Systematic Review and Meta-Analysis

Medicine®

OPEN

Prognostic significance of X-linked inhibitor of apoptosis protein in patients with gastrointestinal tract cancers

A meta-analysis

Chengcheng Ieong, MD[a], Hong Yang, MD[a], Junpeng Ma, MD[b], Wenli Lai, MD[a,*]

Abstract

Background: The aim of this meta-analysis was to systematically evaluate the prognostic significance of X-linked inhibitor of apoptosis protein (XIAP) in patients with gastrointestinal tract (GIT) cancers.

Methods: PubMed, Web of Science, EMBASE, Cochrane Library and China National Knowledge Infrastructure were searched for potentially eligible literature. The baseline characteristics and relevant data were extracted. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated to assess the prognostic role of XIAP in patients with GIT cancers.

Results: Twelve studies with 2,477 patients were included. The pooled HRs of higher expression of XIAP for overall survival (OS) and recurrence free survival (RFS) in patients with GIT cancers were 1.64 (95% CI, 1.27–2.13) and 1.06 (95% CI, 0.96–1.16), respectively. Subgroup analysis and sensitivity analysis were also performed. No significant publication bias was found.

Conclusion: Our results suggested that XIAP could be a prognostic marker for OS but not RFS in patients with GIT cancers. Higher expression of XIAP was related to poorer OS. These findings may help evaluate the prognosis of patients and assist future research on novel therapeutic strategies of GIT cancers by targeting XIAP. However, more well-designed studies are warranted to verify the results.

Abbreviations: CI = confidence interval, EAC = esophageal adenocarcinoma, ESCC = esophageal squamous cell carcinoma, GIT = gastrointestinal tract, HR = hazard ratio, IAP = inhibitor of apoptosis proteins, IHC = immunohistochemical, OS = overall survival, OSCC = oral squamous cell carcinoma, PPA = protein pathway array, RFS = recurrence free survival, XIAP = X-linked inhibitor of apoptosis protein.

Keywords: gastrointestinal tract cancers, prognosis, survival, X-linked inhibitor of apoptosis protein

1. Introduction

Gastrointestinal tract (GIT) cancers mainly include oral cancer, pharyngeal cancer, esophageal cancer, gastric cancer, and colorectal cancer.[1,2] According to the latest global cancer statistics in 2018, colorectal cancer, gastric cancer, and esophageal cancer are the third, fifth and seventh most common cancer types worldwide, respectively.[3] Colorectal cancer, gastric cancer, and esophageal cancer are the second, third and sixth leading cause of cancer-related deaths, respectively. Collectively, colorectal cancer, gastric cancer, and esophageal cancer account for approximately 19% of new cancer cases and 23% of cancer-related deaths. As to oral cancer and pharyngeal cancer, they account about 3% of new cancer cases and cancer-related deaths.[3] The early symptoms of GIT cancers are not obvious and they are easily misdiagnosed with other diseases.[4,5] In recent years, many anticancer strategies and the mechanisms have been explored.[6–9] Despite the great improvements in the diagnosis and treatment of GIT cancers, the 5-year survival rate is still low, especially colorectal cancer, gastric cancer and esophageal cancer.[5] Therefore, it is worthwhile to explore new prognostic biomarkers and potential therapeutic targets for better management of GIT cancers.

Inhibitor of apoptosis proteins (IAPs) are a family of endogenous proteins with anti-apoptotic function.[10] Among the human IAPs, X-linked inhibitor of apoptosis protein (XIAP) has been found to exert the strongest anti-apoptotic function.[11] The anti-apoptotic function of XIAP was shown to be linked to its ability to bind to caspase-3, -7 and -9.[11] Besides the anti-apoptotic function, XIAP has been reported to promote cellular inflammatory signaling and trigger cytokine secretion.[12] XIAP has been found to be highly expressed in GIT cancers.[13–15] For example, Zhang et al found higher expression of XIAP in

Editor: Antonio Palazón-Bru.

The authors have no funding and conflicts of interest to disclose.

[a] State Key Laboratory of Oral Diseases, West China Hospital of Stomatology, Sichuan University, [b] Department of Neurosurgery, West China Hospital, Sichuan University, Chengdu, Sichuan, China.

[*] Correspondence: Wenli Lai, State Key Laboratory of Oral Diseases, West China Hospital of Stomatology, Sichuan University, No. 14, Section 3, South Renmin Road, Chengdu 610041, Sichuan, China (e-mail: wenliLai028@163.com).

How to cite this article: Ieong C, Yang H, Ma J, Lai W. Prognostic significance of X-linked inhibitor of apoptosis protein in patients with gastrointestinal tract cancers: A meta-analysis. Medicine 2020;99:9(e18497).

Received: 22 June 2019 / Received in final form: 31 October 2019 / Accepted: 25 November 2019

http://dx.doi.org/10.1097/MD.0000000000018497

esophageal cancer tissues compared with normal tissues.[13] Ma et al found elevated expression of XIAP in gastric cancer tissues compared with normal tissues (68.8% vs 16.6%).[15] In recent years, many researchers have explored the prognostic value of XIAP in patients with GIT cancers.[12,15–17] However, the results were inconclusive. Chen et al[17] and Xiang et al[18] found that XIAP was a good prognostic marker for colorectal cancer. But Hector et al[19] demonstrated that XIAP was not an independent prognostic marker in either stage II or stage III colorectal cancer. He et al[20] and Kim et al[21] found that higher expression of XIAP was associated with poorer prognosis of gastric cancer. However, the results were not statistically significant in other studies.[15,22] Due to the controversy, the aim of this study was to systematically evaluate the prognostic value of XIAP in patients with GIT cancers through performing a meta-analysis.

2. Methods

2.1. Search strategy

Since this is a meta-analysis, ethical approval was not necessary. We performed this meta-analysis according to the developed guidelines for systematic reviews and meta-analyses.[23] The following 5 databases were searched for potentially eligible literature: PubMed, Web of Science, EMBASE, Cochrane Library and China National Knowledge Infrastructure. The last search was performed on Jun 7th, 2019. The keywords included: ('Mouth Neoplasms' OR 'Pharyngeal Neoplasms' OR 'Esophageal Neoplasms' OR 'Stomach Neoplasms' OR 'Colorectal Neoplasms' OR 'Colonic Neoplasms' OR 'Rectal Neoplasms') AND 'X-linked inhibitor of apoptosis protein' AND ('prognosis' OR 'outcome' OR 'survival' OR 'mortality'). Reference lists of relevant literature were also checked for additional studies. Languages were restricted to English and Chinese.

2.2. Study selection

Two researchers performed the study selection independently, with any disagreements being discussed. First, the titles and abstracts were screened. Then the potentially relevant studies were assessed in full text. The inclusion criteria included:

(1) The patients were diagnosed with any type of gastrointestinal tract cancers by histopathological examination;
(2) The expression of XIAP in the tumor tissue was measured;
(3) Patients were followed up for survival outcomes;
(4) Hazard ratios (HRs) with 95% confidence intervals (95% CIs) for survival analysis were reported or could be calculated from given information.

Studies without enough data (HR with 95% CI were not reported or could not be calculated), letters, case reports, reviews, conference abstracts, and unrelated articles were excluded. If multiple studies were performed in the same center and the cases overlapped, the study with the largest sample size was included.

2.3. Data extraction

The data of the included studies was extracted independently by 2 authors, and disagreements were resolved by consensus. The primary data mainly included HR for overall survival (OS)/recurrence free survival (RFS) with 95% CI, or the survival curves by which the HR and 95% CI could be calculated. HRs calculated from multivariate analyses were extracted over HRs calculated from univariate analyses. The baseline characteristics of the studies and patients included first author, publication year, country of origin, cancer type, sample number, mean or median age of patients, ethnicity of patients, detection method of XIAP, and cut-off value of XIAP.

2.4. Statistical analysis

The log HR and variance were calculated from the HR with 95% CI or survival curves, and were used for aggregation. Forest plots were outlined to estimate the prognostic value of XIAP in patients with GIT cancers. The pooled HR was considered statistically significant if the 95% CI did not overlap 1 and the P value was less than .05. The between-study heterogeneity was also assessed, and $I^2 > 50\%$ or $P < .10$ indicated significant heterogeneity. Random effect models were adopted in the analysis no matter whether significant heterogeneity exited, since heterogeneity between studies was expected due to the different study and patient characteristics across studies. If significant heterogeneity exited, sensitivity analysis was conducted to assess the contribution of every study to heterogeneity by excluding each study 1 at a time. Subgroup analyses were performed according to the different characteristics of the studies and patients, such as cancer type, ethnicity of patients and detection method of XIAP. Publication bias was assessed by Egger test, and $P < .05$ implied significant publication bias. All the above statistical analyses were conducted by STATA 11.0 (STATA Corporation, College Station, TX).

3. Results

3.1. Literature research

The initial database searching identified 589 records. No additional records were identified through other sources. Among them, 84 records were duplicated and were removed. The rest studies were screened by titles and abstracts. According to the predefined inclusion and exclusion criteria, 462 studies were excluded. The rest studies were further evaluated in full text and 31 were excluded due to unrelated, lacking enough data or other reasons. Eventually, 12 studies[12,14–22,24,25] met the inclusion criteria and were included. The study selection process was shown in Figure 1.

3.2. Study characteristics

The baseline characteristics of the 12 included studies were shown in Table 1. The studies were from 5 different countries. The cancer types included oral squamous cell carcinoma (OSCC), esophageal adenocarcinoma (EAC), esophageal squamous cell carcinoma (ESCC), gastric cancer and colorectal cancer. A total of 2477 patients were included. The ethnicity of patients was Asian in 7 studies and Caucasus in 5 studies. Eleven of the twelve studies detected the expression of XIAP by immunohistochemical (IHC) staining, and 1 study used protein pathway array (PPA) analysis. All the studies reported the OS, and 2 studies also reported the RFS.

3.3. Overall analysis

Among the twelve included studies, Dizdar et al reported the OS of EAC and ESCC, Hector et al reported the OS and RFS of patients in stage II and stage III. Thus, a total of 14 data sets were

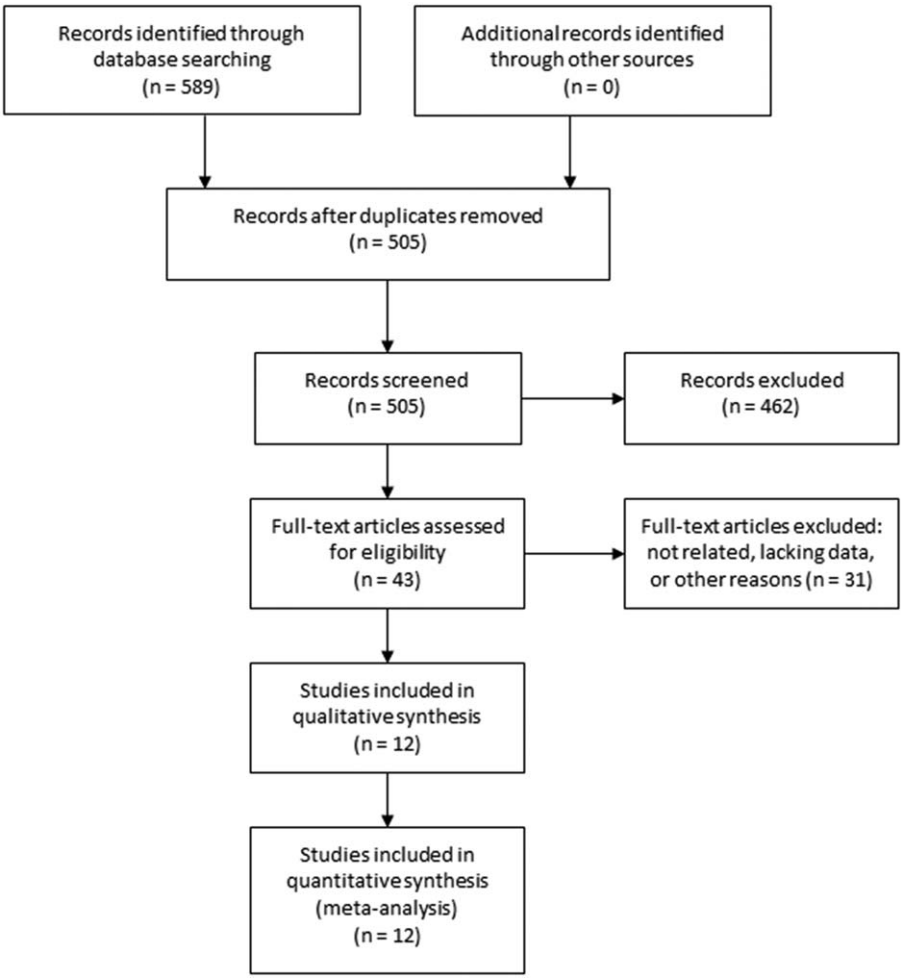

Figure 1. Selection process of studies.

available for OS and 3 data sets were available for RFS. The pooled HR of higher XIAP for OS was 1.64 (95% CI, 1.27–2.13) (Fig. 2A). Significant between-study heterogeneity was observed ($I^2 = 78.9\%$, $P < .001$). After excluding each study at a time, the heterogeneities still exited. The pooled HR of higher XIAP for RFS was 1.06 (95% CI, 0.96–1.16) (Fig. 2B). Significant between-study heterogeneity was also observed ($I^2 = 80.0\%$, $P = .007$). In performing sensitivity analysis, after excluding the study by He et al, the heterogeneity became 0.0% and the pooled HR became statistically significant (1.04, 95% CI, 1.01–1.07).

Table 1

Characteristics of the included studies.

Author	Yr	Country	Cancer type	Samples	Age, yr	Ethnicity	Method	Outcome
Frohwitter	2017	Germany	OSCC	83	—	Caucasian	IHC	OS
Nagata	2011	Japan	OSCC	54	median 71	Asian	IHC	OS
Schiffmann	2019	Germany	EAC	311	mean 62.7	Caucasian	IHC	OS
Dizdar	2018	Germany	ESCC & EAC	194	—	Caucasian	IHC	OS
Zhou	2013	China	ESCC	78	—	Asian	IHC	OS
Ma	2019	China	gastric	90	mean 57.5	Asian	IHC	OS
Dizdar	2017	Germany	gastric	154	—	Caucasian	IHC	OS
He	2016	China	gastric	32	mean 60.2	Asian	PPA	OS RFS
Kim	2001	Korea	gastric	1103	—	Asian	IHC	OS
Chen	2016	China	colorectal	58	—	Asian	IHC	OS
Hector	2012	Ireland	colorectal	224	median 64.1	Caucasian	IHC	OS RFS
Xiang	2009	China	colorectal	96	median 57	Asian	IHC	OS

EAC = esophageal adenocarcinoma, ESCC = esophageal squamous cell carcinoma, IHC = immunohistochemical staining, OS = overall survival, OSCC = oral squamous cell carcinoma, PPA = protein pathway array analysis, RFS = recurrence free survival.

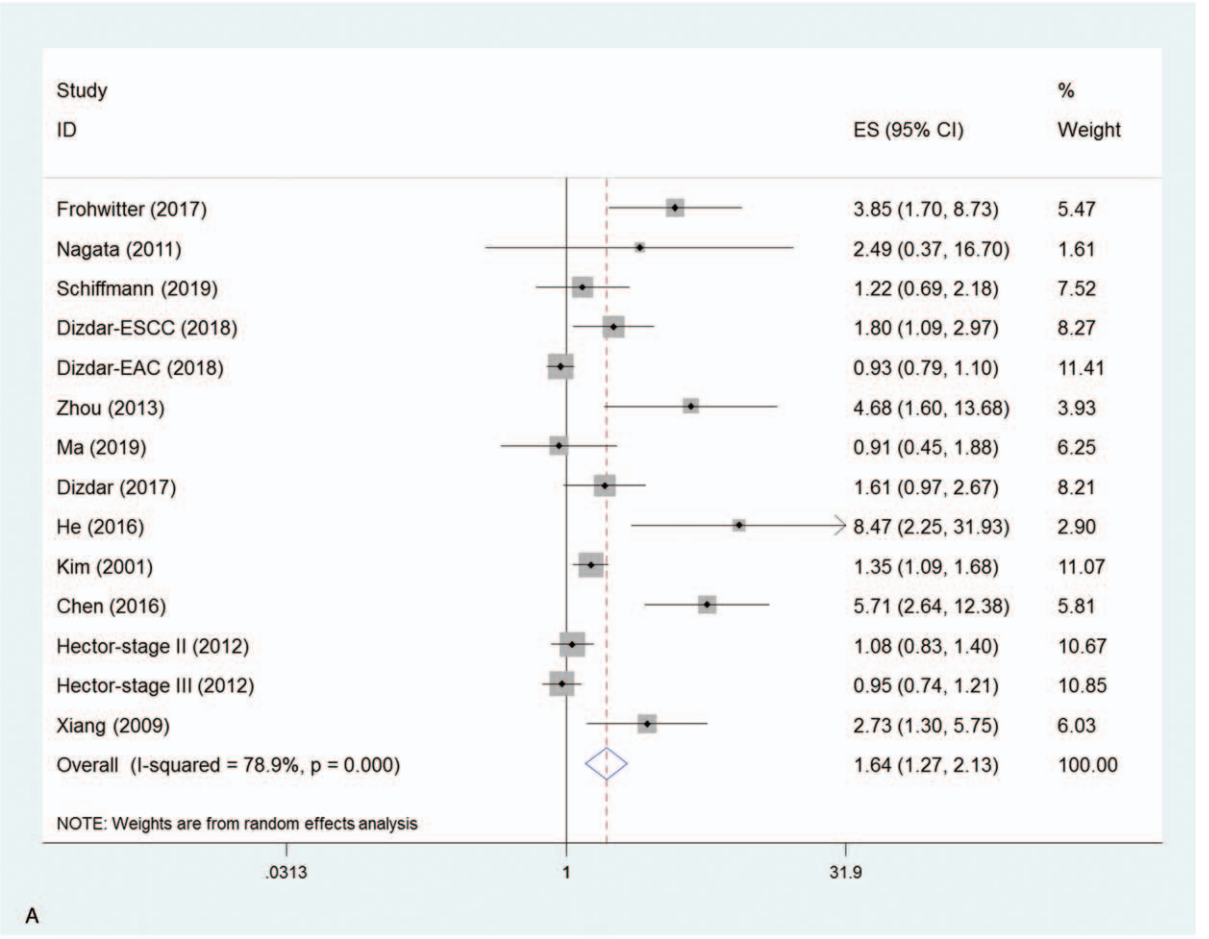

Figure 2. Pooled hazard ratio (HR) of higher XIAP for overall survival (A) and recurrence free survival (B) in patients with GIT cancers. GIT = gastrointestinal tract, XIAP = X-linked inhibitor of apoptosis protein.

Table 2

Summary of meta-analysis results.

	Data sets	Sample size	Pooled HR (95% CI)	*P* value	Heterogeneity (I^2, *P*)	Conclusion
OS						
Total	14	2477	1.64 (1.27–2.13)	<.001	78.9%, <0.001	positive
OSCC	2	137	3.60 (1.70–7.63)	.001	.0%, .679	positive
esophageal	4	583	1.50 (0.88–2.56)	.135	78.7%, .003	negative
EAC	2	391	0.95 (0.81–1.12)	.543	.0%, .375	negative
ESCC	2	192	2.57 (1.04–6.36)	.041	60.1%, .114	positive
Gastric	4	1379	1.57 (0.97–2.54)	.066	65.9%, .032	negative
Colorectal	4	378	1.75 (0.99–3.11)	.055	87.7%, <.001	negative
Caucasian	7	966	1.25 (0.98–1.59)	.075	69.6%, .003	negative
Asian	7	1511	2.66 (1.45–4.90)	.002	77.9%, <.001	positive
IHC	13	2445	1.54 (1.20–1.98)	.001	77.4%, <.001	positive
PPA	1	32	8.47 (2.25–31.93)	—	—	positive
RFS						
	3	256	1.06 (0.96–1.16)	.271	80.0%, .007	negative

CI = confidence interval, EAC = esophageal adenocarcinoma, ESCC = esophageal squamous cell carcinoma, HR = hazard ratio, IHC = immunohistochemical staining, OS = overall survival, OSCC = oral squamous cell carcinoma, PPA = protein pathway array analysis, RFS = recurrence free survival.

3.4. Subgroup analysis

3.4.1. Cancer type. Among the 14 data sets, 2 examined OSCC, 4 examined esophageal cancer, 2 examined EAC, 2 examined ESCC, 4 examined gastric cancer, and 4 examined colorectal cancer. The pooled HRs of higher XIAP for OS in OSCC, esophageal cancer, EAC, ESCC, gastric cancer, and colorectal cancer were 3.60 (95% CI, 1.70–7.63), 1.50 (95% CI, 0.88–2.56), 0.95 (95% CI, 0.81–1.12), 2.57 (95% CI, 1.04–6.36), 1.57 (95% CI, 0.97–2.54), 1.75 (95% CI, 0.99–3.11), respectively.

3.4.2. Ethnicity of patients. Among the 14 data sets, 7 data sets were Caucasian and 7 data sets were Asian. The pooled HRs of higher XIAP for OS in the Caucasian group and Asian group were 1.25 (95% CI, 0.98–1.59) and 2.66 (95% CI, 1.45–4.90), respectively.

3.4.3. Detection method of XIAP. Among the 14 data sets, 13 data sets used IHC staining and 1 data set used PPA analysis. The pooled HRs of higher XIAP for OS in the IHC group and PPA group were 1.54 (95% CI, 1.20–1.98) and 8.47 (95% CI, 2.25–31.93), respectively.

All the meta-analyses results were summarized in Table 2.

3.5. Publication bias

No significant publication bias was found in the meta-analysis. The Egger plots of publication bias of the data sets for OS ($P = .057$) and RFS ($P = .136$) were shown in Figure 3.

4. Discussion

This article aimed to assess the prognostic value of XIAP in patients with GIT cancers. We performed a meta-analysis to evaluate the existing evidence, and twelve studies were included. Our results suggested that higher expression of XIAP was related to poorer OS in patients with GIT cancers, and that the expression level of XIAP was not statistically associated with the RFS.

Subgroup analyses were also performed to further examine the prognostic value of XIAP in patients with GIT cancers. In patients with OSCC and ESCC, higher XIAP was found to be associated with worse OS in patients. However, among patients with esophageal cancer (both EAC and ESCC), EAC, gastric cancer and colorectal cancer, this association was not significant. This finding was interesting. Since most gastric cancer and colorectal cancer are adenocarcinoma, this finding may suggest that XIAP is an independent prognostic marker in squamous cell carcinoma (OSCC and ESCC), but not in adenocarcinoma. However, more studies are needed to verify this finding. As to the ethnicity of patients, the association was also different. For Asian patients,

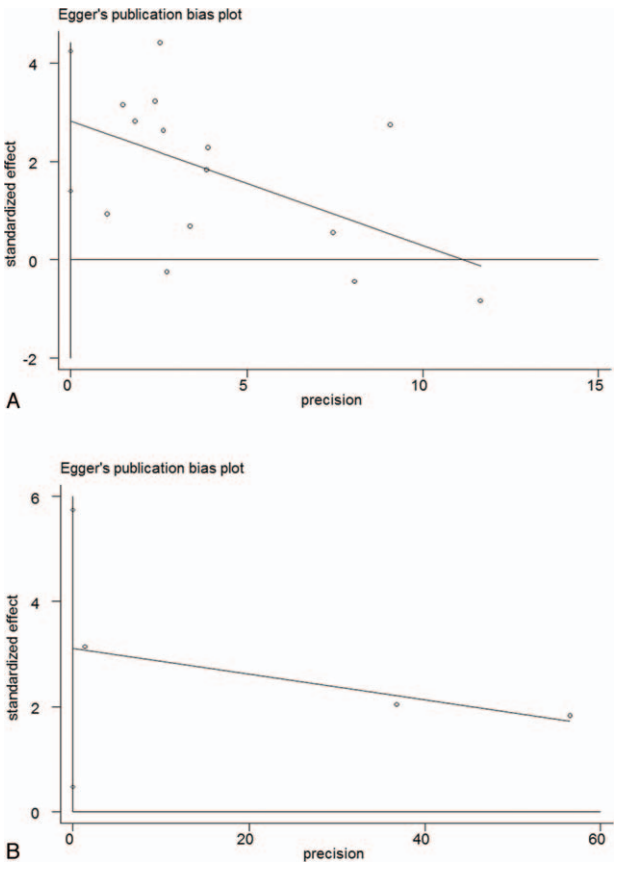

Figure 3. The Egger plots of publication bias of the data sets for OS (A) and RFS (B). OS = overall survival, RFS = recurrence free survival.

higher XIAP was shown to be related to worse OS. But this association was not significant in Caucasian cases. These results suggest that the prognostic value of XIAP may differ among different ethnicities. We also performed subgroup analyses according to the detection method of XIAP. The results showed that XIAP levels detected by either IHC staining or PPA analysis both correlated with the OS, suggesting that the prognostic value of XIAP was not affected by detection method. However, since the numbers of studies in the meta-analysis and in the subgroups were limited, much more studies are warranted to verify our results and to assess the value of XIAP in different cancer types and different ethnicities.

It is shown that cancer cells with elevated expression level of XIAP are more resistant to radiotherapy or chemotherapy through reducing the cell death induced by therapy.[26] Zhang et al[13] used small interfering RNA (siRNA) to block XIAP expression and found that XIAP siRNA could efficiently reduce the expression level of XIAP and induce cell apoptosis. They also explored the combined effects of XIAP siRNA and chemotherapy agents, and found that treatment with XIAP siRNA in combination with chemotherapy agents could enhance chemosensitivity. However, some researchers suggested that the underlying mechanism may also involve the tumor microenvironment.[12] It has been demonstrated that XIAP might be involved in NFκB signaling.[12,27] Overexpression of XIAP may lead to the activation of NFκB signaling pathway and increase the cytokine secretion, thus recruiting immune cells that suppress T-cell response or directly impeding cytotoxic T lymphocytes-mediated cytotoxicity.[12,28] Besides, XIAP has been reported as a positive regulator of Wnt/β-catenin signaling.[29,30] GIT cancers, especially colorectal cancer, often have hyperactive Wnt/β-catenin signaling.[31–33] Thus, high expression of XIAP may over-activate Wnt/β-catenin signaling and promote tumor growth.

Dizdar et al[25] showed that XIAP could be a prognostic marker in ESCC but not in EAC. Their findings were consistent with our subgroup analyses results. This phenomenon may suggest different roles of XIAP in squamous cell carcinoma and adenocarcinoma. Dizdar et al[22] also investigated the prognostic role of XIAP in gastric cancer. Although the pooled HR from multivariate analysis was not significant in all subtypes of gastric cancer, they found that XIAP could be an independent prognostic marker in both diffuse type and mixed type of gastric cancer.

There are several limitations in this meta-analysis. First, the number of eligible studies was limited, especially in each subgroup. As a result, the conclusions should be interpreted with caution, especially the results of the subgroup analysis. Second, significant heterogeneity between the studies was observed in our meta-analysis. Studies that may contribute greatly to heterogeneity were not identified through sensitivity analysis. Potential factors that may contribute to heterogeneity included ethnicity of patients, cancer type, sample size, age, detection method of XIAP and the cut-off of XIAP. We performed subgroup analysis according to ethnicity of patients, cancer type, and detection method of XIAP. In OSCC and EAC, no significant heterogeneity was found, suggesting that cancer type might be a great source of heterogeneity. However, the reason might also be due to the small number of studies in the 2 groups. So, more studies are warranted to verify our results with such heterogeneity. Besides, although no significant publication bias was found in this study, it should not be completely excluded.

In conclusion, our results suggested that XIAP could be a prognostic marker for OS but not RFS in patients with GIT cancers. Higher expression of XIAP was related to poorer OS. These findings may help evaluate the prognosis of patients and assist future research on novel therapeutic strategies of GIT cancers by targeting XIAP. However, due to the limited number of studies, more well-designed studies are warranted to verify the results.

Acknowledgments

We would like to thank the reviewers for their constructive comments.

Author contributions

Conceptualization: Chengcheng Ieong, Hong Yang, Wenli Lai.
Data curation: Chengcheng Ieong, Hong Yang, Junpeng Ma.
Formal analysis: Chengcheng Ieong, Hong Yang, Junpeng Ma, Wenli Lai.
Investigation: Chengcheng Ieong.
Methodology: Chengcheng Ieong, Hong Yang.
Project administration: Chengcheng Ieong.
Resources: Chengcheng Ieong.
Software: Chengcheng Ieong, Junpeng Ma.
Supervision: Wenli Lai.
Validation: Chengcheng Ieong.
Visualization: Chengcheng Ieong.
Writing – original draft: Chengcheng Ieong, Hong Yang, Junpeng Ma, Wenli Lai.
Writing – review and editing: Chengcheng Ieong, Hong Yang, Junpeng Ma, Wenli Lai.

References

[1] Ren JS, Freedman ND, Kamangar F, et al. Tea, coffee, carbonated soft drinks and upper gastrointestinal tract cancer risk in a large United States prospective cohort study. Eur J Cancer 2010;46:1873–81.
[2] Sahami-Fard MH. Association between interleukin-10-592 A/C polymorphism and gastrointestinal tract cancer risk: a meta-analysis. Int J Biol Markers 2018;33:244–53.
[3] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians 2018;68: 394–424.
[4] Spiller RC. ABC of the upper gastrointestinal tract: anorexia, nausea, vomiting, and pain. BMJ 2001;323:1354–7.
[5] Duan X, Hong J, Wang F, et al. The influence of ACYP2 polymorphisms on gastrointestinal cancer susceptibility in the Chinese Han population. Mol Genet Genomic Med 2019;e700.
[6] Miao R, Guo X, Zhi Q, et al. VEZT, a novel putative tumor suppressor, suppresses the growth and tumorigenicity of gastric cancer. PloS One 2013;8:e74409.
[7] Kou Y, Koag MC, Cheun Y, et al. Application of hypoiodite-mediated aminyl radical cyclization to synthesis of solasodine acetate. Steroids 2012;77:1069–74.
[8] Kou Y, Koag MC, Lee S. Structural and kinetic studies of the effect of guanine N7 alkylation and metal cofactors on DNA replication. Biochemistry 2018;57:5105–16.
[9] Kou Y, Koag MC, Lee S. N7 methylation alters hydrogen-bonding patterns of guanine in duplex DNA. J Am Chem Soc 2015;137: 14067–70.
[10] Fulda S, Vucic D. Targeting IAP proteins for therapeutic intervention in cancer. Nat Rev Drug Discov 2012;11:109–24.
[11] Eckelman BP, Salvesen GS, Scott FL. Human inhibitor of apoptosis proteins: why XIAP is the black sheep of the family. EMBO Rep 2006;7:988–94.
[12] Schiffmann LM, Gobel H, Loser H, et al. Elevated X-linked inhibitor of apoptosis protein (XIAP) expression uncovers detrimental prognosis in subgroups of neoadjuvant treated and T-cell rich esophageal adenocarcinoma. BMC Cancer 2019;19:531.

[13] Zhang S, Ding F, Luo A, et al. XIAP is highly expressed in esophageal cancer and its downregulation by RNAi sensitizes esophageal carcinoma cell lines to chemotherapeutics. Cancer Biol Ther 2007;6: 973–80.
[14] Zhou S, Ye W, Shao Q, et al. Prognostic significance of XIAP and NF-kappaB expression in esophageal carcinoma with postoperative radiotherapy. World J Surg Oncol 2013;11:288.
[15] Ma Y, Zhou R, Zhou J, et al. The study of expression of XIAP and Smac in gastric cancer and their correlation with the prognosis. Ningxia Medical Journal 2019;1–6.
[16] Frohwitter G, Buerger H, Korsching E, et al. Site-specific gene expression patterns in oral cancer. Head Face Med 2017;13:6.
[17] Chen YT, Tsao SC, Tsai HP, et al. The X-linked inhibitor of apoptosis protein is an independent prognostic marker for rectal adenocarcinoma after preoperative chemoradiotherapy. Virchows Arch 2016;468: 559–67.
[18] Xiang G, Wen X, Wang H, et al. Expression of X-linked inhibitor of apoptosis protein in human colorectal cancer and its correlation with prognosis. J Surg Oncol 2009;100:708–12.
[19] Hector S, Conlon S, Schmid J, et al. Apoptosome-dependent caspase activation proteins as prognostic markers in Stage II and III colorectal cancer. Br J Cancer 2012;106:1499–505.
[20] He L, Ye F, Qu L, et al. Protein profiling of alpha-fetoprotein producing gastric adenocarcinoma. Oncotarget 2016;7:28448–59.
[21] Kim MA, Lee HE, Lee HS, et al. Expression of apoptosis-related proteins and its clinical implication in surgically resected gastric carcinoma. Virchows Arch 2011;459:503–10.
[22] Dizdar L, Tomczak M, Werner TA, et al. Survivin and XIAP expression in distinct tumor compartments of surgically resected gastric cancer: XIAP as a prognostic marker in diffuse and mixed type adenocarcinomas. Oncol Lett 2017;14:6847–56.
[23] Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.
[24] Nagata M, Nakayama H, Tanaka T, et al. Overexpression of cIAP2 contributes to 5-FU resistance and a poor prognosis in oral squamous cell carcinoma. Br J Cancer 2011;105:1322–30.
[25] Dizdar L, Junemann LM, Werner TA, et al. Clinicopathological and functional implications of the inhibitor of apoptosis proteins survivin and XIAP in esophageal cancer. Oncol Lett 2018;15:3779–89.
[26] Obexer P, Ausserlechner MJ. X-linked inhibitor of apoptosis protein - a critical death resistance regulator and therapeutic target for personalized cancer therapy. Front Oncol 2014;4:197.
[27] Goncharov T, Hedayati S, Mulvihill MM, et al. Disruption of XIAP-RIP2 Association Blocks NOD2-Mediated Inflammatory Signaling. Mol Cell 2018;69:551–65. e557.
[28] Kashkar H, Seeger JM, Hombach A, et al. XIAP targeting sensitizes Hodgkin lymphoma cells for cytolytic T-cell attack. Blood 2006;108: 3434–40.
[29] Hanson AJ, Wallace HA, Freeman TJ, et al. XIAP monoubiquitylates Groucho/TLE to promote canonical Wnt signaling. Molecular cell 2012;45:619–28.
[30] Chen C, Zhao SC, Yang WZ, et al. Potential biological process of X-linked inhibitor of apoptosis protein in renal cell carcinoma based upon differential protein expression analysis. Oncol Lett 2018;15:821–32.
[31] Shi J, Zhu Q, Wu J, et al. FAM46C suppresses gastric cancer by inhibition of Wnt/beta-catenin. Front Biosci 2020;25:549–63.
[32] Liu WG, Xu Q. Upregulation of circHIPK3 promotes the progression of gastric cancer via Wnt/beta-catenin pathway and indicates a poor prognosis. Eur Rev Med Pharmacol Sci 2019;23:7905–12.
[33] Nie X, Xia F, Liu Y, et al. Downregulation of Wnt3 Suppresses Colorectal Cancer Development Through Inhibiting Cell Proliferation and Migration. Front Pharmacol 2019;10:1110.