**Name of Journal**: *World Journal of Gastroenterology*

**Manuscript NO:** 48947

**Manuscript Type**: REVIEW

**Autoantibodies: Potential clinical applications in early detection of** **esophageal squamous cell carcinoma and esophagogastric junction adenocarcinoma**

Xu YW *et al*. Autoantibodies for ESCC and EGJA

Yi-Wei Xu, Yu-Hui Peng, Li-Yan Xu, Jian-Jun Xie, En-Min Li

**Yi-Wei Xu, Yu-Hui Peng****,** Department of Clinical Laboratory Medicine, Cancer Hospital of Shantou University Medical College, Shantou 515041, Guangdong Province, China

**Yi-Wei Xu, Yu-Hui Peng, Li-Yan Xu, Jian-Jun Xie, En-Min Li,**The Key Laboratory of Molecular Biology for High Cancer Incidence Coastal Chaoshan Area, Shantou University Medical College, Shantou 515041, Guangdong Province, China

**Li-Yan Xu,** Institute of Oncologic Pathology, Shantou University Medical College, Shantou 515041, Guangdong Province, China

**Jian-Jun Xie, En-Min Li,** Department of Biochemistry and Molecular Biology, Shantou University Medical College, Shantou 515041, Guangdong Province, China

**ORCID number:** Yi-Wei Xu (0000-0002-8670-592X); Yu-Hui Peng (0000-0002-1866-4679); Li-Yan Xu (0000-0002-1618-4292); Jian-Jun Xie (0000-0002-5141-5076); En-Min Li (0000-0001-6375-3614).

**Author contributions:** Xu YW contributed to the collection of data and writing the manuscript; Peng YH assisted in collection of data; Xu LY, Xie JJ and Li EM supervised the work and revised the manuscript.

**Supported by** the National Natural Science Foundation of China, No. 31600632; and the Natural Science Foundation of Guangdong Province, No. 2018A030307079.

**Conflict-of-interest statement:** The authors have no conflicts of interest to declare.

**Open-Access:** This article is an open-access article which was selected byan in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Corresponding author:** **En-Min Li, PhD, Professor,** Department of Biochemistry and Molecular Biology, Shantou University Medical College, 22 Xinling Road, Shantou 515041, Guangdong Province, China. [nmli@stu.edu.cn](mailto:nmli@stu.edu.cn)

**Telephone:** +86-754-88900847

**Fax:** +86-754-88900847

**Received:** May 15, 2019

**Peer-review started:** May 15, 2019

**First decision:** July 21, 2019

**Revised:** July 28, 2019

**Accepted:** August 19, 2019

**Article in press:**

**Published online:**

**Abstract**

Esophageal squamous cell carcinoma (ESCC) and esophagogastric junction adenocarcinoma (EGJA) are the two main types of gastrointestinal cancers that pose a huge threat to human health. ESCC remains one of the most common malignant diseases around the world. In contrast to the decreasing prevalence of ESCC, the incidence of EGJA is rising rapidly. Early detection represents one of the most promising ways to improve the prognosis and reduce the mortality of these cancers. Current approaches for early diagnosis mainly depend on invasive and costly endoscopy. Non-invasive biomarkers are in great need to facilitate earlier detection for better clinical management of patients. Tumor-associated (TA) autoantibodies can be detected at an early stage before manifestations of clinical signs of tumorigenesis, making them promising biomarkers for early detection and monitoring of ESCC and EGJA. In this review, we summarize recent insights into the identification and validation of TA autoantibodies for the early detection of ESCC and EGJA, and discuss the challenges remaining for clinical validation.

**Key words:** Esophageal squamous cell carcinoma; Esophagogastric junction adenocarcinoma; Biomarker; Autoantibody; Diagnosis

© **The Author(s) 2019**. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** The current protocol for early diagnosis of esophageal squamous cell carcinoma and esophagogastric junction adenocarcinoma is endoscopic imaging followed by biopsy confirmation. However, the invasive nature of the procedure and high cost of endoscopy limit it as a tool for screening the general population. This review highlights autoantibodies as non-invasive biomarkers in the early detection of esophageal squamous cell carcinoma and esophagogastric junction adenocarcinoma.

Xu YW, Peng YH, Xu LY, Xie JJ, Li EM. Autoantibodies: Potential clinical applications in early detection of esophageal squamous cell carcinoma and esophagogastric junction adenocarcinoma. *World J Gastroenterol* 2019; In press

**INTRODUCTION**

Esophageal cancer is the eighth leading malignant disease and the sixth most common cause of cancer-related death worldwide, and therefore represents a serious health problem globally[[1](#_ENREF_1)]. Esophageal cancer is mainly composed of two epidemiologically and histopathologically distinct sub-types designated as esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma. In China, esophageal cancer is the third leading cause of cancer death, with an estimated 246000 new cases and 188000 deaths in 2015[[2]](#_ENREF_2). Although ESCC, which accounts for 70% of cases, remains the most prevalent form of esophageal cancer, the prevalence of ESCC has declined substantially in recent years. In contrast to the decreasing prevalence of ESCC, an alarming rise of the incidence in esophagogastric junction adenocarcinoma (EGJA) has been observed in both developed and developing countries, with 260,000 new cases diagnosed in 2012[[2-4](#_ENREF_2)]. Interestingly, in China, incidence of EGJA appears to be high in areas where the prevalence of ESCC is also high[[5](#_ENREF_5)]. This similar geographic distribution suggests similar environmental factors, similar dietary habits and even similar molecular alterations are involved in both ESCC and EGJA[[6](#_ENREF_6)].

The prognosis of ESCC is poor with an overall 5-year incidence of survival ranging from 15% to 25%[[7](#_ENREF_7),[8](#_ENREF_8)]. The high mortality in ESCC and EGJA mostly results from diagnosis at late stages due to the lack of specific symptoms of patients in early stage disease, but the prognosis is substantially better for patients diagnosed in the early stage (*e.g*., 5-year survival of more than 85% for ESCC patients diagnosed in early stage, and more than 90% for EGJA patients with node-negative T1 tumors)[[9](#_ENREF_9),[10](#_ENREF_10)]. However, effective strategies are lacking for screening or detection of pre-cancerous lesions in early-stage ESCC and EGJA. Although endoscopy is used as a primary screening technique and can identify ESCC and EGJA at an early stage, its extensive utilization is limited by the invasive nature, serious side effects and dependence on the skill of the endoscopist. Moreover, some individuals are unwilling to undergo endoscopy, whereas a simple blood test might be more acceptable. Thus, identification and validation of novel non-invasive, blood-based biomarkers can fulfill a great need for early detection of ESCC and EGJA.

Tumor-associated (TA) autoantibodies are emerging as strong candidates for clinically useful cancer biomarkers, since they are produced early in tumorigenesis and can be detectable up to 5 years before the clinical manifestations of cancer[[11-13](#_ENREF_11)]. Moreover, autoantibodies are also reported as biomarkers used in cancer prognosis and therapeutic monitoring (Table 1)[[11](#_ENREF_11),[14-21](#_ENREF_14)]. A large number of articles have evaluated the potential use of TA autoantibodies for early ESCC detection. Therefore, a systematic review is warranted to assess the current potential of TA autoantibodies for the early diagnosis of patients with ESCC. Considering the similarity of the etiology and epidemiology in EGJA and ESCC, we believe that it would be much desirable to provide together a review of TA autoantibodies in EGJA and ESCC where the field stands at this stage. We focus on the key aspects of the study designs and participant characteristics, the sensitivity, specificity, and area under the receiver operating characteristic (ROC) curve (AUC) of the TA autoantibody biomarkers to help identify the most promising candidates for future clinical screening tests.

**PROPOSED ORIGINS OF AUTOANTIBODY PRODUCTION IN CANCER**

As early as the 1960s, Robert W. Baldwin showed that the immune system could react to a developing tumor[[22-24](#_ENREF_22)]. Most studies have mainly focused on evaluating TA autoantibodies as early cancer biomarkers since their discovery. On the other hand, investigation of the underlying causes of TA autoantibody production may contribute to a clearer understanding of mechanisms concerning the rendering of autologous proteins immunogenic, and also reveal novel therapeutic targets for potential clinical use. It is commonly accepted that autologous cellular antigens expressed in tumors, also referred to as TA antigens, can be recognized early by the immune system and thus trigger a reaction known as cancer immunoediting, which consists of three phases: elimination, equilibration, and escape[[25](#_ENREF_25),[26](#_ENREF_26)]. Immunosurveillance occurs during the elimination phase, when the first few transformed cells are recognized by the immune system and targeted by natural killer cells that secrete certain cytokines to let other immune cells convene to the tumor[[27](#_ENREF_27)]. The ensuing disruption of certain transformed cells and the uptake and disposal of the corresponding fragments, by the recruited immune cells, activate the appropriate immune response. A cascade of dynamic events further boosts the activation of innate immunity and facilitates the expansion and generation of T and B cells, the latter which produce antibodies[[28](#_ENREF_28)]. Tumor cells that escape elimination and are permitted to grow will enter into the equilibrium phase during which tumor cell variants emerge with increasing ability to survive an immune attack. The equilibrium phase is the longest among these three phases and may persist for many years. Escape eventually occurs if the host immune defenses are breached and tumor cell variants grow and proliferate in an uncontrolled manner[[29](#_ENREF_29)].

It is clear that the generation of many abnormal antigens during tumorigenesis can induce the host immune response to produce autoantibodies. However, how factors exactly facilitate an enhancement or disorder of immune surveillance in cancer, resulting in the TA autoantibody production response, is still unclear. The generation of TA autoantibodies is thought to occur in response to mutations[[30](#_ENREF_30),[31](#_ENREF_31)], overexpression[[32](#_ENREF_32),[33](#_ENREF_33)] or abnormal processing[[34](#_ENREF_34),[35](#_ENREF_35)], which lead to the formation of altered or novel epitopes, aberrantly high expression levels resulting in loss of tolerance, and abnormal post-translational modifications, such as acetylation, glycosylation and phosphorylation, all of which could create a neoepitope, enhance self-epitope presentation, or expose antigens normally located in immune-privileged sites (*e.g*., cancer-testis antigens). With these mechanisms, extracellular and intracellular host proteins could be recognized by B cells to produce TA autoantibodies. Recent research has estimated that most TA autoantigens are mutated or overexpressed proteins, among which 42% are cytoplasmatic, 26.1% are expressed predominantly in the nucleus, 21.4% are membrane-bound and 10.3% are extracellular[[36](#_ENREF_36)]. It is surprising that TA autoantibodies seem to be more specific to intracellular molecules rather than their more common cell surface targets. This may be explained by greater vascular permeability for cytoplasmic proteins and enhancement of autoantibody generation by the proinflammatory environment[[37](#_ENREF_37),[38](#_ENREF_38)]. Although the exact role of TA autoantibodies in cancer is largely undefined, that secreted TA autoantibodies reflect tumor burden makes them attractive and promising biomarkers.

**DIAGNOSTIC PERFORMANCE OF SINGLE AUTOANTIBODIES IN ESCC**

Although TA autoantibodies have been described in a wide variety of human malignancies in the past several decades and have shown early diagnostic relevance, most studies evaluating autoantibodies in patients with ESCC and normal controls have emerged within the last 20 years. At least 49 individual TA autoantibodies have been assessed with diagnostic parameters in ESCC. Table 2 represents a list of single TA autoantibodies, reported in the literature, that could serve as potential serum/plasma biomarkers for ESCC. The diagnostic value of the TA autoantibodies, whether for the same autoantibody or for different types of autoantibodies, shows large variation for ESCC in terms of sensitivity and specificity, which might be due to sample size, the ethnic group studied or the [test](javascript:;) [method](javascript:;) of evaluation. In general, the majority of TA autoantibody biomarkers show relatively low sensitivity, but high specificity. The sensitivities and specificities for ESCC range from 3.9% to 93.7% and from 78.7% to 100%, respectively (Table 2). ROC curves as a summary measure will not set cutoff values artificially, but rather considers sensitivity and specificity simultaneously. Nevertheless, only a few studies used ROC curve analysis and AUC values to evaluate the diagnostic performance of TA autoantibodies (Table 2). The graphical representation of the sensitivities and specificities for autoantibodies in ESCC evaluated in more than one study is shown in Figure 1. Of note, the diagnostic ability of the great majority of TA autoantibodies lack independent validation, and the numbers of cases in some of the studies are very small. It is also noteworthy that most of the single TA autoantibodies lack diagnostic assessment in patients with early stage ESCC, which is one of the most important elements for biomarker development and application in early cancer diagnosis.

The most comprehensively investigated TA autoantibodies in ESCC have been p53 autoantibodies, followed by autoantibodies against P16 and c-Myc. Given the prominent feature of p53 in cancers it is not unexpected that this is the most widely studied autoantibody in ESCC. Autoantibodies against p53 in the diagnosis of ESCC have been evaluated in 17 studies (Table 2), and the sensitivities vary largely between reports (7%-60%), while less variance is observed in the specificity (range 89.5%-100%, Table 2). A meta-analysis by Zhang *et al*[[39](#_ENREF_39)] showed the overall sensitivity and specificity of p53 autoantibody for esophageal cancer are 29.6% and 97.9%, respectively. Autoantibodies against P16 and c-Myc were each analyzed in five studies and both exhibited high specificity, but poor sensitivity (Table 2). Therefore, despite the high specificity, all studies show that use of a single autoantibody provides low sensitivity, indicating limited clinical application. The sensitivity and specificity for Hsp70 autoantibodies reported by Fujita *et al*[[40](#_ENREF_40)] can be up to 93.7% and 100%, respectively. However, the very small sample size of this study reduces the stability and power of the results. Overall, quite apparent is the fact that the diagnostic value of individual TA autoantibody biomarkers in ESCC is quite limited.

**DIAGNOSTIC PERFORMANCE OF SINGLE AUTOANTIBODIES IN EGJA**

Very few clinical or translational studies have treated EGJA as a separate entity, which have been generally divided between those targeting esophageal cancer and those targeting gastric cancer. Likewise, a similar phenomenon has been observed in the studies on autoantibodies for the diagnosis of EGJA. As can be seen from Table 3, a total of 13 autoantibodies were investigated, in two studies[[41](#_ENREF_41),[42](#_ENREF_42)], all of which were initially assessed in ESCC by Xu *et al*[[43](#_ENREF_43)] and Zhou *et al*[[44](#_ENREF_44)]. As anticipated, the presence of TA autoantibodies indicates early diagnostic potential for EGJA. The sensitivity of single TA autoantibody biomarkers for EGJA ranged from 11.0% to 54.3%, with generally high specificity ranging from 86.3% to 97% (Table 3). From the list of autoantibodies shown in Table 3, in all conscience, there is no good way of forecasting which TA autoantibodies may work. Like ESCC, the most commonly tested TA autoantibody in EGJA is the p53 autoantibody, which has the highest AUC value (0.799) with moderate sensitivity and specificity in the diagnosis of early stage EGJA (Table 3). However, it remains fact that the capability of a single TA autoantibody biomarker to identify EGJA patients is limited. It also should be pointed out that research on autoantibodies is still in its infancy. Thus, more autoantibody biomarkers need to be identified and evaluated to enlarge the autoantibody pool for EGJA.

**DIAGNOSTIC PERFORMANCE OF AUTOANTIBODY PANELS IN ESCC**

Over the past few years, as single TA autoantibodies do not appear to demonstrate enough diagnostic sensitivity to set up a reliable test for early detection, studies have aimed to identify a suitable panel of TA autoantibodies. These predicaments are presumably due to cancer heterogeneity. In fact, it is unlikely that most patients will respond to the same immunodominant antigens. Even tumors of the same kind are comprised of a mix of diverse biological subtypes; accordingly, cancer patients are more likely to induce an immunoreaction to different sets of TA antigens, and not all cancers are likely to be detected by autoantibodies against a single antigen. Tables 4 and 5 give an overview of different combinations of multiple autoantibodies as potential blood-based biomarkers, for ESCC and EGJA, that have been described in the literature by various research groups.

With improvements in technology, several high-throughput methods, such as proteomics platforms, have enabled the uncovering of autoantibodies and the generation of a panel of TAAs. These discovery techniques encompass serological analysis of tumor antigens by recombinant cDNA expression cloning (SEREX)[[45](#_ENREF_45)], serological proteome analysis (SERPA)[[46](#_ENREF_46)], phage display[[47](#_ENREF_47)], protein microarrays[[48](#_ENREF_48)] and multiple affinity protein profiling[[49](#_ENREF_49)]. Shimada *et al*[[50](#_ENREF_50)] were the first to use the high-throughput method SEREX in ESCC. They showed that several TA antigens that could elicit a humoral immune response could be detected simultaneously, and that the technique enabled the generation of an autoantibody panel that exhibits better diagnostic value (86% sensitivity and 100% specificity) than a single TA autoantibody. Subsequently, a study using SERPA identified some novel TAAs associated with ESCC, and that the combination of two TA antigens (HSP105 and TIM) can give 54.3% sensitivity and 95% specificity in distinguishing ESCC from controls[[51](#_ENREF_51)]. These studies all show that the combined detection of autoantibodies against several antigens in the panel can greatly increase sensitivity in the diagnosis of ESCC. However, except for the two above-mentioned studies, no other relevant literature applying proteomic technology to identify a TA antigen panel has appeared. This indicates, to some extent, that the identification and development of novel autoantibodies by proteomics platforms for ESCC is limited and behindhand, especially compared with other tumor types, such as lung, breast and liver tumors[[52-54](#_ENREF_52)].

On the other hand, researchers have been more inclined to evaluate the diagnostic performance of combinations of several known TA antigens. In accord with such thinking, eight studies reported the diagnostic value of different combinations of autoantibodies for ESCC (Table 4). From the list of autoantibodies examined in the panel (Table 4), p53 autoantibodies were the most common choice for inclusion in the biomarker combinations. As is known, p53 as a tumor suppressor gene has been linked to many cancers, including ESCC, and thus would be a rational biomarker to be investigated. Zhang *et al*[[55](#_ENREF_55)] assessed a combination of six immunoreactive TA antigens in ESCC samples and normal controls with independent validation. Then, they sought to identify which biomarkers used in combination were more informative and allowed a similar discrimination between groups. They finally found a restricted panel of four TA antigens that gave similar sensitivity and specificity in early stage ESCC. Indeed, a similar research strategy had been previously performed by Xu *et al*[[43](#_ENREF_43)] who used two independent cohorts to investigate the combination of autoantibodies against p53, NY-ESO-1, MMP-7, Hsp70, Prx VI, and Bmi-1. This panel distinguished early stage ESCC from normal controls with a sensitivity/specificity of 45%/95% and 46%/96% respectively in the test and validation cohorts. Interestingly, the authors also determined a simplified autoantibody panel retaining four out of six biomarkers that exhibited almost the same diagnostic efficacy (Table 4). Although it is reported that a majority of biomarkers with desirable outcomes in a first data set often result in less promising results in additional independent data sets[[56](#_ENREF_56)], the two above studies with the combinations of known TAAs all showed satisfactory diagnostic value in independent validation cohorts. This suggests potential clinical applications for autoantibody combinations to diagnose ESCC. However, we can see from Table 4 that most of the studies reviewed lack validation in an independent population. In practice, the results of biomarkers need to be validated in larger multicenter cohorts and evaluated as a screening test in high-risk populations. However, no study on evaluation of autoantibodies in ESCC diagnosis has been able to do so. All previously identified autoantibody panels for ESCC should be validated by these procedures to evaluate their true clinical relevance and diagnostic power.

**DIAGNOSTIC PERFORMANCE OF AUTOANTIBODY PANELS IN EGJA**

As the combined detection of selected autoantibodies as a panel could generally increase diagnostic sensitivity while keeping relatively high specificity in ESCC, two studies have attempted to evaluate the same panels of autoantibodies identified in ESCC for early detection of EGJA, and have shown promising results, demonstrating sensitivities above 50%, and specificities above 86% (Table 5). Zhou *et al*[[41](#_ENREF_41)] detected autoantibodies to eight TA antigens, comprised of P53, IMP1, P16, cyclin B1, P62, c-Myc, survivin and Koc, and suggested that successive addition of seven TA antigens (P53, Koc, P62, c-Myc, IMP1, survivin and P16) lead to stepwise increases in sensitivity and specificity, ultimately achieving a sensitivity of 64.0% with a specificity of 87.0%. This optimized combination is somewhat different from an optimized panel identified for ESCC (P53, IMP1, P16, cyclin B1, P62, and c-Myc) studied by the same research team. Subsequently, Xu *et al*[[42](#_ENREF_42)] showed that autoantibodies against a combination of p53, NY-ESO-1, MMP-7, Hsp70, PRDX6 and Bmi-1, which is the same as the panel used for evaluation of ESCC, could be potentially used for early diagnosis of EGJA. When comparing stages I and II patients to normal controls, the authors showed sensitivities and specificities of 50.0% and 90.5%, and 56.0% and 90.0%, respectively, in the training and validation cohorts. It should be noted that a strict panel of p53, NY-ESO-1 and Bmi-1, to comprise informative biomarkers for EGJA, gives similar diagnostic performance. Interestingly, as discussed above, a different restricted combination (p53, NY-ESO-1, PRDX6 and Hsp70) from the same autoantibody panel in early stage ESCC retains high sensitivity and specificity. These studies suggest that the importance of individual autoantibodies in the panel assay varies in different types of cancers. However, we still need to determine which TA autoantibodies applied in combination are more informative and allow a better diagnostic value. In future work, more TA autoantibodies need to be discovered and characterized to identify the best combination for EGJA. Meanwhile, the identified signatures for EGJA should be verified in larger multicenter-appropriated cohorts of early stage patients and controls to test the diagnostic power.

**CONCLUSION AND PERSPECTIVES**

Endoscopic examination is a current, but invasive diagnostic and screening procedure for early detection of ESCC and EGJA. The development and validation of non-invasive biomarkers is of great need for ESCC and EGJA screening. In recent decades, a large number of blood-based cancer biomarkers, such as cell-free circulating tumor DNAs, various non-coding RNAs, proteins and TA autoantibodies, have been identified and indicate the potential for early detection of esophageal cancer. Among these biomarkers, TA autoantibodies are promising biomarker entities in the early cancer detection, as they are capable of identifying cancer in high-risk individuals. Moreover, they are highly stable and can be easily detected by routine methods (*e.g*., ELISA). Recently, a TA autoantibody assay named *EarlyCDT*-Lung (against p53, NY-ESO-1, CAGE, GBU4-5, MAGE A4, SOX2 and Hu-D) approved by the FDA has been clinically and analytically validated. An ongoing prospective randomized trial is evaluating the clinical utility of this TA autoantibody panel and its use in a clinical setting, of which the results are expected to be announced in the near future. Once this assay is successful for lung cancer, we would predict that tests for all solid tumors, including ESCC and EGJA, will follow. Biomarker development needs several gradual steps covering preclinical studies, retrospective studies of stored specimens, multicenter validation studies and prospective screening studies. However, in ESCC and EGJA, autoantibody studies on early detection are hampered by several issues. First, the availability of sera from early stage patients seems limited. Only few studies have investigated the diagnostic value of TA autoantibody panels in patients with early stage tumors. Access to large early stage sample cohorts is an essential and necessary issue to examine a test’s value for early stage disease. Moreover, few patients with pre-diagnostic serum samples or high-risk ESCC or EGJA cohorts are available, and up to now no study has reported on the immune response in the form of autoantibodies in these populations. Thus, an investigation of TA autoantibodies for the early detection of ESCC and EGJA will be limited mainly by the availability of human samples. On the other hand, current studies (Tables 4 and 5) investigating autoantibodies show promise, but still lack the necessary validation stages. These studies need clinical multicenter validation through use of a broader population to further determine diagnostic value.

It seems that there are different patterns of TA autoantibody frequencies in different types of cancers. Thus, one encountered difficulty is the definition of the panel. This leads to the question of how to choose the optimized combination that works best in terms of sensitivity, specificity and predictive value. At this moment, these is no good guiding principle, but more advanced high-throughput proteome technology might be helpful. On the other hand, it should be also pointed out that TA autoantibodies may not be unique for specific types of cancers. Therefore, TA autoantibody panels identified for ESCC or EGJA are likely to be used as a screening test to discover the existence of cancer, and in general, more specific diagnostic tools, such as endoscopy, should be carried out in the event of a positive result.

In conclusion, this review suggests that TA autoantibodies have the potential to serve as diagnostic biomarkers for ESCC and EGJA, possibly as part of a general cancer screen. However, present studies in ESCC and EGJA remain at an early stage. It is clear that extensive efforts are needed to uncover promising autoantibody signatures to detect these cancers, especially at early stage. Moreover, it is too early to evaluate the diagnostic values of the autoantibodies reviewed here for clinical use. Standardized assay protocols facilitating the establishment of autoantibodies as highly accurate biomarkers is of great need in ESCC and EGJA. Finally, future studies performed with precise design and collaborative efforts among groups to build standardized guidelines to report results will contribute greatly in this research area.

**ACKNOWLEDGEMENTS**

We thank Professor Stanley Li Lin who re-read this manuscript carefully.

**REFERENCES**

1 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

2 **Colquhoun A**, Arnold M, Ferlay J, Goodman KJ, Forman D, Soerjomataram I. Global patterns of cardia and non-cardia gastric cancer incidence in 2012. *Gut* 2015; **64**: 1881-1888 [PMID: 25748648 DOI: 10.1136/gutjnl-2014-308915]

3 **Devesa SS**, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 1998; **83**: 2049-2053 [PMID: 9827707 DOI: 10.1002/(SICI)1097-0142(19981115)83:10<2049::AID-CNCR1>3.0.CO;2-2]

4 **Zhou Y**, Zhang Z, Zhang Z, Wu J, Ren D, Yan X, Wang Q, Wang Y, Wang H, Zhang J, Zhu X, Yang Y, Luo C, Guo X, Tang C, Qiao L. A rising trend of gastric cardia cancer in Gansu Province of China. *Cancer Lett* 2008; **269**: 18-25 [PMID: 18501504 DOI: 10.1016/j.canlet.2008.04.013]

5 **Tran GD**, Sun XD, Abnet CC, Fan JH, Dawsey SM, Dong ZW, Mark SD, Qiao YL, Taylor PR. Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. *Int J Cancer* 2005; **113**: 456-463 [PMID: 15455378 DOI: 10.1002/ijc.20616]

6 **Chen H**, Wang LD, Guo M, Gao SG, Guo HQ, Fan ZM, Li JL. Alterations of p53 and PCNA in cancer and adjacent tissues from concurrent carcinomas of the esophagus and gastric cardia in the same patient in Linzhou, a high incidence area for esophageal cancer in northern China. *World J Gastroenterol* 2003; **9**: 16-21 [PMID: 12508343 DOI: 10.3748/wjg.v9.i1.16]

7 **Enzinger PC**, Mayer RJ. Esophageal cancer. *N Engl J Med* 2003; **349**: 2241-2252 [PMID: 14657432 DOI: 10.1056/NEJMra035010]

8 **Kim T**, Grobmyer SR, Smith R, Ben-David K, Ang D, Vogel SB, Hochwald SN. Esophageal cancer--the five year survivors. *J Surg Oncol* 2011; **103**: 179-183 [PMID: 21259254 DOI: 10.1002/jso.21784]

9 **Wang GQ**, Jiao GG, Chang FB, Fang WH, Song JX, Lu N, Lin DM, Xie YQ, Yang L. Long-term results of operation for 420 patients with early squamous cell esophageal carcinoma discovered by screening. *Ann Thorac Surg* 2004; **77**: 1740-1744 [PMID: 15111177 DOI: 10.1016/j.athoracsur.2003.10.098]

10 **Pech O**, Behrens A, May A, Nachbar L, Gossner L, Rabenstein T, Manner H, Guenter E, Huijsmans J, Vieth M, Stolte M, Ell C. Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. *Gut* 2008; **57**: 1200-1206 [PMID: 18460553 DOI: 10.1136/gut.2007.142539]

11 **Chapman CJ**, Thorpe AJ, Murray A, Parsy-Kowalska CB, Allen J, Stafford KM, Chauhan AS, Kite TA, Maddison P, Robertson JF. Immunobiomarkers in small cell lung cancer: Potential early cancer signals. *Clin Cancer Res* 2011; **17**: 1474-1480 [PMID: 21138858 DOI: 10.1158/1078-0432.CCR-10-1363]

12 **Zhong L**, Coe SP, Stromberg AJ, Khattar NH, Jett JR, Hirschowitz EA. Profiling tumor-associated antibodies for early detection of non-small cell lung cancer. *J Thorac Oncol* 2006; **1**: 513-519 [PMID: 17409910 DOI: 10.1016/S1556-0864(15)30352-X]

13 **Trivers GE**, De Benedetti VM, Cawley HL, Caron G, Harrington AM, Bennett WP, Jett JR, Colby TV, Tazelaar H, Pairolero P, Miller RD, Harris CC. Anti-p53 antibodies in sera from patients with chronic obstructive pulmonary disease can predate a diagnosis of cancer. *Clin Cancer Res* 1996; **2**: 1767-1775 [PMID: 9816128 DOI: 10.1093/carcin/17.10.2275]

14 **Takeda A**, Shimada H, Nakajima K, Imaseki H, Suzuki T, Asano T, Ochiai T, Isono K. Monitoring of p53 autoantibodies after resection of colorectal cancer: Relationship to operative curability. *Eur J Surg* 2001; **167**: 50-53 [PMID: 11213822 DOI: 10.1080/110241501750069828]

15 **Anderson KS**, Wong J, Vitonis A, Crum CP, Sluss PM, Labaer J, Cramer D. p53 autoantibodies as potential detection and prognostic biomarkers in serous ovarian cancer. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 859-868 [PMID: 20200435 DOI: 10.1158/1055-9965.EPI-09-0880]

16 **Shan Q**, Lou X, Xiao T, Zhang J, Sun H, Gao Y, Cheng S, Wu L, Xu N, Liu S. A cancer/testis antigen microarray to screen autoantibody biomarkers of non-small cell lung cancer. *Cancer Lett* 2013; **328**: 160-167 [PMID: 22922091 DOI: 10.1016/j.canlet.2012.08.019]

17 **Fosså A**, Berner A, Fosså SD, Hernes E, Gaudernack G, Smeland EB. NY-ESO-1 protein expression and humoral immune responses in prostate cancer. *Prostate* 2004; **59**: 440-447 [PMID: 15065093 DOI: 10.1002/pros.20025]

18 **Jäger E**, Stockert E, Zidianakis Z, Chen YT, Karbach J, Jäger D, Arand M, Ritter G, Old LJ, Knuth A. Humoral immune responses of cancer patients against "Cancer-Testis" antigen NY-ESO-1: Correlation with clinical events. *Int J Cancer* 1999; **84**: 506-510 [PMID: 10502728 DOI: 10.1002/(sici)1097-0215(19991022)84:5<506::aid-ijc10>3.0.co;2-6]

19 **Pedersen JW**, Gentry-Maharaj A, Nøstdal A, Fourkala EO, Dawnay A, Burnell M, Zaikin A, Burchell J, Papadimitriou JT, Clausen H, Jacobs I, Menon U, Wandall HH. Cancer-associated autoantibodies to MUC1 and MUC4--a blinded case–control study of colorectal cancer in UK collaborative trial of ovarian cancer screening. *Int J Cancer* 2014; **134**: 2180-2188 [PMID: 24122770 DOI: 10.1002/ijc.28538]

20 **Kurtenkov O**, Klaamas K, Mensdorff-Pouilly S, Miljukhina L, Shljapnikova L, Chuzmarov V. Humoral immune response to MUC1 and to the Thomsen-Friedenreich (TF) glycotope in patients with gastric cancer: Relation to survival. *Acta Oncol* 2007; **46**: 316-323 [PMID: 17450466 DOI: 10.1080/02841860601055441]

21 **Graus F**, Dalmou J, Reñé R, Tora M, Malats N, Verschuuren JJ, Cardenal F, Viñolas N, Garcia del Muro J, Vadell C, Mason WP, Rosell R, Posner JB, Real FX. Anti-Hu antibodies in patients with small-cell lung cancer: Association with complete response to therapy and improved survival. *J Clin Oncol* 1997; **15**: 2866-2872 [PMID: 9256130 DOI: 10.1200/jco.1997.15.8.2866]

22 **Baldwin RW**. Tumour-specific immunity against spontaneous rat tumours. *Int J Cancer* 1966; **1**: 257-264 [PMID: 5944065 DOI: 10.1002/ijc.2910010305]

23 **Baldwin RW**. An immunological approach to cancer. *Lav Ist Anat Istol Patol Univ Studi Perugia* 1968; **28**: 65-85 [PMID: 4882305]

24 **Baldwin RW**. Tumour-associated antigens and tumour-host interactions. *Proc R Soc Med* 1971; **64**: 1039-1042 [PMID: 4335921]

25 **Dunn GP**, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: From immunosurveillance to tumor escape. *Nat Immunol* 2002; **3**: 991-998 [PMID: 12407406 DOI: 10.1038/ni1102-991]

26 **Schreiber RD**, Old LJ, Smyth MJ. Cancer immunoediting: Integrating immunity's roles in cancer suppression and promotion. *Science* 2011; **331**: 1565-1570 [PMID: 21436444 DOI: 10.1126/science.1203486]

27 **Vivier E**, Ugolini S, Blaise D, Chabannon C, Brossay L. Targeting natural killer cells and natural killer T cells in cancer. *Nat Rev Immunol* 2012; **12**: 239-252 [PMID: 22437937 DOI: 10.1038/nri3174]

28 **Finn OJ**. Immuno-oncology: Understanding the function and dysfunction of the immune system in cancer. *Ann Oncol* 2012; **23 Suppl 8**: viii6-viii9 [PMID: 22918931 DOI: 10.1093/annonc/mds256]

29 **Kim R**, Emi M, Tanabe K, Arihiro K. Tumor-driven evolution of immunosuppressive networks during malignant progression. *Cancer Res* 2006; **66**: 5527-5536 [PMID: 16740684 DOI: 10.1158/0008-5472.can-05-4128]

30 **Winter SF**, Minna JD, Johnson BE, Takahashi T, Gazdar AF, Carbone DP. Development of antibodies against p53 in lung cancer patients appears to be dependent on the type of p53 mutation. *Cancer Res* 1992; **52**: 4168-4174 [PMID: 1322237 DOI: 10.1046/j.1365-2109.2002.00715.x]

31 **Pardoll D**. Does the immune system see tumors as foreign or self? *Annu Rev Immunol* 2003; **21**: 807-839 [PMID: 12615893 DOI: 10.1146/annurev.immunol.21.120601.141135]

32 **Chen YT**, Scanlan MJ, Sahin U, Türeci O, Gure AO, Tsang S, Williamson B, Stockert E, Pfreundschuh M, Old LJ. A testicular antigen aberrantly expressed in human cancers detected by autologous antibody screening. *Proc Natl Acad Sci U S A* 1997; **94**: 1914-1918 [PMID: 9050879 DOI: 10.1073/pnas.94.5.1914]

33 **Goodell V**, Waisman J, Salazar LG, de la Rosa C, Link J, Coveler AL, Childs JS, Fintak PA, Higgins DM, Disis ML. Level of HER-2/neu protein expression in breast cancer may affect the development of endogenous HER-2/neu-specific immunity. *Mol Cancer Ther* 2008; **7**: 449-454 [PMID: 18319334 DOI: 10.1158/1535-7163.MCT-07-0386]

34 **Plotz PH**. The autoantibody repertoire: Searching for order. *Nat Rev Immunol* 2003; **3**: 73-78 [PMID: 12511877 DOI: 10.1038/nri976]

35 **Burford B**, Gentry-Maharaj A, Graham R, Allen D, Pedersen JW, Nudelman AS, Blixt O, Fourkala EO, Bueti D, Dawnay A, Ford J, Desai R, David L, Trinder P, Acres B, Schwientek T, Gammerman A, Reis CA, Silva L, Osório H, Hallett R, Wandall HH, Mandel U, Hollingsworth MA, Jacobs I, Fentiman I, Clausen H, Taylor-Papadimitriou J, Menon U, Burchell JM. Autoantibodies to MUC1 glycopeptides cannot be used as a screening assay for early detection of breast, ovarian, lung or pancreatic cancer. *Br J Cancer* 2013; **108**: 2045-2055 [PMID: 23652307 DOI: 10.1038/bjc.2013.214]

36 **Reuschenbach M**, von Knebel Doeberitz M, Wentzensen N. A systematic review of humoral immune responses against tumor antigens. *Cancer Immunol Immunother* 2009; **58**: 1535-1544 [PMID: 19562338 DOI: 10.1007/s00262-009-0733-4]

37 **Matsumoto I**, Maccioni M, Lee DM, Maurice M, Simmons B, Brenner M, Mathis D, Benoist C. How antibodies to a ubiquitous cytoplasmic enzyme may provoke joint-specific autoimmune disease. *Nat Immunol* 2002; **3**: 360-365 [PMID: 11896391 DOI: 10.1038/ni772]

38 **Binstadt BA**, Patel PR, Alencar H, Nigrovic PA, Lee DM, Mahmood U, Weissleder R, Mathis D, Benoist C. Particularities of the vasculature can promote the organ specificity of autoimmune attack. *Nat Immunol* 2006; **7**: 284-292 [PMID: 16444258 DOI: 10.1038/ni1306]

39 **Zhang H**, Xia J, Wang K, Zhang J. Serum autoantibodies in the early detection of esophageal cancer: A systematic review. *Tumour Biol* 2015; **36**: 95-109 [PMID: 25433500 DOI: 10.1007/s13277-014-2878-9]

40 **Fujita Y**, Nakanishi T, Miyamoto Y, Hiramatsu M, Mabuchi H, Miyamoto A, Shimizu A, Takubo T, Tanigawa N. Proteomics-based identification of autoantibody against heat shock protein 70 as a diagnostic marker in esophageal squamous cell carcinoma. *Cancer Lett* 2008; **263**: 280-290 [PMID: 18334280 DOI: 10.1016/j.canlet.2008.01.013]

41 **Zhou SL**, Ku JW, Fan ZM, Yue WB, Du F, Zhou YF, Liu YL, Li Y, Tang S, Hu YL, Hu XP, Hou ZC, Liu J, Liu Y, Feng XS, Wang LD. Detection of autoantibodies to a panel of tumor-associated antigens for the diagnosis values of gastric cardia adenocarcinoma. *Dis Esophagus* 2015; **28**: 371-379 [PMID: 24612004 DOI: 10.1111/dote.12206]

42 **Xu YW**, Chen H, Guo HP, Yang SH, Luo YH, Liu CT, Huang XY, Tang XM, Hong CQ, Li EM, Xu LY, Peng YH. Combined detection of serum autoantibodies as diagnostic biomarkers in esophagogastric junction adenocarcinoma. *Gastric Cancer* 2019; **22**: 546-557 [PMID: 30426295 DOI: 10.1007/s10120-018-0894-y]

43 **Xu YW**, Peng YH, Chen B, Wu ZY, Wu JY, Shen JH, Zheng CP, Wang SH, Guo HP, Li EM, Xu LY. Autoantibodies as potential biomarkers for the early detection of esophageal squamous cell carcinoma. *Am J Gastroenterol* 2014; **109**: 36-45 [PMID: 24296751 DOI: 10.1038/ajg.2013.384]

44 **Zhou SL**, Yue WB, Fan ZM, Du F, Liu BC, Li B, Han XN, Ku JW, Zhao XK, Zhang P, Cui J, Zhou FY, Zhang LQ, Fan XP, Zhou YF, Zhu LL, Liu HY, Wang LD. Autoantibody detection to tumor-associated antigens of P53, IMP1, P16, cyclin B1, P62, C-myc, Survivn, and Koc for the screening of high-risk subjects and early detection of esophageal squamous cell carcinoma. *Dis Esophagus* 2014; **27**: 790-797 [PMID: 24147952 DOI: 10.1111/dote.12145]

45 **Sahin U**, Türeci O, Schmitt H, Cochlovius B, Johannes T, Schmits R, Stenner F, Luo G, Schobert I, Pfreundschuh M. Human neoplasms elicit multiple specific immune responses in the autologous host. *Proc Natl Acad Sci U S A* 1995; **92**: 11810-11813 [PMID: 8524854 DOI: 10.1073/pnas.92.25.11810]

46 **Klade CS**, Voss T, Krystek E, Ahorn H, Zatloukal K, Pummer K, Adolf GR. Identification of tumor antigens in renal cell carcinoma by serological proteome analysis. *Proteomics* 2001; **1**: 890-898 [PMID: 11503213 DOI: 10.1002/1615-9861(200107)1:7<890::aid-prot890>3.0.co;2-z]

47 **Mintz PJ**, Kim J, Do KA, Wang X, Zinner RG, Cristofanilli M, Arap MA, Hong WK, Troncoso P, Logothetis CJ, Pasqualini R, Arap W. Fingerprinting the circulating repertoire of antibodies from cancer patients. *Nat Biotechnol* 2003; **21**: 57-63 [PMID: 12496764 DOI: 10.1038/nbt774]

48 **Kijanka G**, Murphy D. Protein arrays as tools for serum autoantibody marker discovery in cancer. *J Proteomics* 2009; **72**: 936-944 [PMID: 19258055 DOI: 10.1016/j.jprot.2009.02.006]

49 **Hardouin J**, Lasserre JP, Sylvius L, Joubert-Caron R, Caron M. Cancer immunomics: From serological proteome analysis to multiple affinity protein profiling. *Ann N Y Acad Sci* 2007; **1107**: 223-230 [PMID: 17804550 DOI: 10.1196/annals.1381.024]

50 **Shimada H**, Nakashima K, Ochiai T, Nabeya Y, Takiguchi M, Nomura F, Hiwasa T. Serological identification of tumor antigens of esophageal squamous cell carcinoma. *Int J Oncol* 2005; **26**: 77-86 [PMID: 15586227 DOI: 10.3892/ijo.26.1.77]

51 **Gao H**, Zheng Z, Mao Y, Wang W, Qiao Y, Zhou L, Liu F, He H, Zhao X. Identification of tumor antigens that elicit a humoral immune response in the sera of Chinese esophageal squamous cell carcinoma patients by modified serological proteome analysis. *Cancer Lett* 2014; **344**: 54-61 [PMID: 24157810 DOI: 10.1016/j.canlet.2013.10.007]

52 **Macdonald IK**, Parsy-Kowalska CB, Chapman CJ. Autoantibodies: Opportunities for Early Cancer Detection. *Trends Cancer* 2017; **3**: 198-213 [PMID: 28718432 DOI: 10.1016/j.trecan.2017.02.003]

53 **Qiu J**, Keyser B, Lin ZT, Wu T. Autoantibodies as Potential Biomarkers in Breast Cancer. *Biosensors (Basel)* 2018; **8**: pii: E67 [PMID: 30011807 DOI: 10.3390/bios8030067]

54 **Hong Y**, Huang J. Autoantibodies against tumor-associated antigens for detection of hepatocellular carcinoma. *World J Hepatol* 2015; **7**: 1581-1585 [PMID: 26085917 DOI: 10.4254/wjh.v7.i11.1581]

55 **Zhang HF**, Qin JJ, Ren PF, Shi JX, Xia JF, Ye H, Wang P, Song CH, Wang KJ, Zhang JY. A panel of autoantibodies against multiple tumor-associated antigens in the immunodiagnosis of esophageal squamous cell cancer. *Cancer Immunol Immunother* 2016; **65**: 1233-1242 [PMID: 27553002 DOI: 10.1007/s00262-016-1886-6]

56 **Mischak H**, Allmaier G, Apweiler R, Attwood T, Baumann M, Benigni A, Bennett SE, Bischoff R, Bongcam-Rudloff E, Capasso G, Coon JJ, D'Haese P, Dominiczak AF, Dakna M, Dihazi H, Ehrich JH, Fernandez-Llama P, Fliser D, Frokiaer J, Garin J, Girolami M, Hancock WS, Haubitz M, Hochstrasser D, Holman RR, Ioannidis JP, Jankowski J, Julian BA, Klein JB, Kolch W, Luider T, Massy Z, Mattes WB, Molina F, Monsarrat B, Novak J, Peter K, Rossing P, Sánchez-Carbayo M, Schanstra JP, Semmes OJ, Spasovski G, Theodorescu D, Thongboonkerd V, Vanholder R, Veenstra TD, Weissinger E, Yamamoto T, Vlahou A. Recommendations for biomarker identification and qualification in clinical proteomics. *Sci Transl Med* 2010; **2**: 46ps42 [PMID: 20739680 DOI: 10.1126/scitranslmed.3001249]

57 **Xiu Y**, Sun B, Jiang Y, Wang A, Liu L, Liu Y, Sun S, Huangfu M. Diagnostic Value of the Survivin Autoantibody in Four Types of Malignancies. *Genet Test Mol Biomarkers* 2018; **22**: 384-389 [PMID: 29924656 DOI: 10.1089/gtmb.2017.0278]

58 **Qin JJ**, Wang XR, Wang P, Ren PF, Shi JX, Zhang HF, Xia JF, Wang KJ, Song CH, Dai LP, Zhang JY. Mini-array of multiple tumor-associated antigens (TAAs) in the immunodiagnosis of esophageal cancer. *Asian Pac J Cancer Prev* 2014; **15**: 2635-2640 [PMID: 24761876 DOI: 10.7314/APJCP.2014.15.6.2635]

59 **Megliorino R**, Shi FD, Peng XX, Wang X, Chan EK, Tan EM, Zhang JY. Autoimmune response to anti-apoptotic protein survivin and its association with antibodies to p53 and c-myc in cancer detection. *Cancer Detect Prev* 2005; **29**: 241-248 [PMID: 15896923 DOI: 10.1016/j.cdp.2005.03.002]

60 **Zhang JB**, Cao M, Chen J, Ye SR, Xie K, He X, Ma XL, Zhang J, Yie SM. Serum anti-TOPO48 autoantibody as a biomarker for early diagnosis and prognosis in patients with esophageal squamous cell carcinoma. *Clin Res Hepatol Gastroenterol* 2018; **42**: 276-284 [PMID: 29170084 DOI: 10.1016/j.clinre.2017.09.007]

61 **Xu YW**, Peng YH, Ran LQ, Zhai TT, Guo HP, Qiu SQ, Chen HL, Wu ZY, Li EM, Xie JJ. Circulating levels of autoantibodies against L1-cell adhesion molecule as a potential diagnostic biomarker in esophageal squamous cell carcinoma. *Clin Transl Oncol* 2017; **19**: 898-906 [PMID: 28181176 DOI: 10.1007/s12094-017-1623-4]

62 **Li L**, Liu M, Lin JB, Hong XB, Chen WX, Guo H, Xu LY, Xu YW, Li EM, Peng YH. Diagnostic Value of Autoantibodies against Ezrin in Esophageal Squamous Cell Carcinoma. *Dis Markers* 2017; **2017**: 2534648 [PMID: 28298808 DOI: 10.1155/2017/2534648]

63 **Xu YW**, Liu CT, Huang XY, Huang LS, Luo YH, Hong CQ, Guo HP, Xu LY, Peng YH, Li EM. Serum Autoantibodies against STIP1 as a Potential Biomarker in the Diagnosis of Esophageal Squamous Cell Carcinoma. *Dis Markers* 2017; **2017**: 5384091 [PMID: 28852266 DOI: 10.1155/2017/5384091]

64 **Chen WX**, Hong XB, Hong CQ, Liu M, Li L, Huang LS, Xu LY, Xu YW, Peng YH, Li EM. Tumor-associated autoantibodies against Fascin as a novel diagnostic biomarker for esophageal squamous cell carcinoma. *Clin Res Hepatol Gastroenterol* 2017; **41**: 327-332 [PMID: 27956255 DOI: 10.1016/j.clinre.2016.10.011]

65 **Peng YH**, Xu YW, Guo H, Huang LS, Tan HZ, Hong CQ, Li SS, Xu LY, Li EM. Combined detection of serum Dickkopf-1 and its autoantibodies to diagnose esophageal squamous cell carcinoma. *Cancer Med* 2016; **5**: 1388-1396 [PMID: 26988995 DOI: 10.1002/cam4.702]

66 **Jin Y**, Guan S, Liu L, Sun S, Lee KH, Wei J. Anti-p16 autoantibodies may be a useful biomarker for early diagnosis of esophageal cancer. *Asia Pac J Clin Oncol* 2015; **11**: e37-e41 [PMID: 24811068 DOI: 10.1111/ajco.12198]

67 **Looi K**, Megliorino R, Shi FD, Peng XX, Chen Y, Zhang JY. Humoral immune response to p16, a cyclin-dependent kinase inhibitor in human malignancies. *Oncol Rep* 2006; **16**: 1105-1110 [PMID: 17016600 DOI: 10.3892/or.16.5.1105]

68 **Chai Y**, Peng B, Dai L, Qian W, Zhang Y, Zhang JY. Autoantibodies response to MDM2 and p53 in the immunodiagnosis of esophageal squamous cell carcinoma. *Scand J Immunol* 2014; **80**: 362-368 [PMID: 24965442 DOI: 10.1111/sji.12202]

69 **Cai HY**, Wang XH, Tian Y, Gao LY, Zhang LJ, Zhang ZY. Changes of serum p53 antibodies and clinical significance of radiotherapy for esophageal squamous cell carcinoma. *World J Gastroenterol* 2008; **14**: 4082-4086 [PMID: 18609695 DOI: 10.3748/wjg.14.4082]

70 **Müller M**, Meyer M, Schilling T, Ulsperger E, Lehnert T, Zentgraf H, Stremmel W, Volkmann M, Galle PR. Testing for anti-p53 antibodies increases the diagnostic sensitivity of conventional tumor markers. *Int J Oncol* 2006; **29**: 973-980 [PMID: 16964393 DOI: 10.3892/ijo.29.4.973]

71 **Shimada H**, Ochiai T, Nomura F; Japan p53 Antibody Research Group. Titration of serum p53 antibodies in 1,085 patients with various types of malignant tumors: A multiinstitutional analysis by the Japan p53 Antibody Research Group. *Cancer* 2003; **97**: 682-689 [PMID: 12548611 DOI: 10.1002/cncr.11092]

72 **Shimada H**, Nabeya Y, Okazumi S, Matsubara H, Funami Y, Shiratori T, Hayashi H, Takeda A, Ochiai T. Prognostic significance of serum p53 antibody in patients with esophageal squamous cell carcinoma. *Surgery* 2002; **132**: 41-47 [PMID: 12110794 DOI: 10.1067/msy.2002.125307]

73 **Ralhan R**, Arora S, Chattopadhyay TK, Shukla NK, Mathur M. Circulating p53 antibodies, p53 gene mutational profile and product accumulation in esophageal squamous-cell carcinoma in India. *Int J Cancer* 2000; **85**: 791-795 [PMID: 10709097 DOI: 10.1002/(sici)1097-0215(20000315)85:6<791::aid-ijc9>3.0.co;2-k]

74 **Shimada H**, Takeda A, Arima M, Okazumi S, Matsubara H, Nabeya Y, Funami Y, Hayashi H, Gunji Y, Suzuki T, Kobayashi S, Ochiai T. Serum p53 antibody is a useful tumor marker in superficial esophageal squamous cell carcinoma. *Cancer* 2000; **89**: 1677-1683 [PMID: 11042560 DOI: 10.1002/1097-0142(20001015)89:8<1677::AID-CNCR5>3.0.CO;2-9]

75 **Hagiwara N**, Onda M, Miyashita M, Sasajima K. Detection of circulating anti-p53 antibodies in esophageal cancer patients. *J Nippon Med Sch* 2000; **67**: 110-117 [PMID: 10754600 DOI: 10.1272/jnms.67.110]

76 **Shimada H**, Nakajima K, Ochiai T, Koide Y, Okazumi SI, Matsubara H, Takeda A, Miyazawa Y, Arima M, Isono K. Detection of serum p53 antibodies in patients with esophageal squamous cell carcinoma: Correlation with clinicopathologic features and tumor markers. *Oncol Rep* 1998; **5**: 871-874 [PMID: 9625835 DOI: 10.3892/or.5.4.871]

77 **Sobti RC**, Parashar K. A study on p53 protein and anti-p53 antibodies in the sera of patients with oesophageal cancer. *Mutat Res* 1998; **422**: 271-277 [PMID: 9838161 DOI: 10.1016/s0027-5107(98)00207-3]

78 **Cawley HM**, Meltzer SJ, De Benedetti VM, Hollstein MC, Muehlbauer KR, Liang L, Bennett WP, Souza RF, Greenwald BD, Cottrell J, Salabes A, Bartsch H, Trivers GE. Anti-p53 antibodies in patients with Barrett's esophagus or esophageal carcinoma can predate cancer diagnosis. *Gastroenterology* 1998; **115**: 19-27 [PMID: 9649454 DOI: 10.1016/s0016-5085(98)70360-9]

79 **Oshima Y**, Shimada H, Yajima S, Nanami T, Matsushita K, Nomura F, Kainuma O, Takiguchi N, Soda H, Ueda T, Iizasa T, Yamamoto N, Yamamoto H, Nagata M, Yokoi S, Tagawa M, Ohtsuka S, Kuwajima A, Murakami A, Kaneko H. NY-ESO-1 autoantibody as a tumor-specific biomarker for esophageal cancer: Screening in 1969 patients with various cancers. *J Gastroenterol* 2016; **51**: 30-34 [PMID: 25906289 DOI: 10.1007/s00535-015-1078-8]

80 **Fujita S**, Wada H, Jungbluth AA, Sato S, Nakata T, Noguchi Y, Doki Y, Yasui M, Sugita Y, Yasuda T, Yano M, Ono T, Chen YT, Higashiyama M, Gnjatic S, Old LJ, Nakayama E, Monden M. NY-ESO-1 expression and immunogenicity in esophageal cancer. *Clin Cancer Res* 2004; **10**: 6551-6558 [PMID: 15475443 DOI: 10.1158/1078-0432.ccr-04-0819]

81 **Zhou JH**, Zhang B, Kernstine KH, Zhong L. Autoantibodies against MMP-7 as a novel diagnostic biomarker in esophageal squamous cell carcinoma. *World J Gastroenterol* 2011; **17**: 1373-1378 [PMID: 21455340 DOI: 10.3748/wjg.v17.i10.1373]

82 **Zhang J**, Wang K, Zhang J, Liu SS, Dai L, Zhang JY. Using proteomic approach to identify tumor-associated proteins as biomarkers in human esophageal squamous cell carcinoma. *J Proteome Res* 2011; **10**: 2863-2872 [PMID: 21517111 DOI: 10.1021/pr200141c]

83 **Fujita Y**, Nakanishi T, Hiramatsu M, Mabuchi H, Miyamoto Y, Miyamoto A, Shimizu A, Tanigawa N. Proteomics-based approach identifying autoantibody against peroxiredoxin VI as a novel serum marker in esophageal squamous cell carcinoma. *Clin Cancer Res* 2006; **12**: 6415-6420 [PMID: 17085654 DOI: 10.1158/1078-0432.ccr-06-1315]

84 **Liu WL**, Guo XZ, Zhang LJ, Wang JY, Zhang G, Guan S, Chen YM, Kong QL, Xu LH, Li MZ, Song LB, Zeng MS. Prognostic relevance of Bmi-1 expression and autoantibodies in esophageal squamous cell carcinoma. *BMC Cancer* 2010; **10**: 467 [PMID: 20809956 DOI: 10.1186/1471-2407-10-467]

85 **Li Y**, Zhang Q, Peng B, Shao Q, Qian W, Zhang JY. Identification of glutathione S-transferase omega 1 (GSTO1) protein as a novel tumor-associated antigen and its autoantibody in human esophageal squamous cell carcinoma. *Tumour Biol* 2014; **35**: 10871-10877 [PMID: 25085586 DOI: 10.1007/s13277-014-2394-y]

86 **Ren P**, Ye H, Dai L, Liu M, Liu X, Chai Y, Shao Q, Li Y, Lei N, Peng B, Yao W, Zhang J. Peroxiredoxin 1 is a tumor-associated antigen in esophageal squamous cell carcinoma. *Oncol Rep* 2013; **30**: 2297-2303 [PMID: 24009050 DOI: 10.3892/or.2013.2714]

87 **Ye L**, Guan S, Zhang C, Lee KH, Sun S, Wei J, Liu B. Circulating autoantibody to FOXP3 may be a potential biomarker for esophageal squamous cell carcinoma. *Tumour Biol* 2013; **34**: 1873-1877 [PMID: 23483489 DOI: 10.1007/s13277-013-0729-8]

88 **Guan S**, Liu B, Zhang C, Lee KH, Sun S, Wei J. Circulating autoantibody to CD25 may be a potential biomarker for early diagnosis of esophageal squamous cell carcinoma. *Clin Transl Oncol* 2013; **15**: 825-829 [PMID: 23423807 DOI: 10.1007/s12094-013-1007-3]

89 **Cheng Y**, Xu J, Guo J, Jin Y, Wang X, Zhang Q, Liu L. Circulating autoantibody to ABCC3 may be a potential biomarker for esophageal squamous cell carcinoma. *Clin Transl Oncol* 2013; **15**: 398-402 [PMID: 23054755 DOI: 10.1007/s12094-012-0941-9]

90 **Zhang B**, Zhang Z, Zhang X, Gao X, Kernstine KH, Zhong L. Serological antibodies against LY6K as a diagnostic biomarker in esophageal squamous cell carcinoma. *Biomarkers* 2012; **17**: 372-378 [PMID: 22515502 DOI: 10.3109/1354750X.2012.680609]

91 **Kagaya A**, Shimada H, Shiratori T, Kuboshima M, Nakashima-Fujita K, Yasuraoka M, Nishimori T, Kurei S, Hachiya T, Murakami A, Tamura Y, Nomura F, Ochiai T, Matsubara H, Takiguchi M, Hiwasa T. Identification of a novel SEREX antigen family, ECSA, in esophageal squamous cell carcinoma. *Proteome Sci* 2011; **9**: 31 [PMID: 21696638 DOI: 10.1186/1477-5956-9-31]

92 **Dong J**, Zeng BH, Xu LH, Wang JY, Li MZ, Zeng MS, Liu WL. Anti-CDC25B autoantibody predicts poor prognosis in patients with advanced esophageal squamous cell carcinoma. *J Transl Med* 2010; **8**: 81 [PMID: 20813067 DOI: 10.1186/1479-5876-8-81]

93 **Liu WL**, Zhang G, Wang JY, Cao JY, Guo XZ, Xu LH, Li MZ, Song LB, Huang WL, Zeng MS. Proteomics-based identification of autoantibody against CDC25B as a novel serum marker in esophageal squamous cell carcinoma. *Biochem Biophys Res Commun* 2008; **375**: 440-445 [PMID: 18722351 DOI: 10.1016/j.bbrc.2008.08.039]

94 **Tsunemi S**, Nakanishi T, Fujita Y, Bouras G, Miyamoto Y, Miyamoto A, Nomura E, Takubo T, Tanigawa N. Proteomics-based identification of a tumor-associated antigen and its corresponding autoantibody in gastric cancer. *Oncol Rep* 2010; **23**: 949-956 [PMID: 20204278 DOI: 10.3892/or\_00000719]

95 **Shimada H**, Shiratori T, Yasuraoka M, Kagaya A, Kuboshima M, Nomura F, Takiguchi M, Ochiai T, Matsubara H, Hiwasa T. Identification of Makorin 1 as a novel SEREX antigen of esophageal squamous cell carcinoma. *BMC Cancer* 2009; **9**: 232 [PMID: 19604354 DOI: 10.1186/1471-2407-9-232]

96 **Shimada H**, Kagaya A, Shiratori T, Nomura F, Takiguchi M, Matsubara H, Hiwasa T. Detection of anti-CUEC-23 antibodies in serum of patients with esophageal squamous cell carcinoma: A possible new serum marker for esophageal cancer. *J Gastroenterol* 2009; **44**: 691-696 [PMID: 19407926 DOI: 10.1007/s00535-009-0060-8]

97 **Shimada H**, Kuboshima M, Shiratori T, Nabeya Y, Takeuchi A, Takagi H, Nomura F, Takiguchi M, Ochiai T, Hiwasa T. Serum anti-myomegalin antibodies in patients with esophageal squamous cell carcinoma. *Int J Oncol* 2007; **30**: 97-103 [PMID: 17143517 DOI: 10.3892/ijo.30.1.97]

98 **Kuboshima M**, Shimada H, Liu TL, Nomura F, Takiguchi M, Hiwasa T, Ochiai T. Presence of serum tripartite motif-containing 21 antibodies in patients with esophageal squamous cell carcinoma. *Cancer Sci* 2006; **97**: 380-386 [PMID: 16630135 DOI: 10.1111/j.1349-7006.2006.00192.x]

99 **Kuboshima M**, Shimada H, Liu TL, Nakashima K, Nomura F, Takiguchi M, Hiwasa T, Ochiai T. Identification of a novel SEREX antigen, SLC2A1/GLUT1, in esophageal squamous cell carcinoma. *Int J Oncol* 2006; **28**: 463-468 [PMID: 16391802 DOI: 10.3892/ijo.28.2.463]

100 **Nakashima K**, Shimada H, Ochiai T, Kuboshima M, Kuroiwa N, Okazumi S, Matsubara H, Nomura F, Takiguchi M, Hiwasa T. Serological identification of TROP2 by recombinant cDNA expression cloning using sera of patients with esophageal squamous cell carcinoma. *Int J Cancer* 2004; **112**: 1029-1035 [PMID: 15386348 DOI: 10.1002/ijc.20517]

101 **Werner S**, Chen H, Butt J, Michel A, Knebel P, Holleczek B, Zörnig I, Eichmüller SB, Jäger D, Pawlita M, Waterboer T, Brenner H. Evaluation of the diagnostic value of 64 simultaneously measured autoantibodies for early detection of gastric cancer. *Sci Rep* 2016; **6**: 25467 [PMID: 27140836 DOI: 10.1038/srep25467]

**P-Reviewer:** Carbone J, Gheita TA, Matsui K, Mavridis K **S-Editor:** Yan JP

**L-Editor:** **E-Editor:**

**Specialty type:** Gastroenterology and hepatology   
**Country of origin:** China   
**Peer-review report classification**  
**Grade A (Excellent):** 0  
**Grade B (Very good):** B, B  
**Grade C (Good):** C, C  
**Grade D (Fair):** 0 **Grade E (Poor):** 0

**Table 1 A brief summary of the biological significance of some common tumor-associated autoantibodies**

|  |  |  |  |
| --- | --- | --- | --- |
| **Representative tumor-associated autoantigens** | **Authors, year** | **Tumor type** | **Biological significance** |
| p53 | Chapman *et al*[[11](#_ENREF_11)], 2012 | Lung | Early detection |
|  | Takeda *et al*[14], 2001 | Colorectal | Increased recurrence |
|  | Anderson *et al*[[15](#_ENREF_11)], 2010 | Ovarian | Increased survival |
| NY-ESO-1 | Shan *et al*[[16](#_ENREF_11)], 2013 | Lung | Early detection |
|  | Fosså *et al*[[17](#_ENREF_11)], 2004 | Prostate | Decreased survival |
|  | Elke *et al*[[18](#_ENREF_11)], 1999 | Melanoma | Therapeutic monitoring |
| MUC1 | Pedersen *et al*[[19](#_ENREF_11)], 2014 | Ovarian | Early detection |
|  | Kurtenkov *et al*[[20](#_ENREF_11)], 2007 | Gastric | Increased survival |
| Hu | Chapman *et al*[[11](#_ENREF_11)], 2011 | Lung | Early detection |
|  | Graus *et al*[[21](#_ENREF_11)],  1997 | Lung | Therapeutic monitoring and increased survival |

MUC1: Mucin-1.

**Table 2 Diagnostic performance of single tumor-associated autoantibody biomarkers in esophageal squamous cell carcinoma**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Target antigen of autoantibodies** | **Authors, year** | **ESCC cases (*n*)** | **Stage (*n*)** | | | | | **Controls (*n*)** | ***P* value** | **Sensitivity (all stages/early stage)** | **Specificity (all stages/early stage)** | **AUC (all stages/early stage)** | **Method** |
| **0/Ⅰ** | **Ⅱ** | **Ⅲ** | **Ⅳ** | **Tx** |
| Survivin | Xiu *et al*[[57](#_ENREF_57)], 2018 | 159 | - | - | - | - | 159 | 362 | 0.524 | 14.5%/- | 90.0%/- | 0.327/- | ELISA |
|  | Qin *et al*[[58](#_ENREF_57)], 2014 | 174 | 3/8 | 79 | 52 | 18 | - | 242 | < 0.05 | 12.1%/- | 99.6%/- | 99.6/- | ELISA |
|  | Zhou *et al*[[44](#_ENREF_57)], 2014 | 88 | - | - | - | - | 88 | 200 | 0.06 | 9.0%/- | 96.0%/- | - | ELISA |
|  | Megliorino *et al*[[59](#_ENREF_57)], 2005 | 77 | - | - | - | - | 77 | 82 | < 0.05 | 10.4%/- | 97.6%/- | - | ELISA |
| TOPO48 | Zhang *et al*[[60](#_ENREF_57)], 2018 | 112 | 29 | 28 | 28 | 27 | - | 112 healthy volunteers and 75 esophageal benign tumor patients | 0.001 | 49.1%/61.4% | 100.0%/100% | -/0.860 | ELISA |
| L1CAM | Xu *et al*[[61](#_ENREF_57)], 2017 | 191 (Cohort 1) | 10 | 104 | 77 | - | - | 94 (Cohort 1) | 0.005 | 26.2%/25.2% | 90.4%/90.4% | 0.603/0.611 | ELISA |
|  |  | 47 (Cohort 2) | 5 | 18 | 24 | - | - | 47 (Cohort 2) | 0.032 | 27.7%/33.3% | 91.5%/91.5% | 0.628/0.636 | ELISA |
| Ezrin | Li *et al*[[62](#_ENREF_57)], 2017 | 149 | 4/14 | 57 | 71 | 3 | 149 | 98 | < 0.0001 | 27.5%/27.8% | 95.9%/95.9% | - | ELISA |
| STIP1 | Xu *et al*[[63](#_ENREF_57)], 2017 | 148 (Training) | 3/17 | 48 | 76 | 4 | 148 | 111 (Training) | < 0.001 | 41.9%/35.7% | 90.1%/90.1% | 0.682/0.684 | ELISA |
|  |  | 60 (Validation) | 1/8 | 20 | 30 | 1 | 60 | 40 (Validation) | < 0.001 | 40.0%/38.5% | 92.5%/92.5% | 0.710/0.756 | ELISA |
| Fascin | Chen *et al*[[64](#_ENREF_57)], 2017 | 149 | 4/14 | 57 | 71 | 3 | 149 | 98 | < 0.001 | 24.8%/20.6% | 99.0%/99.0% | 0.636/0.632 | ELISA |
| DKK-1 | Peng *et al*[[65](#_ENREF_57)], 2016 | 185 (Training) | 4/23 | 69 | 85 | 4 | 185 | 97 (Training) | < 0.0001 | 33.5%/34.6% | 91.8%/91.8% | 0.643/0.640 | ELISA |
|  |  | 104 (Validation) | 1/12 | 35 | 53 | 3 | 104 | 53 (Validation) | < 0.0001 | 33.7%/26.9% | 92.5%/92.5% | 0.629/0.603 | ELISA |
| P16 | Zhang *et al*[[55](#_ENREF_57)], 2016 | 324 (Training) | 5/13 | 130 | 50 | 39 | 87 | 324 (Training) | < 0.001 | 29.3%/- | 81.8%/- | 0.60/- | ELISA |
|  |  | 186 (Validation) | 1 | 29 | 14 | 46 | 96 | 186 (Validation) | < 0.01 | - | - | - | ELISA |
|  | Jin *et al*[[66](#_ENREF_57)], 2015 | 88 | 24 | 42 | 15 | 2 | 5 | 208 | 0.0052 | 5.7%/- | 99.1%/- | - | ELISA |
|  | Qin *et al*[[58](#_ENREF_57)], 2014 | 174 | 3/8 | 79 | 52 | 18 | - | 242 | < 0.05 | 18.4%/- | 98.8%/- | 0.6/- | ELISA |
|  | Zhou *et al*[[44](#_ENREF_57)], 2014 | 88 | - | - | - | - | 88 | 200 | 0.004 | 11.0%/- | 97.0%/- | - | ELISA |
|  | Looi *et al*[[67](#_ENREF_57)], 2006 | 71 | - | - | - | - | - | 82 | < 0.05 | 14.1%/- | 98.8%/- | - | ELISA |
| P53 | Zhang *et al*[[55](#_ENREF_57)], 2016 | 324 (Training) | 5/13 | 130 | 50 | 39 | 87 | 324 (Training) | < 0.001 | 55.9%/- | 89.5%/- | 0.784/- | ELISA |
|  |  | 186 (Validation) | 1 | 29 | 14 | 46 | 96 | 186 (Validation) | < 0.001 | -/- | -/- | -/- | ELISA |
|  | Xu *et al*[[43](#_ENREF_57)], 2014 | 388 (Test) | 2/29 | 96 | 229 | 27 | 5 | 125 (Test) | < 0.0001 | 30.0%/- | 98.0%/- | - | ELISA |
|  |  | 237 (Validation) | 2/31 | 114 | 90 | - | - | 134 (Validation) | < 0.0001 | 29.0%/- | 97.0%/- | - | ELISA |
|  | Qin *et al*[[58](#_ENREF_57)], 2014 | 174 | 3/8 | 79 | 52 | 18 | - | 242 | < 0.05 | 21.8%/- | 96.3%/- | 0.6/- | ELISA |
|  | Chai *et al*[[68](#_ENREF_57)], 2014 | 157 | - | - | - | - | 157 | 85 | < 0.01 | 22.9%/- | 100%/- | - | ELISA |
|  | Zhou *et al*[[44](#_ENREF_57)], 2014 | 88 | - | - | - | - | 88 | 200 | < 0.001 | 22.0%/- | 98.0%/- | - | ELISA |
|  | Cai *et al*[[69](#_ENREF_57)], 2008 | 46 | 10 | 17 | 14 | 5 | - | 30 | < 0.0001 | 39.1%/22.2% | 100%/100% | - | ELISA |
|  | Looi *et al*[[67](#_ENREF_57)], 2006 | 71 | - | - | - | - | 71 | 82 | < 0.05 | 7%/- | 98.8%/- | - | ELISA |
|  | Müller *et al*[[70](#_ENREF_57)], 2006 | 50 | - | - | - | - | 50 | 436 | < 0.05 | 20.0%/- | 100%/- | - | Western blot |
|  | Megliorino *et al*[[59](#_ENREF_57)], 2005 | 77 | - | - | - | - | 77 | 82 | < 0.01 | 14.3%/- | 97.6%/- | - | ELISA |
|  | Shimada *et al*[[71](#_ENREF_57)], 2003 | 301 | - | - | - | - | 301 | 205 | < 0.05 | 30.0%/- | 95.5%/- | - | ELISA |
|  | Shimada *et al*[[72](#_ENREF_57)], 2002 | 105 | 50 | 24 | 21 | 10 | - | 153 | < 0.001 | 26.7%/20.0% | 95.5%/95.5% | - | ELISA |
|  | Ralhan *et al*[[73](#_ENREF_57)], 2000 | 60 | - | - | - | - | 60 | 50 | < 0.05 | 60.0%/- | 92.0%/- | - | ELISA |
|  | Shimada *et al*[[74](#_ENREF_57)], 2000 | 35 | - | - | - | - | 35 | 69 | < 0.0001 | 40.0%/- | 100.0%/- | - | ELISA |
|  | Hagiwara *et al*[[75](#_ENREF_57)], 2000 | 46 | 6 | 15 | 24 | 2 | - | 13 | < 0.05 | 28.0%/28.6% | 100%/100% | - | ELISA |
|  | Shimada *et al*[[76](#_ENREF_57)], 1998 | 57 | 6/9 | 9 | 11 | 11 | 1 | 208 | < 0.05 | 58.0%/- | 99.0%/- | - | ELISA |
|  | Sobti *et al*[[77](#_ENREF_57)], 1998 | 20 | - | - | - | - | 20 | 20 | 0.0202 | 30.0%/- | 100%/- | - | ELISA |
|  | Cawley *et al*[[78](#_ENREF_57)], 1988 | 23 | - | - | - | - | 23 | 19 | 0.0372 | 34.8%/- | 94.7%/- | - | ELISA |
| NY-ESO-1 | Xu *et al*[[43](#_ENREF_57)], 2014 | 388 (Test) | 2/29 | 96 | 229 | 27 | 5 | 125 (Test) | < 0.0001 | 26.0%/- | 100%/- | - | ELISA |
|  |  | 237 (Validation) | 2/31 | 114 | 90 | - | - | 134 (Validation) | < 0.0001 | 24.0%/- | 99.0%/- | - | ELISA |
|  | Oshima *et al*[[79](#_ENREF_57)], 2016 | 172 | - | - | - | - | 172 | 74 | < 0.001 | 32.0%/16.0% | 100%/100% | - | ELISA |
|  | Fujita *et al*[[80](#_ENREF_57)], 2004 | 51 | - | - | - | - | 51 | 29 | 0.532 | 3.9%/- | 100%/- | - | ELISA |
| P90 | Zhang *et al*[[55](#_ENREF_57)], 2016 | 324 (Training) | 5/13 | 130 | 50 | 39 | 87 | 324 (Training) | < 0.001 | 31.5%/- | 84.9%/- | 0.617/- | ELISA |
|  |  | 186 (Validation) | 1 | 29 | 14 | 46 | 96 | 186 (Validation) | < 0.001 | - | - | - | ELISA |
| Mmp-7 | Xu *et al*[[43](#_ENREF_57)], 2014 | 388 (Test) | 2/29 | 96 | 229 | 27 | 5 | 125 (Test) | < 0.001 | 9.0%/- | 100%/- | - | ELISA |
|  |  | 237 (Validation) | 2/31 | 114 | 90 | - | - | 134 (Validation) | < 0.001 | 10.0%/- | 100%/- | - | ELISA |
|  | Zhou *et al*[[81](#_ENREF_57)], 2011 | 50 | - | - | - | - | 50 | 58 | < 0.001 | 78.0% | 81.0% | 0.87/- | ELISA |
| Hsp70 | Xu *et al*[[43](#_ENREF_57)], 2014 | 388 (Test) | 2/29 | 96 | 229 | 27 | 5 | 125 (Test) | < 0.001 | 11.0%/- | 99.0%/- | - | ELISA |
|  |  | 237 (Validation) | 2/31 | 114 | 90 | - | - | 134 (Validation) | < 0.01 | 8.0%/- | 99.0%/- | - | ELISA |
|  | Zhang *et al*[[82](#_ENREF_57)], 2011 | 69 | - | - | - | - | 69 | 76 | > 0.01 | 39.1%/- | 92.3%/- | - | ELISA |
|  | Fujita *et al*[[40](#_ENREF_57)], 2008 | 16 | 2 | 7 | 4 | 3 | - | 13 | < 0.001 | 93.7%/- | 100%/- | - | ELISA |
| PRDX 6 | Xu *et al*[[43](#_ENREF_57)], 2014 | 388 (Test) | 2/29 | 96 | 229 | 27 | 5 | 125 (Test) | < 0.001 | 11.0%/- | 100%/- | - | ELISA |
|  |  | 237 (Validation) | 2/31 | 114 | 90 | - | - | 134 (Validation) | < 0.001 | 10.0%/- | 100%/- | - | ELISA |
|  | Fujita *et al*[[83](#_ENREF_57)], 2006 | 30 | 7 | 8 | 11 | 4 | - | 30 | < 0.05 | 50.0%/53.5% | 93.4%/93.4% | - | Western blot |
| Bmi-1 | Xu *et al*[[43](#_ENREF_57)], 2014 | 388 (Test) | 2/29 | 96 | 229 | 27 | 5 | 125 (Test) | < 0.01 | 11.0%/- | 98.0%/- | - | ELISA |
|  |  | 237 (Validation) | 2/31 | 114 | 90 | - | - | 134 (Validation) | < 0.01 | 8.0%/- | 100%/- | - | ELISA |
|  | Liu *et al*[[84](#_ENREF_57)], 2010 | 159 | 6 | 72 | 69 | 12 | - | 102 | < 0.001 | 39.0%/- | 100%/- | - | ELISA |
| Imp1 | Zhang *et al*[[55](#_ENREF_57)], 2016 | 324 (Training) | 5/13 | 130 | 50 | 39 | 87 | 324 (Training) | < 0.001 | 26.9%/- | 81.2%/- | 0.576/- | ELISA |
|  |  | 186 (Validation) | 1 | 29 | 14 | 46 | 96 | 186 (Validation) | < 0.01 | - | - | - | ELISA |
|  | Qin *et al*[[58](#_ENREF_57)], 2014 | 174 | 3/8 | 79 | 52 | 18 | - | 242 | < 0.05 | 16.1%/- | 98.3%/- | 0.6/- | ELISA |
|  | Zhou *et al*[[44](#_ENREF_57)], 2014 | 88 | - | - | - | - | 88 | 200 | < 0.001 | 14.0%/- | 99.0%/- | - | ELISA |
| Cyclin B1 | Qin *et al*[[58](#_ENREF_57)], 2014 | 174 | 3/8 | 79 | 52 | 18 | - | 242 | < 0.05 | 16.1%/- | 97.9%/- | 0.6/- | ELISA |
|  | Zhou *et al*[[44](#_ENREF_57)], 2014 | 88 | - | - | - | - | 88 | 200 | 0.02 | 10.0%/- | 97.0%/- | - | ELISA |
| C-Myc | Zhang *et al*[[55](#_ENREF_57)], 2016 | 324 (Training) | 5/13 | 130 | 50 | 39 | 87 | 324 (Training) | < 0.001 | 49.1%/- | 81.5%/- | 0.699/- | ELISA |
|  |  | 186 (Validation) | 1 | 29 | 14 | 46 | 96 | 186 (Validation) | < 0.001 | - | - | - | ELISA |
|  | Qin *et al*[[58](#_ENREF_57)], 2014 | 174 | 3/8 | 79 | 52 | 18 | - | 242 | < 0.05 | 15.5%/- | 98.8%/- | 0.6/- | ELISA |
|  | Zhou *et al*[[44](#_ENREF_57)], 2014 | 88 | - | - | - | - | 88 | 200 | < 0.001 | 18.0%/- | 96.0%/- | - | ELISA |
|  | Looi *et al*[[67](#_ENREF_57)], 2006 | 71 | - | - | - | - | - | 82 | < 0.05 | 7%/- | 100%/- | - | ELISA |
|  | Megliorino *et al*[[59](#_ENREF_57)], 2005 | 77 | - | - | - | - | 77 | 82 | < 0.01 | 11.7%/- | 100%/- | - | ELISA |
| RalA | Qin *et al*[[58](#_ENREF_57)], 2014 | 174 | 3/8 | 79 | 52 | 18 | - | 242 | < 0.05 | 15.5%/- | 96.7%/- | 0.6/- | ELISA |
| P62 | Zhang *et al*[[55](#_ENREF_57)], 2016 | 324 (Training) | 5/13 | 130 | 50 | 39 | 87 | 324 (Training) | < 0.001 | 29.3%/- | 81.8%/- | 0.60/- | ELISA |
|  |  | 186 (Validation) | 1 | 29 | 14 | 46 | 96 | 186 (Validation) | < 0.001 | - | - | - | ELISA |
|  | Qin *et al*[[58](#_ENREF_57)], 2014 | 174 | 3/8 | 79 | 52 | 18 | - | 242 | < 0.05 | 12.1%/- | 95.9%/- | 0.5/- | ELISA |
|  | Zhou *et al*[[44](#_ENREF_57)], 2014 | 88 | - | - | - | - | 88 | 200 | 0.001 | 13.0%/- | 98.0%/- | - | ELISA |
| Koc | Zhang *et al*[[55](#_ENREF_57)], 2016 | 324 (Training) | 5/13 | 130 | 50 | 39 | 87 | 324 (Training) | < 0.001 | 35.8%/- | 82.1%/- | 0.63/- | ELISA |
|  |  | 186 (Validation) | 1 | 29 | 14 | 46 | 96 | 186 (Validation) | < 0.05 | - | - | - | ELISA |
|  | Qin *et al*[[58](#_ENREF_57)], 2014 | 174 | 3/8 | 79 | 52 | 18 | - | 242 | < 0.05 | 11.5%/- | 97.9%/- | 0.5/- | ELISA |
|  | Zhou *et al*[[44](#_ENREF_57)], 2014 | 88 | - | - | - | - | 88 | 200 | 0.05 | 10.0%/- | 96.0%/- | - | ELISA |
| Cyclin D1 | Qin *et al*[[58](#_ENREF_57)], 2014 | 174 | 3/8 | 79 | 52 | 18 | - | 242 | < 0.05 | 10.3%/- | 96.3%/- | 0.5/- | ELISA |
| Cyclin E | Zhang *et al*[[55](#_ENREF_57)], 2016 | 324 (Training) | 5/13 | 130 | 50 | 39 | 87 | 324 (Training) | < 0.001 | 26.5%/- | 83.0%/- | 0.581/- | ELISA |
|  |  | 186 (Validation) | 1 | 29 | 14 | 46 | 96 | 186 (Validation) | < 0.05 | - | - | - | ELISA |
|  | Qin *et al*[[58](#_ENREF_57)], 2014 | 174 | 3/8 | 79 | 52 | 18 | - | 242 | < 0.05 | 10.3%/- | 99.2%/- | 0.5/- | ELISA |
| HCCR | Zhang *et al*[[55](#_ENREF_57)], 2016 | 324 (Training) | 5/13 | 130 | 50 | 39 | 87 | 324 (Training) | < 0.001 | 34.6%/- | 80.0%/- | 0.596/- | ELISA |
|  |  | 186 (Validation) | 1 | 29 | 14 | 46 | 96 | 186 (Validation) | < 0.001 | - | - | - | ELISA |
| GSTO1 | Li *et al*[[85](#_ENREF_57)], 2014 | 67 | - | - | - | - | 67 | 90 | < 0.01 | 44.8%/- | 93.3%/- | - | ELISA |
| MDM2 | Chai *et al*[[68](#_ENREF_57)], 2014 | 157 | - | - | - | - | 157 | 85 | < 0.01 | 14.0%/- | 98.8%/- | - | ELISA |
| HSP105 | Gao *et al*[[51](#_ENREF_57)], 2014 | 46 | 7 | - | - | - | 39 | 40 | < 0.01 | 39.1%/42.9% | 95%/95% | 0.794/- | Western blot |
| TIM | Gao *et al*[[51](#_ENREF_57)], 2014 | 46 | 7 | - | - | - | 39 | 40 | < 0.01 | 34.8%/28.6% | 95%/95% | 0.786/- | Western blot |
| Prdx1 | Ren *et al*[[86](#_ENREF_57)], 2013 | 68 | - | - | - | - | 68 | 89 | < 0.01 | 13.2%/- | 100%/- | - | ELISA, Western blot |
| FOXP3 | Ye *et al*[[87](#_ENREF_57)], 2013 | 97 | 26 | 45 | 19 | 2 | 5 | 227 | < 0.0001 | 22.7%/- | 95.2%/- | 0.70/- | ELISA, |
| CD25 | Guan *et al*[[88](#_ENREF_57)], 2013 | 97 | 26 | 45 | 17 | 3 | 6 | 226 | < 0.001 | 37.2%/- | 90.0%/- | 0.69/- | ELISA |
| ABCC3 (IgA) | Cheng *et al*[[89](#_ENREF_57)], 2013 | 114 | - | - | - | - | - | 226 | < 0.001 | 13.2%/- | >95%/- | 0.65/- | ELISA |
| LY6K | Zhang *et al*[[90](#_ENREF_57)], 2012 | 62 | 13 | | 27 | 22 | - | 58 | < 0.001 | 80.6%/73.2% | 78.7%/78.7% | 0.85/- | ELISA |
| HMGB1 | Zhang *et al*[[82](#_ENREF_57)], 2011 | 69 | - | - | - | - | 69 | 76 | > 0.05 | 7.2%/- | 98.7%/- | - | ELISA |
| ESCA-1 | Kagaya *et al*[[91](#_ENREF_57)], 2011 | 146 | 32 | 29 | 42 | 43 | - | 118 | 0.0001 | 21.2%/- | 98.3%/- | - | ELISA |
| ESCA-2 | Kagaya *et al*[[91](#_ENREF_57)], 2011 | 72 | 37 | | 35 | | 72 | 98 | 0.0026 | 15.3%/8.1% | 99.0%/99.0% | - | ELISA |
| ESCA-3 | Kagaya *et al*[[91](#_ENREF_57)], 2011 | 68 | - | - | - | - | 68 | 74 | 0.0079 | 16.2%/- | 98.6%/- | - | ELISA |
| CDC25B | Dong *et al*[[92](#_ENREF_57)], 2010 | 134 | 80 | | 54 | | - | 134 | < 0.001 | 56.7%/- | 91.0% | 0.87/- | ELISA |
|  | Liu *et al*[[93](#_ENREF_57)], 2008 | 124 | - | - | - | - | 123 | 102 | < 0.05 | 36.3%/- | 100%/- | - | ELISA |
| GRP78 | Tsunemi *et al*[[94](#_ENREF_57)], 2010 | 15 | - | - | - | - | 15 | 20 | < 0.05 | 26.7%/- | 100%/- | - | Western blot |
| Makorin 1 | Shimada *et al*[[95](#_ENREF_57)], 2009 | 73 | 1/13 | 21 | 27 | 11 | - | 43 | < 0.05 | 25.0%/22.9% | 100%/100% | - | Western blot |
| CUEC-23 | Shimada *et al*[[96](#_ENREF_57)], 2009 | 54 | 7 | 13 | 18 | 16 | - | 46 | < 0.05 | 26.0%/33.3% | 96.0%/- | - | Western blot |
|  | Shimada *et al*[[96](#_ENREF_57)], 2009 | 29 | 1 | 11 | 8 | 9 | - | 46 | 0.036 | 17.0%/- | 100%/- | - | ELISA |
| MMGL | Shimada *et al*[[97](#_ENREF_57)], 2007 | 91 | 21 | 22 | 35 | 13 | - | 45 | < 0.05 | 47.0%/38.0% | 97.8%/97.8% | - | Western blot |
| TRIM21 | Kuboshima *et al*[[98](#_ENREF_57)], 2006 | 91 | 39 | | 52 | | - | 42 | < 0.05 | 20.0%/13.0% | 100%/100% | - | Western blot |
|  | Kuboshima *et al*[[98](#_ENREF_57)], 2006 | 54 | - | - | - | - | 54 | 42 | 0.013 | 15.0%/- | 98.0%/- | - | ELISA |
| SLC2A1 | Kuboshima *et al*[[99](#_ENREF_57)], 2006 | 57 | 19 | 6 | 13 | 19 | - | 31 | < 0.001 | 21.0%/22.0% | 100%/100% | - | ELISA |
| SURF1 | Shimada *et al*[[50](#_ENREF_57)], 2005 | 21 | - | 3 | 13 | 5 | - | 37 | 0.0003 | 48%/- | 95%/- | - | ELISA |
| LOC 146223 | Shimada *et al*[[50](#_ENREF_57)], 2005 | 21 | - | 3 | 13 | 5 | - | 37 | 0.0028 | 38%/- | 95%/- | - | ELISA |
| HOOK2 | Shimada *et al*[[50](#_ENREF_57)], 2005 | 21 | - | 3 | 13 | 5 | - | 37 | 0.0431 | 14%/- | 100%/- | - | ELISA |
| AGENCOURT\_7565913 | Shimada *et al*[[50](#_ENREF_57)], 2005 | 21 | - | 3 | 13 | 5 | - | 37 | 0.0431 | 14%/- | 100%/- | - | ELISA |
| TROP2 | Nakashima *et al*[[100](#_ENREF_57" \o "Xiu, 2018 #551)], 2004 | 75 | 14 | 14 | 24 | 23 | - | 43 | < 0.05 | 31.0%/21.0% | 97.7%/97.7% | - | Western blot |

ESCC: Esophageal squamous cell carcinoma; AUC: Area under the curve; L1CAM: L1-cell adhesion molecule; STIP1: Stress induced phosphoprotein 1; DKK-1: Dickkopf 1; Mmp-7: Matrix metallopeptidase 7; Hsp70: Heat shock protein 70; PRDX 6: Peroxiredoxin 6; Bmi-1: BMI1 proto-oncogene, polycomb ring finger; Imp1: Insulin like growth factor 2 mRNA binding protein 1; C-Myc: MYC proto-oncogene, bHLH transcription factor; Koc: Insulin like growth factor 2 mRNA binding protein 3; HCCR: LETM1 domain containing 1; GSTO1: Glutathione S-transferase omega 1; MDM2: MDM2 proto-oncogene; HSP105: Heat shock protein family H (Hsp110) member 1; TIM: Rho guanine nucleotide exchange factor 5; Prdx1: Peroxiredoxin 1; FOXP3: Forkhead box P3; CD25: Interleukin 2 receptor subunit alpha; ABCC3: ATP binding cassette subfamily C member 3; LY6K: Lymphocyte antigen 6 family member K; HMGB1, high mobility group box 1; CDC25B: Cell division cycle 25B; GRP78: Heat shock protein family A (Hsp70) member 5; Makorin 1: Makorin ring finger protein 1; MMGL: Myomegalin; TRIM21: Tripartite motif containing 21; SLC2A1: Solute carrier family 2 member 1; SURF1: SURF1 cytochrome c oxidase assembly factor; HOOK2: Hook microtubule tethering protein 2; TROP2: Tumor associated calcium signal transducer 2.

**Table 3 Diagnostic performance of single tumor-associated autoantibody biomarkers in esophagogastric junction adenocarcinoma**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Target antigen of autoantibodies** | **Authors, year** | **EGJA cases (*n*)** | **Stage (*n*)** | | | | | **Controls (*n*)** | ***P* value** | **Sensitivity (all stages/early stage)** | **Specificity (all stages/early stage)** | **AUC (all stages/early stage)** | **Method** |
| **Ⅰ** | **Ⅱ** | **Ⅲ** | **Ⅳ** | **Tx** |
| P53 | Xu *et al*[[42](#_ENREF_99)], 2019 | 122 (Training) | 2 | 16 | 87 | 17 | 122 | 169 (Validation) | < 0.0001 | 35.2%/33.3% | 90.5%/90.5% | 0.718/0.648 | ELISA |
|  |  | 70 (Training) | 11 | 14 | 30 | 15 | 80 | 80 (Validation) | < 0.0001 | 35.7%/40.0% | 96.3%/96.3% | 0.766/0.799 | ELISA |
|  | Zhou *et al*[[41](#_ENREF_99)], 2015 | 75 | - | - | - | - | 75 | 140 | < 0.001 | 24.0%/- | 92%/- | 0.67/- | ELISA |
| NY-ESO-1 | Xu *et al*[[42](#_ENREF_99)], 2019 | 122 (Training) | 2 | 16 | 87 | 17 | 122 | 169 (Validation) | < 0.0001 | 37.7%/27.8% | 90.5%/90.5% | 0.718/0.654 | ELISA |
|  |  | 70 (Training) | 11 | 14 | 30 | 15 | 80 | 80 (Validation) | < 0.0001 | 34.3%/28.0% | 95.0%/95.0% | 0.747/0.714 | ELISA |
| PRDX6 | Xu *et al*[[42](#_ENREF_99)], 2019 | 122 (Training) | 2 | 16 | 87 | 17 | 122 | 169 (Validation) | 0.033 | 34.4%/38.9% | 90.5%/90.5% | 0.573/0.602 | ELISA |
|  |  | 70 (Training) | 11 | 14 | 30 | 15 | 80 | 80 (Validation) | 0.002 | 30.0%/28.0% | 90.0%/90.0% | 0.647/0.629 | ELISA |
| MMP-7 | Xu *et al*[[42](#_ENREF_99)], 2019 | 122 (Training) | 2 | 16 | 87 | 17 | 122 | 169 (Validation) | 0.005 | 30.3%/33.3% | 90.5%/90.5% | 0.597/0.575 | ELISA |
|  |  | 70 (Training) | 11 | 14 | 30 | 15 | 80 | 80 (Validation) | 0.036 | 24.3%/28.0% | 95.0%/95.0% | 0.599/0.609 | ELISA |
| Hsp70 | Xu *et al*[[42](#_ENREF_99)], 2019 | 122 (Training) | 2 | 16 | 87 | 17 | 122 | 169 (Validation) | < 0.0001 | 18.0%/16.7% | 90.5%/90.5% | 0.652/0.697 | ELISA |
|  |  | 70 (Training) | 11 | 14 | 30 | 15 | 80 | 80 (Validation) | < 0.0001 | 28.6%/32.0% | 86.3%/86.3% | 0.686/0.702 | ELISA |
| Bmi-1 | Xu *et al*[[42](#_ENREF_99)], 2019 | 122 (Training) | 2 | 16 | 87 | 17 | 122 | 169 (Validation) | < 0.0001 | 22.1%/27.8% | 90.5%/90.5% | 0.686/0.685 | ELISA |
|  |  | 70 (Training) | 11 | 14 | 30 | 15 | 80 | 80 (Validation) | < 0.0001 | 54.3%/40.0% | 90.0%/90.0% | 0.711/0.682 | ELISA |
| Koc | Zhou *et al*[[41](#_ENREF_99)], 2015 | 75 | - | - | - | - | 75 | 140 | 0.05 | 19.0%/- | 91%/- | - | ELISA |
| P62 | Zhou *et al*[[41](#_ENREF_99)], 2015 | 75 | - | - | - | - | 75 | 140 | 0.02 | 16.0%/- | 94%/- | - | ELISA |
| C-Myc | Zhou *et al*[[41](#_ENREF_99)], 2015 | 75 | - | - | - | - | 75 | 140 | 0.18 | 11.0%/- | 94%/- | - | ELISA |
| IMP1 | Zhou *et al*[[41](#_ENREF_99)], 2015 | 75 | - | - | - | - | 75 | 140 | 0.04 | 13.0%/- | 95%/- | - | ELISA |
| Survivin | Zhou *et al*[[41](#_ENREF_99)], 2015 | 75 | - | - | - | - | 75 | 140 | 0.002 | 17.0%/- | 96%/- | - | ELISA |
| P16 | Zhou *et al*[[41](#_ENREF_99)], 2015 | 75 | - | - | - | - | 75 | 140 | 0.01 | 15.0%/- | 96%/- | - | ELISA |
| Cyclin B1 | Zhou *et al*[[41](#_ENREF_99)], 2015 | 75 | - | - | - | - | 75 | 140 | 0.01 | 12.0%/- | 97%/- | - | ELISA |

EGJA: Esophagogastric junction adenocarcinoma; AUC: Area under the curve; PRDX 6: Peroxiredoxin 6; Mmp-7: Matrix metallopeptidase 7; Hsp70: Heat shock protein 70; Bmi-1: BMI1 proto-oncogene, polycomb ring finger; Koc: Insulin like growth factor 2 mRNA binding protein 3; C-Myc: MYC proto-oncogene, bHLH transcription factor; IMP1: Insulin like growth factor 2 mRNA binding protein 1.

**Table 4 Diagnostic performance of tumor-associated autoantibody panel in esophageal squamous cell carcinoma**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Target antigen of autoantibodies** | **Authors, year** | **ESCC cases (*n*)** | **Stage (*n*)** | | | | | **Controls (*n*)** | **Sensitivity (all stages/early stage)** | **Specificity (all stages/early stage)** | **AUC (all stages/early stage)** | **Method** |
| **0/Ⅰ** | **Ⅱ** | **Ⅲ** | **Ⅳ** | **Unknown** |
| c-Myc, HCCR, IMP1, Koc, p53 and p62 | Zhang *et al*[[55](#_ENREF_55)], 2016 | 324 (Training) | 5/13 | 130 | 50 | 39 | 87 | 324 (Training) | 67.9%/66.9% | 86.7%/86.7% | 0.838/0.829 | ELISA |
|  |  | 186 (Validation) | 1 | 29 | 14 | 46 | 96 | 186 (Validation) | 67.7%/56.7% | 85.5%/85.5% | 0.859/0.818 | ELISA |
| c-Myc, HCCR, p53 and p62 | Zhang *et al*[[55](#_ENREF_55)], 2016 | 324 (Training) | 5/13 | 130 | 50 | 39 | 87 | 324 (Training) | 67.6%/67.6% | 86.4%/86.4% | 0.838/0.831 | ELISA |
|  |  | 186 (Validation) | 1 | 29 | 14 | 46 | 96 | 186 (Validation) | 72.0%/63.3% | 85.0%/85.0% | 0.872/0.837 | ELISA |
| MAGEA4, CTAG1, TP53, SDCCAG8 and ERBB2\_C | Werner *et al*[[101](#_ENREF_55)], 2016 | 31 | - | - | - | - | 31 | 321 | 26.0%/- | 88.5%/- | - | Bead-based multiplex serology |
| P53 and MDM2 | Chai *et al*[[68](#_ENREF_55)], 2014 | 157 | - | - | - | - | 157 | 85 | 35.0%/- | 98.8%/- | - | ELISA |
| p53, pl6, Impl, CyclinB1, c-Myc, RalA, p62, Survivin, Koc, Cyclin D1 and Cyclin E | Qin *et al*[[58](#_ENREF_55)], 2014 | 174 | 3/8 | 79 | 52 | 18 | - | 242 | 75.3%/- | 81.0%/- | 0.78/- | ELISA |
| P53, NY-ESO-1, MMP-7, Hsp70, PRDX 6 and Bmi-1 | Xu *et al*[[43](#_ENREF_55)], 2014 | 388 (Test) | 2/29 | 96 | 229 | 27 | 5 | 125 (Test) | 57.0%/45.0% | 95.0%/95.0% | - | ELISA |
|  |  | 237 (Validation) | 2/31 | 114 | 90 | - | - | 134 (Validation) | 51.0%/46.0% | 96.0%/96.0% | - | ELISA |
| P53, NY-ESO-1, Hsp70 and PRDX 6 | Xu *et al*[[43](#_ENREF_55)], 2014 | 388 (Test) | 2/29 | 96 | 229 | 27 | 5 | 125 (Test) | 55.0%/45.0% | 98.0%/98.0% | - | ELISA |
|  |  | 237 (Validation) | 2/31 | 114 | 90 | - | - | 134 (Validation) | 48.0%/45.0% | 96.0%/96.0% | - | ELISA |
| P53, IMP1, P16, Cyclin B1, P62, and C-myc | Zhou *et al*[[44](#_ENREF_55)], 2014 | 88 | - | - | - | - | 88 | 200 | 64.0%/- | 94.0%/- | 0.78/- | ELISA |
| HSP105 and TIM | Gao *et al*[[51](#_ENREF_55)], 2014 | 46 | 7 | - | - | - | 39 | 40 | 54.3%/- | 95.0%/- | 0.823/- | Western blot |
| p16, c-Myc and p53 | Looi *et al*[[67](#_ENREF_55)], 2006 | 71 | - | - | - | - | 71 | 82 | 7%/- | 100%/- | - | ELISA |
| SURF1, LOC146223, HOOK2 and AGENCOURT\_7565913 | Shimada *et al*[[50](#_ENREF_55)], 2005 | 21 | - | 3 | 13 | 5 | - | 37 | 86%/- | 100%/- | - | ELISA |
| Survivin, p53 and C-myc | Megliorino *et al*[[59](#_ENREF_55)], 2005 | 77 | - | - | - | - | 77 | 82 | 29.9%/- | 95.1%/- | - | ELISA |

ESCC: Esophageal squamous cell carcinoma; AUC: Area under the curve; C-Myc: MYC proto-oncogene, bHLH transcription factor; HCCR: LETM1 domain containing 1; IMP1: Insulin like growth factor 2 mRNA binding protein 1; Koc: Insulin like growth factor 2 mRNA binding protein 3; MAGEA4: MAGE family member A4; CTAG1: Cancer/testis antigen 1B; SDCCAG8: Serologically defined colon cancer antigen 8; ERBB2: Erb-b2 receptor tyrosine kinase 2; MDM2: MDM2 proto-oncogene; HSP105: Heat shock protein family H (Hsp110) member 1; TIM: Rho guanine nucleotide exchange factor 5; SURF1: SURF1 cytochrome c oxidase assembly factor; HOOK2: Hook microtubule tethering protein 2.

**Table 5 Diagnostic performance of tumor-associated autoantibody panel in esophagogastric junction adenocarcinoma**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Target antigen of autoantibodies** | **Authors, year** | **EGJA cases (*n*)** | **Stage (*n*)** | | | | | **Controls (*n*)** | **Sensitivity (all stages/early stage)** | **Specificity (all stages/early stage)** | **AUC (all stages/ early stage)** | **Method** |
| **0/Ⅰ** | **Ⅱ** | **Ⅲ** | **Ⅳ** | **Unknown** |
| P53, NY-ESO-1, MMP-7, Hsp70, PRDX6 and Bmi-1 | Xu *et al*[[42](#_ENREF_99)], 2019 | 122 (Training) | 2 | 16 | 87 | 17 | 122 | 169 (Validation) | 59.0%/50.0% | 90.5%/90.5% | 0.818/0.786 | ELISA |
|  |  | 70 (Validation) | 11 | 14 | 30 | 15 | 80 | 80 (Validation) | 61.4%/56.0% | 90.0%/90.0% | 0.815/0.786 | ELISA |
| P53, NY-ESO-1 and Bmi-1 | Xu *et al*[[42](#_ENREF_99)], 2019 | 122 (Training) | 2 | 16 | 87 | 17 | 122 | 169 (Validation) | 53.5%/55.6% | 90.5%/90.5% | 0.814/0.744 | ELISA |
|  |  | 70 (Validation) | 11 | 14 | 30 | 15 | 80 | 80 (Validation) | 60.0%/52.0% | 93.7%/93.7% | 0.823/0.773 | ELISA |
| P53, Koc, P62, c-Myc, IMP1, Survivin and P16 | Zhou *et al*[[41](#_ENREF_99)], 2015 | 75 | - | - | - | - | 75 | 140 | 64.0%/- | 87.0%/- | 0.73/- | ELISA |

EGJA: Esophagogastric junction adenocarcinoma; AUC: Area under the curve; Mmp-7: Matrix metallopeptidase 7; Hsp70: Heat shock protein 70; PRDX 6: Peroxiredoxin 6; Bmi-1: BMI1 proto-oncogene, polycomb ring finger; Koc: Insulin like growth factor 2 mRNA binding protein 3; C-Myc: MYC proto-oncogene, bHLH transcription factor; IMP1: Insulin like growth factor 2 mRNA binding protein 1.

****

**Figure 1 Graphical representation of sensitivity versus specificity for single tumor-associated autoantibody biomarkers in esophageal squamous cell carcinoma reported in more than one study.** Mmp-7: Matrix metallopeptidase 7; Hsp70: Heat shock protein 70; PRDX 6: Peroxiredoxin 6; Bmi-1: BMI1 proto-oncogene, polycomb ring finger; Koc: Insulin like growth factor 2 mRNA binding protein 3; C-Myc: MYC proto-oncogene, bHLH transcription factor; IMP1: Insulin like growth factor 2 mRNA binding protein 1.