EP300 ASSOCIATION WITH GASTROESOPHAGEAL CANCER SURVIVAL: A META-ANALYSIS

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ABSTRACT

Introduction*: Gastroesophageal cancer (GSC) is heavy burden world-wide. In recent decade, lots of genetic/proteomic studies among cancer susceptibility and prognosis has been established. One of the proteins called P300 has been well studied. This meta-analysis was trying to confirm if EP300 could have impact on 5-year overall survival.*

Materials and methods*: Medline and web of knowledge, using the following search terms: "oesophageal" or "esophageal" or "Laryngeal carcinoma" or "Gastric cancer" or "gastroesophageal" and "EP300" or "P300" or "KATB" and "cancer" or "carcinoma" and "survival" or "outcome" or "response rate" . After reviewing, we collected research data from 8 studies, including 1351 GSC cases.*

Results*: In this study, we collected 8 studies with a total of 1,361 cases of GSC subjects. The results showed that P300 positive is overall associated with 5-year survival (OR: 3.01 [95% CI, 2.32-3.90], P<0.001), in subgroup analysis, esophageal cancer subgroup showed no heterogeneity and significantly result in P300 positive and with 5-year survival (OR=3.16, 95%CI [2.14-4.67], P<0.001). However, other cancer type patients showed a high heterogeneity.*

Conclusion*: In this analysis, we found that P300 positive might be a good biomarker for esophageal cancer 5-year overall survival.*

Keywords: *Gastroesophageal cancer, esophageal cancer, gastric cancer, laryngeal carcinoma, EP300, KATB.*

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Introduction

Gastroesophageal cancer (GSC) accounts for about 4% of new cancer diagnoses in the United States annually and 6% of cancer-related deaths[(1)]. More than 50% of GSC patients present with unresectable or metastatic disease, contributing to its dismal overall 5-year survival rate of 14% in the United States[(2)]. The 5-year overall survival (OS) is poor but has improved from 4% (1970s) to 14% currently. After surgery, 5-year OS could be 95%, 50-80%, 30-40%, 10-30% and 10-15% for stage 0, stage 1, stage IIA, stage IIB, and stage III, respectively. For those patients with metastatic site (stage IV), a median survival is less than 1 year. Other risk factors that influence survival includes significant weight loss (10% body mass), lymphatic micro-metastases and dysphagia[(3)].

In recent decade, genetic study among cancer susceptibility and prognosis has been established widely. For cancer risk, ALDH2/ADH1B[(4)], FAT family[(5)], CCND1[(6)], and for survival prognosis, GSTP1, ERCC1(7), VEGF, etc[(8)] gene polymorphism have been found to be related to GSC, including squamous-cell carcinoma and adenocarcinoma. A recent study has found that several gene expression

might relate to lymph node metastasis such as SPANXN5, which ultimately influence overall survival[9].

One of the variations has been well studied called EP300/KATB/p300, P300 proteins worked as a regulator for gene transcription. They activate down-stream pathway as co-activators that can integrate multiple inflammation gene expression[10]. The potential role of tumorigenesis of P300 has been reported in multiple organs including lung, colorectal, breast and prostate, a high level of P300 expression is associated with poorer outcome[10-14].

Compare to those studies developing susceptibility genes, a prognosis protein might be more useful in clinical practice. This meta-analysis aimed to confirm if EP300 could have influence on 5-year overall survival.

Materials and methods

Search strategy and selection criteria

Papers published before July 2019 were identified through a search of Medline and web of knowledge, using the following search terms: ''oesophageal'' or ''esophageal'' or "Laryngeal carcinoma" or "Gastric cancer" or "gastroesophageal" and ''EP300'' or ''P300'' or "KATB" and "cancer" or "carcinoma" and "survival" or "outcome" or "response rate". Two authors "Qi Wang " and "Quan-Li Han" independently reviewed the titles and abstracts. Those candidate articles would be screened in full article, and their reference was also carried out. Articles reporting on EP300 expression in cases of GSC patients were identified. When there were any duplication population published, we will select the most recent publication. Also, there is no dose or arms limitation for the therapy administrated.

For outcome, we extracted those with detailed survival data for EP300 positive and negative subjects. Study design need to have follow-up for at least 5 years to achieve 5 year survival outcome. There were no language, time or geographical restrictions for candidate studies. We excluded reviews as well but will check their references.

Statistical analysis

We were using Revman 5.3 for this meta-analysis, and using I2 for heterogeneity for pooled studies. If the heterogeneity I2 is lower than 50%, it would be considered as an acceptable variety among studies, since then we would use fixed effect model for analysis.

Results

Eight studies[15-22] with a total of 1,361 cases of GSC were identified and these are summarized in Table 1.

Reference	Year	Cancer type	P300 +	P300 -
Lu et al. [15]	2018	ESC	3	12
Wang et al. [16]	2019	ESCC	66	40
Gao et al. [17]	2014	ESCC	26	333
Chen et al. [18]	2012	LSCC	40	40
Liang et al. [19]	2017	ESC	32	33
Li et al. [20]	2011	ESCC	150	90
Zhang et al. [21]	2013	GEJ	72	18
Ying et al. [22]	2010	GC	228	178

Table 1: Study summary of included articles.
ESC: esophageal cancer, ESCC: esophageal squamous cell carcinoma, LSCC: laryngeal squamous cell carcinoma, GC: gastric cancer, GEJ: gastroesophageal junction cancer

Our meta-analysis gave an overall OR: 3.01 [95% CI, 2.32-3.90] for the risk of P300 positive among GSC patients' 5 year overall survival (as shown in Fig 1), without any overall heterogeneity (I2=0) between two subgroups: esophageal squamous cell carcinoma+ esophageal cancer vs laryngeal squamous cell carcinoma+ gastric cancer+ gastroesophageal junction cancer.

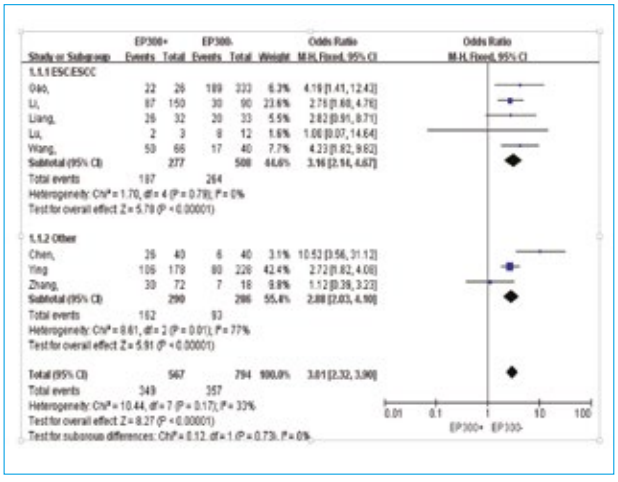

Figure 1: Forest plot of included studies.

In subgroup analysis, there is no heterogeneity in ESC/ESCC (esophageal cancer/esophageal squamous cell carcinoma) subgroup, with a significant association (OR=3.16, 95%CI [2.14-4.67], P<0.001) was found, but a high heterogeneity (I2=77%) was observed in other GSC subgroups, suggesting that there might be some difference in laryngeal squamous cell carcinoma or gastroesophageal junction cancer among P300 expression influence. Also, the funnel plot was shown as Figure 2. The outlier is Chen et al study.

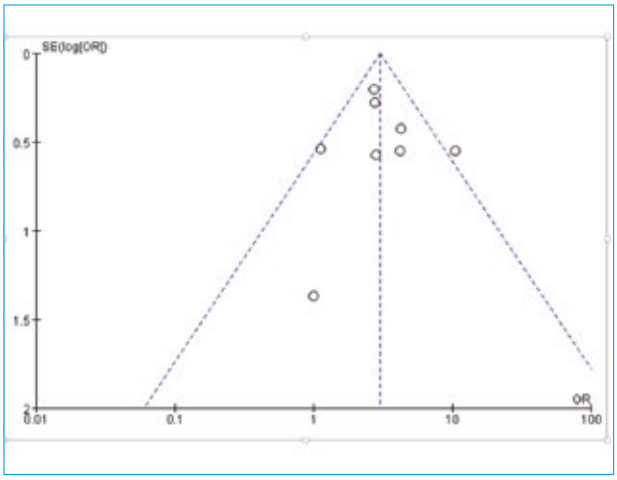

Figure 2: Funnel plot for all studies.

Discussion

This meta-analysis has shown the evidence that EP300 could affect 5 year overall survival among ESC/ESCC, but if this conclusion could extrapolate into all types of GSCs is still remain doubted. In mechanism perspective, EP300 and CBP (cAMP response element binding protein) would activate each other that evolve with other factors to regulate cell-differentiation and signal transduction gene expression. EP300 could acetylate TP53 to response DNA damage where regulates the DNA functions, including binding or transcription. Nevertheless, direct demonstration of the role of EP300 in tumorigenesis by inactivating mutations in human cancers has been lacking.

Nowadays, precision medicine for ESCC treatment has not been established, the intratumorally heterogeneity might be a major issue for this kind of therapy. The robustness of EP300+ in these ESCC/ESC subjects might make this protein a promising biomarker as prognostic factor.

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