Y et al., 2010[27]	East China	451	-	69	52	17	-	Y	3	4	4	8	32	32
Cheng Q et al., 2011[28]	North China	48	47	32	21	11	-	N	-	-	-	-	-	-
Cheng XH et al., 2015[29]	East China	-	-	60	48	12	-	N	-	-	-	-	60	60
Fang AN., 2017[30]	East China	32	-	23	-	-	40-89	N	-	-	-	-	-	-
Fang GZ et al., 2016[31]	North China	160	130	20	11	9	-	N	-	-	-	-	-	-
Fang H et al., 2014[32]	East China	70	32	32	20	12	48-79	N	-	-	-	-	32	32
Gao W et al., 2019[33]	North China	50	100	50	28	22	43-69	N	-	-	-	-	-	-
Gu GD., 2009[34]	East China	30	37	112	59	53	34-73	N	-	-	-	-	-	-
Guo L et al., 2008[35]	East China	38	35	102	73	29	29-77	N	-	-	-	-	28	28
Hu X et al., 2021[36]	East China	63	64	115	62	53	50-68	Y	21	39	36	19		
Hu ZS et al., 2015[37]	East China	42	-	60	32	28	50-78	N	-	-	-	-	-	-
Jia B et al., 2018[38]	North China	-	75	45	24	21	40-70	Y	4	15	22	4	-	-
Jiang JY et al., 2013[39]	Central China	35	37	34	23	11	40-65	N	-	-	-	-	-	-
Lin L et al., 2014[40]	South China	35	-	68	42	26	20-63	Y	14	20	18	16	43	43
Liu X et al., 2015[41]	South China	600	137	68	-	-	22-67	N	-	-	-	-	-	-
Li WB et al., 2018[42]	East China	80	72	106	74	32	36-84	N	-	-	-	-	-	-
Li ZS et al., 2010[43]	North China	95	-	39	-	-	-	Y	-	-	12	27	-	-
Ning SF et al., 2018[44]	South China	75	-	169	-	-	-	N	-	-	-	-	-	-
Shen J et al., 2011[45]	East China	60	50	32	24	11	28-75	N	-	-	-	-	-	-
Shen LS et al., 2011[46]	East China	32	-	59	-	-	40-80	N	-	-	-	-	-	-
Wang CM et al., 2013[47]	East China	76	70	204	146	58	29-77	N	-	-	-	-	56	56

Wang YF et al., 2014[48]	East China	30	30	100	-	-	30-72	N	-	-	-	-	-	-
Yan B et al., 2016[49]	East China	0	67	38	20	18	45-72	N	-	-	-	-	-	-
Zhang XY et al., 2012(50)	North West	45	45	46	27	19	31-66	N	-	-	-	-	-	-
Zhang YF et al., 2015[51]	East China	35	35	60	-	-	-	N	-	-	-	-	-	-
Zhao F et al., 2016[52]	East China	28	66	46	26	18	-	N	-	-	-	-	-	-
Zhang X., 2021[53]	North China	50	100	120	77	43	50-72	N	-	-	-	-	-	-
Total number		**2,260**	**1,229**	**1,909**	**889**	**503**	**-**	**-**	**42**	**78**	**92**	**74**	**251**	**251**

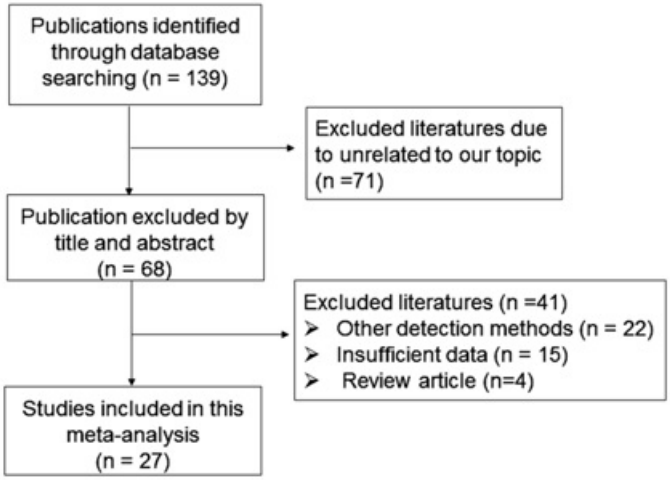
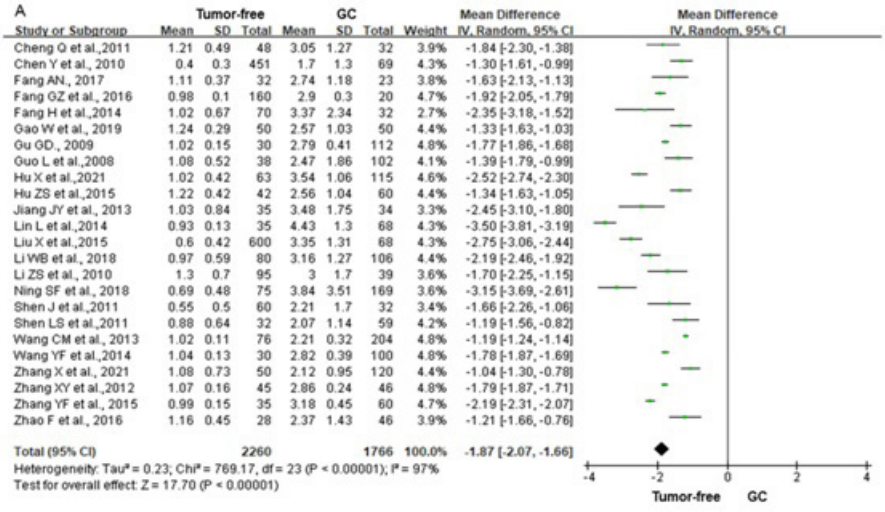


Figure 1. Article retrieval and study selection.

4.2. STK1p of Tumor-Free Persons Versus GC Patients

Of the 27 studies collected in this study, 24 studies were used for comparing between tumor-free group and GC patient group (Figure. 2A and 3A). The number of cases of tumor-free group and GC group were 2,260 and 1,766, respectively. There were significant differences between the two groups after heterogeneity test ($P<0.00001$, $i^2=97\%$). Therefore, random effects model was used to carry out the effect of the merger. The results showed that the difference between the two groups was statistically significant (MD=-1.87, 95% CI (-2.07~-1.66), $P<0.00001$). Thus, the level of STK1p of the GC patients was significantly higher than that of the tumor-free persons.



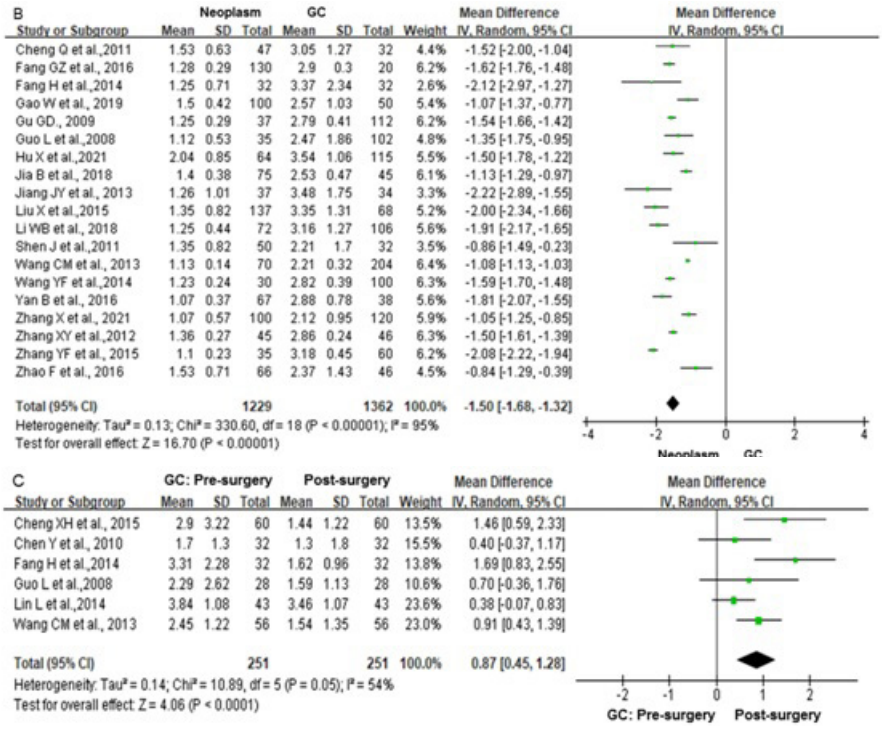


Figure 2A-C. A. Individual STK1p data of tumor-free and GC group; **B.** Individual STK1p data of neoplasm and GC group; **C.** Individual STK1p data of pre- and post-surgery group.

4.3. STK1p of Neoplasm Patients Versus GC Patients

Of the 27 studies used in this meta-study, 19 studies were used when compare the neoplasm patients with the GC patients (Figure 2B and 3A). The number of cases of neoplasms group and GC group were 1,229 and 1,362, respectively. There were significant differences between the groups after heterogeneity test (P<0.00001, i²=95%). Therefore, random effects model was used to carry out the effect of the merger. The results showed that the difference between the two groups was statistically significant (MD=-1.50, 95%CI (-1.68~-1.32), p<0.00001). Therefore, the level of STK1p of the GC patients was significantly higher than that of the neoplasms.

STK1p values from tumor-free group, different neoplasm patients to primary GCS Six studies of pathological different neoplasms and GC patients are summarized in figure 3B. The STK1p level of the GC patients was significantly higher than the tumor -free controls and the neoplasm patients. The STK1p level increased significantly in the following manner: tumor-free < superficial gastritis (SG) < chronic gastritis (CG) <atrophic gastritis (AG) < gastric ulcers (GU) < GCs.

4.4. STK1p Values Pre- and Post-Surgery

The STK1p values of 251 GC patients pre- and one-month post-surgery were compared in 6 studies. The GC patients were mainly from primary tumours (clinical stage I-III and part were from clinical stage IV). The forest plots of the 6 studies together are shown in figure 2C. By heterogeneity testing, the results showed a P-value of 0.05. The i2 was 54%. Therefore, the random effects model was used to find out the effect of the merger, showing statistical significance (MD=0.87, 95%CI (0.45-1.28), P <0.0001). The level of STK1p of the patient's post-surgery were significantly lower (1.83±1.46 pM) compare to pre-surgery patients (2.79±2.23 pM) (Figure 3C).

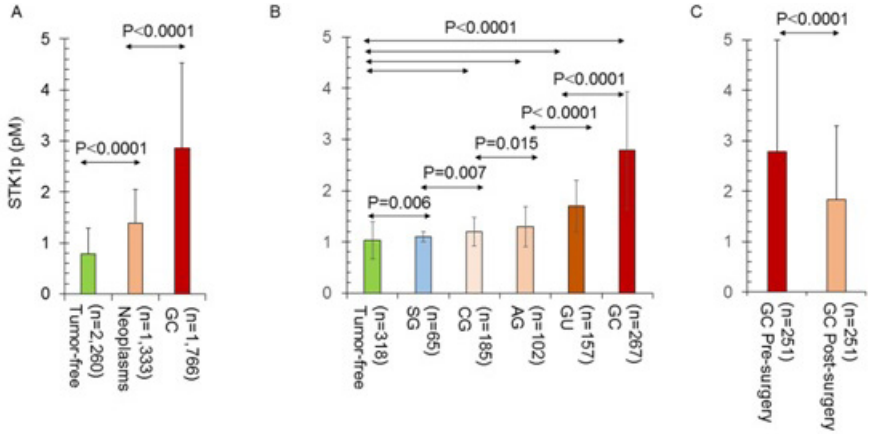


Figure: **3A-C.** Comparative analysis (2-tailed). **A**: STK1p values of tumor-free and neoplasm and GC group; **B.** STK1p values of tumor-free, neoplasm including to superficial gastritis (SG), chronic gastritis (CG) and atrophic gastritis (AG), gastritis ulcer (GU) and GC group; **C.** STK1p values of GC pre- and post-surgery group.

4.5. Funnel Plots and Egger's Test

Funnel plots were conducted to evaluate the degree of bias in a graphic way. Figures 4A-C show a high degree of symmetry in the three groups studied (A. tumor-free versus GC group; B. neoplasm versus GC group; C. GC versus pre- and post-GC surgery group.), indicate low degree of bias. Running the Egger's test further confirms the low degree of bias (all P-values >0.05) (**Table 3**).

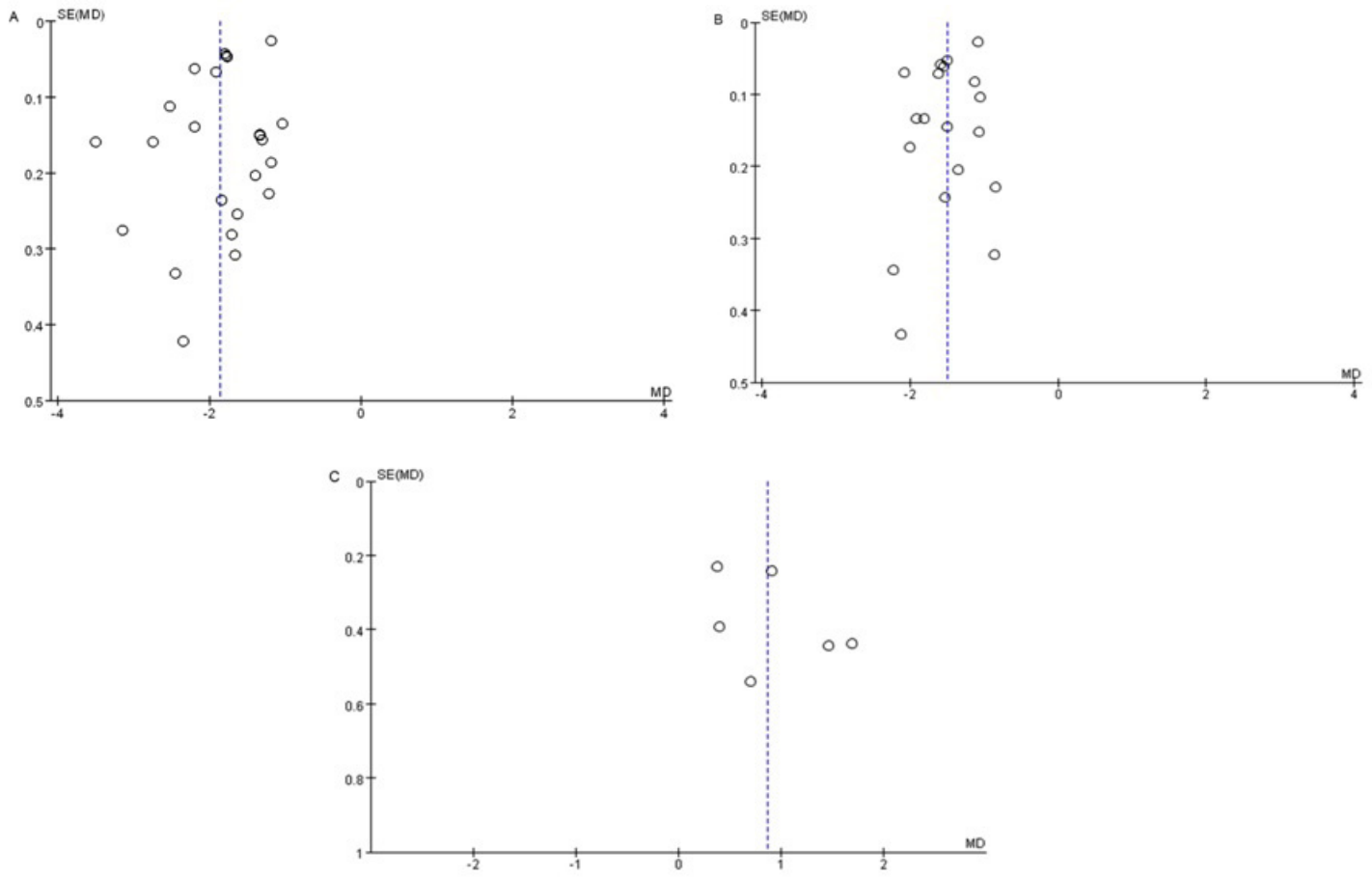


Figure 4A-C. Funnel plot. **A**. Funnel plot of tumor-free versus GCs group; **B.** Funnel plot of neoplasm and GCs group; **C.** Funnel plot of GCs pre- and post-surgery group. *MD: mean difference. *SE: standard error.

Table 2: Literature quality evaluation by Newcastle-Ottawa Scale Document Quality Assessment Scale (NOS).

Author and issuing time	Selection				Comparability	Exposure		
	The definition adequate	Representativeness of the cases	Section Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design and analysis	Ascertainment of exposure	Exposure same method of ascertainment for cases and controls	Non-response rate
Chen Y et al., 2010[27]	*	*	*	*	*	*	*	*
Cheng Q et al., 2011[28]	*	*	*	*	*	*	*	*
Cheng XH et al., 2015[29]	*	*	*	*	*	*	*	*
Fang AN., 2017[30]	*	*	*	*	*	*	*	*
Fang GZ et al., 2016[31]	*	*	*	*	**	*	*	*
Fang H et al., 2014[32]	*	*	*	*	**	*	*	*

Gao W et al., 2019[33]	*	*	*	*	**	*	*	*
Gu GD., 2009[34]	*	*	*	*	*	*	*	*
Guo L et al., 2008[35]	*	*	*	*	*	*	*	*
Hu X et al., 2021[36]	*	*	*	*	**	*	*	*
Hu ZS et al., 2015[37]	*	*	*	*	**	*	*	*
Jia B et al., 2018[38]	*	*	*	*	**	*	*	*
Jiang JY et al., 2013[39]	*	*	*	*	**	*	*	*
Lin L et al., 2014[40]	*	*	*	*	**	*	*	
Liu X et al., 2015[41]	*	*	*	*	*	*	*	*
Li WB et al., 2018[42]	*	*	*	*	**	*	*	*
Li ZS et al., 2010[43]	*	*	*	*	*	*	*	*
Ning SF et al., 2018[44]	*	*	*	*	**	*	*	*
Shen J et al., 2011[45]	*	*	*	*	**	*	*	*
Shen LS et al., 2011[46]	*	*	*	*	*	*	*	*
Wang CM et al., 2013[47]	*	*	*	*	*	*	*	*
Wang YF et al., 2014[48]	*	*	*	*	**	*	*	*
Yan B et al., 2016[49]	*	*			**	*	*	*
Zhang XY et al., 2012(50)	*	*	*	*	**	*	*	*
Zhang YF et al., 2015[51]	*	*	*	*	**	*	*	*
Zhao F et al., 2016[52]	*	*	*	*	**	*	*	*
Zhang X., 2021[53]	*	*	*	*	*	*	*	*

Note: A study can be awarded a maximum of one star for each item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability. See more details from http://www.ohri.ca/programs/clinical-epidemiology/oxford.asp.

Table 3: Egger's tests for the assessment of publication bias.

	Coefficient	**Standard error**	**T value**	**p>|t|**	**95% CI**
Tumor-free vs. GCS					
Slope	-1.40702	0.12552	-11.21	0	-1.66885 to 1.14519
Bias	-3.45364	1.66470	-2.07	0.051	-6.92615 to 0.01887
Neoplasm vs. GCS					
Slope	-1.20004	0.12379	-9.69	0	-1.46390 to 0.93618
Bias	-2.89110	1.64432	-1.76	0.099	-6.39589 to 0.61369
Pre- vs. Post-surgery					
Slope	0.13138	0.61529	0.21	0.841	-1.57695 to 1.83970
Bias	2.09453	1.87538	1.12	0.327	-3.11236 to 7.30141

vs.=versus

5. Discussion

GC is one of the leading causes of cancer deaths with high heterogeneity and interrelations, involving metabolic, environmental, and infective and inflammations [2]. In spite of the improvements in diagnosis and treatment, currently, the long-term survival rate for a large number of GC patients is still dismal [1]. So, it is crucial and urgent to explore more sensitive serum biomarkers for early prediction of risk of GCs, especially in gastric neoplasms (precancerous) progression to GCs. Serum biomarkers related to tumor cell proliferation is clinically valuable because they could improve early detection of tumours and monitoring tumour treatment [7]. Serum thymidine kinase 1 is one of these proliferation biomarkers and may be used for early risk prediction of GCs and for monitoring the responses of radical surgery in GCs [21]. A meta-analysis is an analytical review of data from several research studies, aiming to combine the results based on a larger number of samples and create a more comprehensive picture of research problems [54]. In the present meta-analysis study, we strictly followed the rules of PRISMA. The STK1p level in GC patients was significantly higher compare to tumor-free persons and patients with neoplasm diseases, being able to distinguish GCs from these groups. These findings suggest that the level of STK1p can be used as an early risk warning indicator for GCs. Similar results were also reported in other studies proving that the level of STK1p measured using TK1-IgY-pAb approach based on an ECL-dot blot assay is a reliable indicator for an early prediction of risk of malignancies in health screening [7,19,20]. The STK1p levels were also closely correlated to sub-groups of neoplasm diseases: tumor-free persons < SG < CG < AG < GU< GC. It implies that the STK1p is a sensitive biomarker measuring the proliferation rate in early risk neoplasms by dynamic monitoring the level of STK1p. In addition, the level of STK1p one month after surgery was significantly lower compared to the STK1p level before radical surgery, indicating that STK1p may be a useful clinical dynamic monitoring index when evaluating the efficacy of surgical treatment in GC patients. This monitoring index corresponds to a half-life of STK1p in GC patients with primary tumors (clinical stage I-III) of about one month, means that if the STK1p value is reduced by about 50% one-month post-surgery, it indicates a successful treatment [21]. It should be noted that extensive open surgery injury might induce a systemic endocrine-metabolic response which is proportional to the severity of the surgical stress, such as activation of immunological, inflammatory, metabolic and endocrine mediators. Li et al. reported that a transient increase of the STK1p value by 100-234% within one week after extensive surgery was found correlated with changes in the blood status (RBC, anemia) and activation of the immunological system in non-small cell lung, esophageal, cardial and gastric carcinoma patients [55]. After one month, the STK1p values decreased by 40-50%, approximately parallel to a half-life of about one month. Thus, it seems that the transient increase in STK1p after extensive open surgery is a result of serious injury of physiological metabolism, stimulating the immune prevention system. Therefore, in respect to extensive open surgery, STK1p should not be used during the first week after the surgery in order to avoid transient non-tumour-related increases in the STK1p value [55,21]. Instead, STK1p should be determined just pre-and one-month post- surgery of primary tumors to receive the full benefits of this biomarker in clinical use. However, it should be noted that the half-life of STK1p after treatment of primary tumors may be different depending on the types of treatments, for example extensive open surgery, minimally invasive surgery or chemotherapy, and also depending on the types of tumors [55,21]. In a previous study on primary bladder carcinoma patients, the half-life of STK1p was six days after cystectomy by electro-surgical technique [56]. The STK1p value in patients with non-Hodgkin's lymphoma during the treatment with chemotherapy was also investigated. STK1p increased to 127% during the first few days, and then declines by 79% one month after start of the chemotherapy [57]. Anyhow, the half-life of STK1p is an important tool for monitoring the response to surgery of patients with GC. The half-life index may provide valuable information to the doctor how to assess the patient's treatment effect and give reasonable treatment plan in the future, allowing individual therapy for different carcinomas, avoiding overtreatment or changes of treatment strategy. The elevated levels of STK1p in patients with recurrence after curative surgery therapy also give new options to evaluate the therapy in a short time period. Thus, the half-life index of STK1p may give information that could improve the survival, enhancing the quality of life of the cancer patients. Since the phylogenetic distance between mammals and birds, the birds cause high immune response to mammalian antigens [7,56], the immunoglobulin Y antibodies (IgYs) from the yolk of chicken eggs offer a series of advantages as compared to mammalian immunoglobulin G antibodies (IgGs) [57]. Particular, IgYs have potential to induce antibodies with high specificity and sensitivity [7,57,58]. Our results showed that the sensitivity and specificity of chicken anti-human TK1 polyclonal antibodies (TK1-IgY-pAb) is of 0.80 and 0.997, respectively, with an area under the curve (AUC) in the receiver operation characteristic (ROC) statistically analysis of 0.96 [7,19,20]. This assay is able to measure TK1 in serum down to 0.01 pM with no or very limited risk of unspecific immunoreactions [7,20]. Thus, TK1-IgY-pAb [18,20] are more reliable to measure TK1 in serum as compared to different methods [7]. According to previously published studies, the AUC, sensitivity and specificity of the different TK1 assays are summarized in table 4 [7,19,59-62], showing that the ECL dot blot assay is the most reliable test on the market today (AUC 0.96). Based on the AUC-value from the ROC-analysis the reliability is in the order SSTK Ltd > Arocell AB > O'Neil group> BioVica > Diasorin. Hence, the ECL dot blot assay is the most reliable serum TK1 assay for risk process of early tumorigenesis in

health screening at the present [7] as compared to mAb-TK1 assay kit (Araceli AB and O'Neil group) and TK activity assay kit (Biotical and Diasporic). The STK1p assay is now improved by using recombinant TK1 monoclonal antibodies in an automatic machine, developed by us. In the present meta-analysis study, we focused on STK1p data obtained by a commercial ECL dot blot assay. Publication bias is a major problem in meta-analysis since studies are more likely to be published if their results are "significant" than if their results are negative or inconclusive, which may cause publication bias. Investigating publication bias is necessary because such bias may lead to incorrect conclusions of meta-analysis. Funnel plots are a visual tool for examining publication bias. Asymmetrical funnel plots suggest publication bias may exist in a meta-analysis study. Meanwhile, various statistical tests have also been proposed for publication bias in the funnel plot, such as Egger's regression test. In the absence of publication bias, the P value in Egger's test is expected to be more than 0.05. The present study has no significant selection bias, not only it retains the best quality and excludes separated publication or similar materials, but it is in strict accordance with the inclusion and exclusion criteria of the literature and eliminates incomplete data and designing unqualified research. This study has some limitations: (1) although no significant bias was found, there may be some bias, because of the possible error from original research data; (2) this meta-analyses are based on heterogeneous, small sample size studies. The results of this study cannot be generalized to a large target population similar to the target population in each group of the studies (3) limitations in the assessment of publication bias. The reason is that the subjective influence of the researchers may affect the conclusion [63]. Regarding the limitation, the Egger's test was employed to evaluate the effects of publication bias in order to make up the deficiency [64].

Table 4: Commercial kits for detection of human TK1 concentration in serum and TK activity (STKa) in serum

Serum TK1 assay	AUC	Risk cut-off	Sens.	Spec.	L.h. (+)	References	Manufacturer -website
STK1 conc. ECL Dot Blot Kit. Chicken anti human-TK1 IgY-pAbs	0.96	2.0 (pM)	79.90 %	99.9 %	233.75	Meta-analysis: Tumor-free (n=6,354), 10 types of cancers (n=720) [19]	SSTK Biotech Ltd. China. www.sstkbiosstk.com
STK1 conc. TK1 ELISA Kit. Mouse anti-human-TK1 -mAb	0.9	0.35 (ng/ml)	50 %	98.0 %	nd	Breast cancers (n= 124) [56]	Arocel AB. Sweden, www.arocell.com
STK1 conc. ELISA Kit. Mouse anti-human-TK1 -mAb	0.79	4.9 (nM)	75 %	8 3 . 3 0 %	nd	Lung cancers (n=40). Tumor-free (n=18) [57]	O'Neill KL., USA
STK act. DiviTum Assay Kit.	0.71	80 (U/L)	26.30 %	nd	nd	Breast cancers (n=161). Tumor-free(n=149) [58]	Biovica AB, Sweden www.biovica.com
STK act. DiviTum Assay Kit.	nd	134 (Du/L)	56.30 %	88.4 %	nd	Breast cancers (n=160). Tumor-free (n=120) [59]	Biovica AB, Sweden www.biovica.comn
STK act. Liaison Assay Kit	0.69	8.2 (U/L)	25 %	nd	nd	Breast cancers (n=161). Tumor-free (n=149) [58]	CLIA, Diasorin USA www.diasorin.com

*STK1 conc: human TK1 concentration in serum; *STK act: human TK activity in serum; *sens: Sensitivity; *Spec: Sensitivity; *L.h. (+): Likelihood (+); *AUC: area under the curve; nd: not determined.

6. Future Perspectives

1. TK1 is a proliferating biomarker. A normative STK1p value has been recommended corresponding to investigations of larger data based on 14,960 Chinese people (age 20-79, male 9,586, female 5,374) in a health screening cohort of 42,383 persons [65]. All people associated with tumor diseases were excluded, including diagnosed tumor patients, moderate/severe proliferating diseases, virus-infectious and severe inflammation diseases, obese, un-normal values of blood, urea or faecal tests, but may containing some minor proliferating/chronic/non-tumor diseases. The STK1p mean and median values were of 0.36 and 0.37 pM, respectively, similar to total disease-free STK1p value of 0.38 pM [7]. There was no difference in the mean STK1p value between men and women and gender. However, in the present meta-analysis, the STK1p value of tumor-free persons were more than 2-fold higher (Fig. 3A and B) as compared to the normative STK1p value by Cao [65], may be due to that the donors of the present study only excluded GCs by imaging and infectious diseases, but did not excluded tumor-related proliferating diseases. We strongly suggest that it is necessary to follow our recommend literature [65,7], to set up a normalized STK1p value as control.

2. The relationship between GC and Helicobacter pylori (H. pylori) infection is highly positive, where the GC incidence is high in Eastern countries. The H. pylori is a class of carcinogen which causes chronic atrophic gastritis, gastric intestinal metaplasia, dysplasia and adenocarcinoma [66]. The gastric microbial composition and interaction shifted in SG, AG, IM and GC [67]. The majority of gastric Mucosa-Associated Lymphoid Tissue Lymphomas

(92%) have been shown to be associated with H. pylori infection [68]. In the present meta-analysis, there were no data providing insufficient of H. pylori infection in relation to the early gastric neoplasms process. In the future, we need to cooperate with hospitals to perform prospective individual data meta-analysis on the gastric neoplasms process in relation to STK1p levels and the presence of H. pylori.

3. With the rapid progress of technology, we developed successfully a new generation of TK1 IgY recombinant antibody by using phage display library technology to produce a large amount of TK1 IgY recombinant antibody with high specificity, sensitivity and stability. Additionally, we also set up a full-automatic immunoluminescence instrument to replace the semi-automatic ECL dot blot assay. The clinicians and researchers will be more convenient to use STK1p focusing on early gastric neoplasms progression combined with artificial intelligence (AI) gastroenteroscope technology. It will be great interest for unique characteristics among various pathological neoplasms to improve survival.

7. Conclusion

The present study demonstrated that the level of STK1p in gastric neoplasms progression GC patients was significantly higher than that in the tumor-free persons. The level of STK1p in GC patients decreased significantly one month after surgery. The STK1p detection may have certain clinical value in health screening for an early warning indicator of gastric neoplasms progression into GCs. STK1p may also be a helpful index for monitoring the response to surgery in patients with GC. Further studies with larger sample size to confirm these findings are necessary.

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