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ORIGINAL ARTICLE

Survivin As an Immunohistochemical Prognostic Biomarker in Colorectal Cancer: A Meta-Analysis

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OBJECTIVE

Genome-level research qualifies survivin as the fourth-best "transcriptome" for colon, lung, brain, breast, and melanoma cancers. To date, it has been stated as a prognostic marker and therapeutic target in colorectal cancer (CRC). However, researchers on survivin expression in CRC are heterogeneous. Our current study aimed to reveal prognostic importance of survivin by investigating all CRC articles up to January 2021 that have performed analysis of survivin by immunohistochemical staining method.

METHODS

A comprehensive literature search for relevant studies published up to January 2021 was performed using SCOPUS and Pubmed databases. Only articles in which survivin was detected by IHC staining were included in the study. All analyses were conducted by using Comprehensive Meta-Analysis. Eight articles and data of 1535 patients were included in the study. The Hazard Ratio was used to examine the relationship between CRC and survivin protein, for the relative weights of each research article. HR and 95% confidence interval values and general summary HR were calculated and forest plot graph was obtained.

RESULTS

Statistical heterogeneity Cochrane's Q test statistics 24.156; p=0.004 and I^2 value was obtained as 62,742. In line with the assumption that the data consisted of different populations, the HR and 95% CI values were calculated as 1.446 (1.103-1.897) using the Dersimonian and Laird random effects model. In order to evaluate the risk of publication bias, funnel plots were obtained, including log HR and standard error values on the x and y axes, respectively.

CONCLUSION

The analyzes obtained suggest that survivin overexpression in CRC is associated with poor prognosis. (HR=1.446; 95% CI: 1.103-1.897).

Keywords: BIRC5; colorectal cancer; forest plot; metaanalysis; prognostic; survivin.
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Introduction

Colorectal cancer (CRC) is the third most common type of cancer in men and the second most common type of cancer in women.[1] Surgery is the primary method of treatment and provides a high cure rate when the disease is localized. In patients with CRC chemotherapy is used as adjuvant or palliative treatment. The systemic chemotherapy regimen is mainly based on the use of fluoropyrimidines. Drugs such as irinotecan and oxaliplatin are used in combination with fluoropyrimidines which increase response rates, time to progression, and overall survival.[2] However, postoperative recurrence and metastasis are common conditions in CRC and are often associated with poor prognosis and overall survival. In the case of metastasis, the 5-year survival rate of CRC is expressed as 14%.[1,2]

Survivin/BIRC5 is one of the first inhibitors of apoptosis protein (IAPs) family to stimulate apoptosis. The survivin gene, which consists of 3 introns and 4 exons in humans, is located in the 17q25 region of the chromosome and is 14.7 kb in length. It encodes the survivin protein which is 142 amino acids long and 16.5KD weigh.[3,4] It is expressed in high amounts in embryonic and fetal organs, but not in most normally differentiated tissues. It is also known to be highly expressed in most cancer types.[5,6] This makes survivin a unique candidate for cancer research. Studies conducted to date have shown a dramatic increase in survivin in the lung, breast, colon, stomach, esophagus, pancreas, bladder, uterus, ovary, large cell non-Hodgkin lymphoma, leukemia, neuroblastoma, melanoma, and non-melanoma skin cancers when compared to normal tissues.[7] Furthermore, genome-level research qualifies survivin as the fourth-best "transcriptome" for colon, lung, brain, breast, and melanoma cancers. On the other hand, it is stated that survivin is not only effective in distinguishing between CRC patients and healthy individuals but also that its high expression causes poor prognosis. However, its expression was accepted as an unfavorable prognostic indicator in esophageal and lung cancer, in addition to that it may have prognostic value in breast, colorectal, pancreatic ductal adenocarcinoma, and hepatic carcinoma.[8]

Prognostic biomarkers identify patients who are probabilistically at either higher risk for adverse disease-related events or a faster rate of decline in their health status.[9] An ideal biomarker is expected to be easily detectable, highly specific, reproducible, preferably noninvasive, and inexpensive.[10] "Survivin," an important protein family member known as IAPs that regulates apoptosis, appears to meet these criteria with (1) expressed in high amounts in most cancer types while it is not expressed in most of the normal differentiated tissues, (2) reacquired from routine biopsy/surgical samples taken from patients (3) relatively inexpensive in use diagnosed immunohistochemically. To date, it has been stated as prognostic marker and therapeutic target in CRC. However, researchs on survivin expression in CRC are heterogeneous. Our current study aimed to reveal its prognostic importance by investigating all CRC research articles to date that have performed analysis of survivin immunohistochemically.

Materials and Methods

Literature Search

For this purpose, a search was carried out with relevant keywords from SCOPUS and PUBMED database (up to January 2021); for title-summary-key "IMMUNOHISTOCHEMISTRY" and "SURVIVIN" or "BIRC5" and "COLORECTAL CANCER" and "PATIENT" and for limitation type of document, "ar" and for language: english was entered (https://pubmed.ncbi.nlm.nih.gov/; https://www.scopus.com/). In addition, to search the existing meta-analysis studies analyzing the prognostic value of survivin in CRC a searched was performed from SCOPUS, PUBMED databases with the keywords "SURVIVIN" or "BIRC5" and "COLORECTAL CANCER" and "METAANALYSIS" and only 1 relevant article was found although the article was not related with our research.[11] Besides, a search with "Google Search" tool was performed with the keywords "SURVIVIN" or "BIRC5" and "COLORECTAL CANCER" and "METAANALYSIS" and Huang et al.[12] article has been obtained. The study found in "Google Search" is also available in Pubmed. Thus, three articles whose initial search results were neglected by SCOPUS and PUBMED databases were included in our meta-analysis.

Total, 53 articles from Pubmed database and nine articles from Scopus database were obtained. Twenty-five articles were remained after reduction as can be shown in Table 1 and detailed reduction reasons can be seen in Appendix 1. Finally, eight articles were selected for meta-analysis. Presentation of the procedure of literature searching and selection with numbers of articles at each stage (Fig. 1).

Table 1 Full-text articles related with designed study

First author	Year	PMID/ DOI	Country	Cases	Disease	Survivin localization	% of staning	Stage	OS/p	OR/HR/ AUC	95% CI
Heidari	2019	PMID: 30128768	Iran	90	CRC	NA	NA	NA	<0.001	NA	NA
Wang	2016	PMID: 28693267									
China	139	CRC	Cytoplasm	39.5	NA	<0.001	NA	NA			
Li W	2017	PMID: 27989099									
Korea	187	CRC	Nucleus	NA	II-III	=0.044	NA	NA			
Fu Q	2016	PMID: 27714672	China	122	CRC	Cytoplasm	73.77	I-IV	<0.001	NA	NA
Jakubowska K	2016	PMID: 27900041	Poland	55	CRC	Nucleus	81.8	I-IV	0.020	NA	NA
Kim ST	2014	PMID: 25331798	Korea,USA	188	CRC	NA	NA	I-IV	0.0015	26,509	NA
I J Goossens-Beumer	2014	PMID: 24786601	Netherlands	309	CRC	NA	86.5	I-IV	0.04	4.6	1.02-1.95
Li XB	2013	PMID: 23581553									
China	152	CRC	NA	NA	I-IV	NA	NA	NA			
Choi J		PMID: 22287745	South Korea	37	CRC	Nucleus	83.3	NA	NA	NA	NA
Xi RC	2011	PMID: 21934342	China	61	CRC	Cytoplasm	60.7	1-2b-3a-4	0.8836	2.7	NA
Hernandez JM	2011	PMID: 21855041	USA	168	CRC	NA	NA	I-IV	0.1881	NA	NA
Wu XY	2010	PMID: 21472255	China	32	CRC	Cytoplasm	68.75	I,II,III	NA	NA	NA
Kalliakmanis JG	2010	PMID: 20033843	Greece	77	CRC	Cytoplasm	88.3	NA	NA	1.5	NA
Xiaoyuan C.	2009	PMID: 19921309	China	68	CRC	Cytoplasm	57.8 high/ 42 low	G1-G3	0.0142	1.99	1.36-2.73
Qi G	2009	PMID: 19639203	Japan	142	CRC	Nucleus/ cytoplasm	76.8 /20.4	NA	0.002	NA	NA
Liang Q.L	2009	PMID: 19735100	China	100	CRC	NA	0.65	NA	<0.01	NA	NA
Lima FDO	2009	PMID: 19578769	Brazil	130	CRC	NA	NA	NA	0.4458	NA	NA
Fang Y.J.	2009	PMID: 19421758	China	620	NA	Cytoplasm	NA	I-IV	0.003	1.63	1.44-2.04
Yantiss RK	2009	PMID: 19047896	USA	24	CRC	Nucleus	11	I-IV	<0.005	NA	NA
Fan LF	2008	10.1007/ s00384-008-0511-3	China	69	61 CRC, 8 mucinous	Nucleus/ cytoplasm	56.5	I–II and III	NA	NA	NA
Cao J	2007	PMID: 17373735	China	80	CRC	Nucleus/ cytoplasm	77.50	NA	0	NA	NA
Hsiao HL	2006	PMID: 16364925	Taiwan	41	CRC	NA	NA	III	0.041	3.13	NA
Boman BM	2004	PMID: 15509520	USA	11	FAB	NA	NA	NA	NA	NA	NA
Lin LJ.	2003	10.3748/wjg.v9.i5.974	China	87	CRC	NA	63.6	NA	NA	NA	NA
Kawasaki H.	1998	PMID: 9823313	USA	171	CRC	Cytoplasm	53.2	0-IV	0.103	0.86	0.42-1.17

PMID: PubMed identifier; DOI: Digital Object Identifier; OS: Overall survival; OR: Odds ratio; HR: Hazard ratio; AUC: Area under the curve; CI: Confidence interval; NA: Not applicable; CRC: Colorectal cancer

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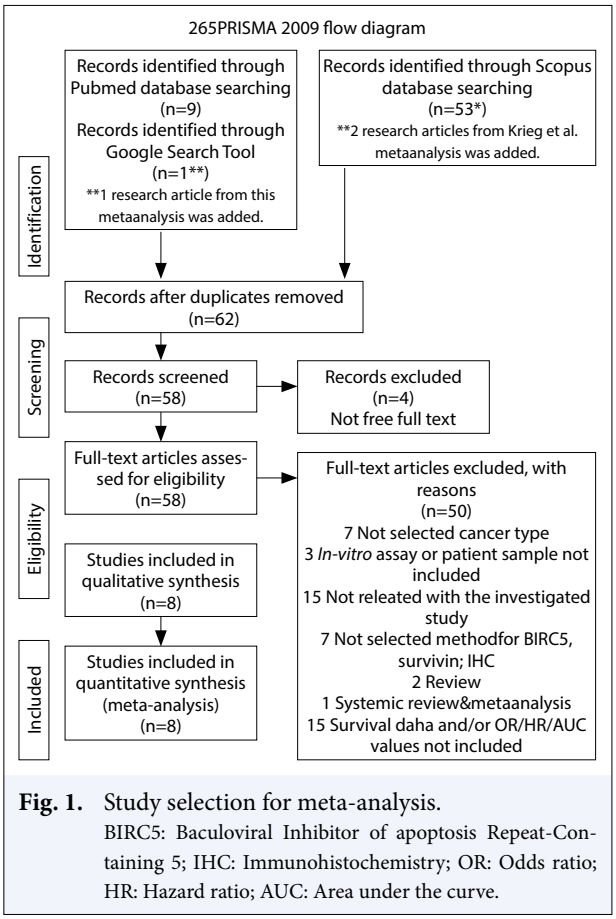

Fig. 1. Study selection for meta-analysis.
BIRC5: Baculoviral Inhibitor of apoptosis Repeat-Containing 5; IHC: Immunohistochemistry; OR: Odds ratio; HR: Hazard ratio; AUC: Area under the curve.

Selection and Extraction Criteria

The articles indicated the expression of survivin immunohistochemically and overall survival in CRC were selected. Articles associated with general staining were taken without considering the relationship with cytoplasmic and nuclear staining. After entering the keywords, the compliance of the articles obtained with the selection criteria was also confirmed from the article title and abstract. If there are relevant articles in the literature discussions of the included articles, they are also included in the study. From these articles with patient clinicopathological characteristics and overall survival data were selected. HR for overall survival was provided or could be calculated from the data presented were selected. Articles that provided sufficient data comparing the expression of survivin with clinicopathological data and that enabled us to calculate the HR. The publications in which a different analysis was made other than the immunohistochemistry analysis, the publications published in a different language other than English, and the publications without survival data were excluded. Articles were examined by two independent investigators; Aktas SH. and Akin-Bali DF. Extracted data were recorded by including first author's name, year of publication, PMID or DOI, region, number of cases, tumor stage, neoadjuvant therapy, cut off value, HR estimate, HR, and confidence interval (95% CI).

Statistical Analysis

Statistical data analysis was performed in the comprehensive meta-analysis (version 3-trial edition) program. The HR was used to examine the relationship between CRC and survivin protein, for the relative weights of each research article. HR and 95% confidence interval values and general summary HR were calculated and forest plot graph was obtained. HR>1 indicates that patients with survivin overexpression show a worse prognosis. Pooled estimates of HR were estimated by a random-effects model due to high between-study heterogeneity. Heterogeneity was assessed using Higgin's I2 statistic and Cochran's Q-test. Tau-squared statistics as a part of the statistical analysis performed in the study and is the estimated variation between the effects for test accuracy observed in different studies. HR and 95% CI values were calculated by Dersimonian and Laird random-effects model, assuming that the data consisted of different populations. In order to evaluate the risk of publication bias, funnel plots were obtained, including log Hazard ratio and standard error values on the x and y axes, respectively. $P<0.05$ was accepted as the statistical significance level.

Results

Relative Weights of Literature Studies and Forest Plot

The distribution of the relative weights of the eight literature studies included in the meta-analysis according to the fixed and random effects model, and the calculated HR and 95% confidence interval values were obtained (Table 2 and Fig.2). The study that made the greatest contribution to meta-analysis is the study conducted by Fang et al. (2009). Heterogeneity was tested with the Cochran Q test statistic. As a matter of fact, the heterogeneity test statistic was obtained as Q=24.156, p=0.004 (Fig. 3). Therefore, heterogeneity was found between studies. In our study, heterogeneity was found I^2: 62.74%. Random effects model results were preferred since there was high heterogeneity between studies. According to the random-effects model, the effect size of the model was obtained as 1.446 (95% CI: 1.103-1.897).

Table 2 Clinical and methodological data of studies included in the meta-analysis

First author	Year	PMID or DOI	Region	Cases	Stage	Neoadjuvant therapy	Cutt off value	HR estimate	HR	95% CI
Kim ST.	2014	10.1016/S0959-8049(14)70327-2	Korea, USA	188	I-IV	No	NA	HR (MV)	2.6509	1-6.9
Goossens-Beumer IJ.	2014	10.1038/bjc.2014.226	Netherlands	309	I-IV	No	86.5%	HR (MV)	1.40	1-1.9
Xi RC.	2011	10.1159/000331132	China	61	I-IV	No	10%	Sur. Curve (UV)	2.7	1.07-6.84
Kalliakmanis	2010	10.1007/s10620-009-1088-6	Greece	77	I-IV	No	5%	Sur.Curve (UV)	1.5	0.80-2.80
Xiaoyuan C.	2009	10.1007/s11845-009-0448-8	China	68	NA	No	>0%	HR (MV)	1.99	1.36-2.73
Fang YJ.	2009	10.1007/s00384-009-0725-z	China	620	I-IV	No	10%	HR (MV)	1.63	1.44-2.04
Hsiao	2006	10.1093/carcin/bgi316	Taiwan	41	III	NA	>0%	Sur. Curve (UV)	3.13	1.14-8.62
Kawasaki H	1998	PMID: 9823313	USA	171	I-IV	No	5%	HR (MV)	0.86	0.42-1.77

PMID: PubMed identifier; DOI: Digital object identifier; HR: Hazard ratio; CI: Confidence interval; MV: Multivariate; UV: Univariate

Funnel Plots a graphical representation of effect size and standard error. To determine the publication bias the bottom left of the funnel is analyzed. Negative or insignificant studies are listed on the lower left. If the lower left side is blank (asymmetric plot), it is stated as publication bias. According to the results of the analysis in the graph above, there is no publication bias for the literatures included in our study (Fig. 4). The symmetrical graph indicates the absence of publication bias. Our results show that overexpression of survivin in CRC is associated with poor prognosis (HR=1.446; % 95 CI: 1.103-1.897).

Discussion

The current meta analysis demonstrated that immunohistochemical staining of survivin in patients with CRC has a poor prognosis. To date, survivin has been the subject of many cancer researches. There are several main reasons for this situation, which have also been important in creating our current meta-analysis. Most importantly, survivin is not expressed in most normal differentiated tissues but is highly expressed in most cancer types.[5,6] Other important roles of survivin could be summarized as follows; it has important roles in the regulation of cell division and as an apoptosis inhibitor.[6] Survivin interacts with many different molecules in cancer, and it is stated that the important effects of these molecules are realized through survivin.[13-15] Important findings regarding survivin function can be obtained from knock down studies that reveal the function of a gene. Studies have shown that knocking this gene stimulates apoptosis and inhibits cell invasion in colorectal adenocarcinoma cells.[16,17] In addition, there are studies showing that m-RNA over-expression and protein over-expression of survivin, which has important roles in cancer, increase cancer prognosis.[18] However, the prognostic value of survivin is not significant for all cancer types. For example, while its expression is expressed as an unfavorable prognostic indicator in esophageal and lung cancer, it may have prognostic value in breast, colorectal, pancreatic ductal adenocarcinoma, and hepatic carcinoma.[8]

Essentially, survivin has been subjected to some meta-analysis studies in terms of CRC prognosis due to these important features mentioned above. Huang et al.[12] conducted a meta-analysis study with data from 14 studies, 1784 CRC patients, and they obtained an output that matched the results of our current study. Krieg et al.[19] conducted a meta-analysis study with data from 15 studies and 1934 CRC patients. However, in the meta-

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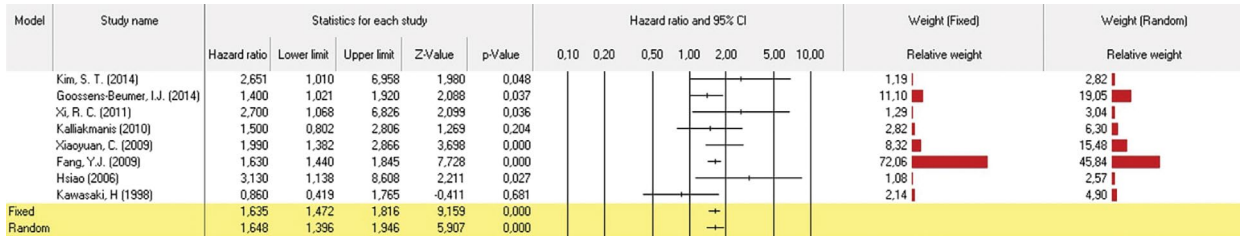

Fig. 2. Relative weights of studies included in the meta-analysis.

Model	Effect size and 95% interval				Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	8	1,635	1,472	1,816	9,159	0,000	8,855	7	0,263	20,947	0,012	0,031	0,001	0,108
Random	8	1,648	1,396	1,946	5,907	0,000								

Fig. 3. Heterogeneity of studies included in the meta-analysis.

analysis study of Krieg et al. included research articles using the real-time polymerase chain reaction method as well as the immunohistochemistry method of survivin.

Our current meta-analysis study was performed for 8 of 25 research articles in which survivin was stained immunohistochemically in CRC to date. The study of Kallikmanis et al. was extracted from Huang et al. metaanalysis and Krieg et al. metaanalysis. Hsiao et al. and Lin et al. study were extracted from Krieg et al. metaanalysis. Ponnelle, Qui, Sarela articles were not included although they were related to the overall survival in CRC and immunohistochemical staining of survivin from the Huang et al. meta-analysis study. [20-23] The reasons for this are; in the article of Lee et al., the relationship of survivin with overall survival was evaluated according to the low and high amount of survivin. In the Ponnelle et al. and Qi et al. articles, the relationship between nuclear/cytoplasmic localization of survivin and overall survival was evaluated. In the article of Sarela et al. immunohistochemical analysis was not performed, the polymerase chain reaction was performed from paraffin tissues.

Eight articles define the criteria for the meta-analysis we performed; survival data HR, HR estimate, 95% CI data. Immunohistochemical method was chosen for meta-analysis. Thus, it was aimed to create relatively less heterogeneity in the meta-analysis of the articles, which were basically carried out using a single technique.

Investigating the articles that we have meta-analyzed, the article of Fang et al.[24] appears to be made the greatest contribution to the meta-analysis. Multivariate analyzes of the study conducted by Fang et al. from a total of 602 CRC paraffin tissue samples showed that survivin, MMP7 and TROP2 are significant predictors for lower patient survival.

The contribution to the meta-analysis of the 2009 article by Fang et al. was determined as 45.84%. After this study, Goossens Beumer et al. made the highest contribution in the study they carried out in 2014. The contribution of the research to the meta-analysis was 19.05% (HR=1.63 CI % 95 1.440-1.845 p<0.001; HR=1.40, CI % 95 1.021-1.920 p<0.037).

Conclusion

Our meta-analysis performed from a total of eight articles and 535 CRC patients showed that expression of survivin was significantly associated with overall survival in CRC patients and can serve as a prognostic marker in CRC patients.

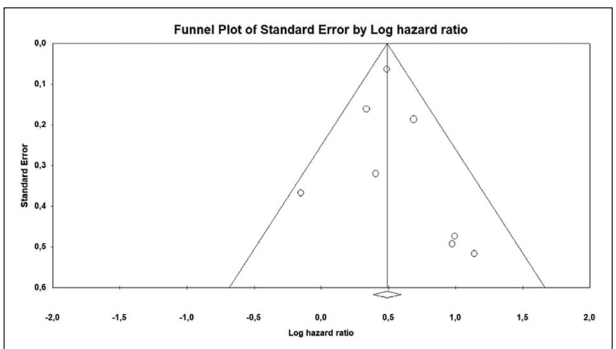

Fig. 4. Funnel plot of studies included in the meta-analysis to visualize a potential publication bias.

Peer-review: Externally peer-reviewed.

Conflict of Interest: All authors declared no conflict of interest.

Ethics Committee Approval: Ethical approval is not applicable, because this article does not contain any studies with human or animal subjects. The analyzed data are publicly available.

Financial Support: This study has received no financial support.

Authorship contributions: Concept – S.H.A.; Design – S.H.A., O.Y.; Supervision – S.H.A., D.F.A.B.; Funding – None; Materials – None; Data collection and/or processing – B.E.; Data analysis and/or interpretation – S.H.A., B.E., D.F.A.B.; Literature search – S.H.A., D.F.A.B., O.Y.; Writing – S.H.A., B.E.; Critical review – S.H.A., D.F.A.B., O.Y.

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Appendix 1 Studies screened for meta-analysis

Scopus

Key words: (TITLE-ABS-KEY (immunohistochemistry) AND TITLE-ABS-KEY(survivin) OR TITLE-ABS-KEY(BIRC5) AND TITLE-ABS-KEY ("colorectal cancer") AND TITLE-ABS-KEY (patient)) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (LANGUAGE, "English"))

S. No.	DOI	First Author	Results excluded with reasons	Selection/rejection reasons for metaanalysis
1.	10.1007/s00394-019-01948-z	Navarra M.	Not releated with the investigated study	x
2.	10.1002/jso.25805	Leiphrakpam P.D.	Not releated with the investigated study	x
3.	10.1038/s41419-019-1922-5	Lin Qi.	Not related with the investigated study	x
4.	10.3892/ol.2019.10474	Gu J.	Not related with the investigated study	x
5.	10.1007/s00795-018-0204-0	Heidari Z.	SELECTED	Not analyzed. OS value was not included
6.	10.1007/s00432-018-2757-7	Harpain F.	Not related with the investigated study	x
7.	10.3892/mmr.2017.7860	Geng W.	Not related with the investigated study	x
8.	10.1053/j.gastro.2017.03.053	Srivatsa S.	*In-vitro* assay or patient sample was not included	x
9.	10.3892/or.2017.5441	Wang H.	SELECTED	Not analyzed. OS value was not included
10.	10.4132/jptm.2016.09.23	Li W.	SELECTED	Not analyzed. OR/HR/AUC value was not included
11.	10.1155/2017/7615736	Ding S.	Not selected method for survivin	x
12.	10.1007/s13277-016-5438-7	Fu Q.	SELECTED	Not analyzed. OR/HR/AUC value was not included
13.	10.3892/ol.2016.5075	Jakubowska K.	SELECTED	Not analyzed. OR/HR/AUC value was not included
14.	10.1038/bjc.2016.257	Prasad S.	*In-vitro* assay or patient sample was not included	x
15.	10.2174/1566524016666151222144656	Hu J.	Not related with the investigated study	x
16.	10.1080/15384047.2015.1095408	Meng W.-J	Not selected method for survivin	x
17.	10.1038/onc.2014.348	Gao J	Not selected method for survivin	x
18.	10.18632/oncotarget.4354	Lee S.C.	Not related with the investigated study	x
19.	PMID: 25331798	Kim S.T.	SELECTED	SELECTED
20.	10.1038/bjc.2014.226	Goossens-Beumer I.J	SELECTED	SELECTED
21.	10.1371/journal.pone.0096767	Christensen L.L	Not selected method for survivin	x
22.	10.1158/1940-6207.CAPR-14-0140	Gupta S	Not related with the investigated study	x
23.	10.1371/journal.pone.0065338	Krieg A	SELECTED metaanalysis	SELECTED ARTICLES: Appendix 2
24.	10.1089/dna.2012.1912	Li X.-B.	SELECTED	Not analyzed. OS,OR/HR/AUC value was not included
25.	10.1615/CritRevOncog.v17.i4.70	Dineen S.P.	Review	x
26.	10.1097/COC.0b013e31821dedf7	Guan J.	Not related with the investigated study	x
27.	PMID: 22287745	Choi J.	SELECTED	Not analyzed. OS,OR/HR/AUC value was not included
28.	10.1159/000331132	Xi R.C.	SELECTED	SELECTED
29.	10.1136/jcp.2011.089631	Chen W.-B	Not free full text	x
30.	10.3748/wjg.v17.i12.1614	Pavlidou A.	Not selected method for survivin	x
31.	10.1016/j.clcc.2011.03.014	Hernandez J.M.	SELECTED	Not analyzed. OR/HR/AUC value was not included
32.	10.1007/s12032-009-9353-2	Li H.-X.	*In-vitro* assay or patient sample was not included	x
33.	10.1007/s11845-009-0448-8	Xiaoyuan C.	SELECTED	SELECTED
34.	10.1002/ibd.21178	Švec J.	Not releated with the investigated study	x
35.	10.3892/mmr-00000273	Wu X.-Y.	SELECTED	Not analyzed. OS,OR/HR/AUC value was not included
36.	10.3892/or_00000471	Qi G.	SELECTED	Not analyzed. OR/HR/AUC value was not included

Appendix 1 Cont.

Scopus

Key words: (TITLE-ABS-KEY (immunohistochemistry) AND TITLE-ABS-KEY(survivin) OR TITLE-ABS-KEY(BIRC5) AND TITLE-ABS-KEY ("colorectal cancer") AND TITLE-ABS-KEY (patient)) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (LANGUAGE, "English"))

S. No.	DOI	First Author	Results excluded with reasons	Selection/rejection reasons for metaanalysis
37.	10.1631/jzus.B0920077	Liang Q.-L	SELECTED	Not analyzed. OR/HR/AUC value was not included
38.	10.3892/or_00000437	Lima F.D.O.	SELECTED	Not analyzed. OR/HR/AUC value was not included
39.	10.1007/s00384-009-0725-z	Fang Y.J.	SELECTED	SELECTED
40.	10.1097/PAS.0b013e31818afd6b	Yantiss R.K.	SELECTED	Not analyzed. OR/HR/AUC value was not included
41.	10.1007/s00384-008-0511-3	Fan L.-F.	SELECTED	Not analyzed. OR/HR/AUC value was not included
42.	10.1007/s00384-007-0424-6	Søreide K.	Not selected cancer type, benign tumor	x
43.	10.1038/sj.bjc.6604184	Mounier C.M.	Not selected method for survivin	x
44.	10.1158/1078-0432.CCR-07-0751	Ma Q.	Not related with the investigated study	x
45.	10.1155/2007/457427	Soreide K	Not selected cancer type, benign tumor	x
46.	10.3748/wjg.v13.i7.1018	Cao J.	SELECTED	Not analyzed. OR/HR/AUC value was not included
47.	10.1126/science.1129139	Galon J.	Not selected method for survivin	x
48.	10.1007/s10620-006-3206-z	Konturek P.C.	Not selected method for survivin	x
49.	10.1007/s00432-005-0682-z	Ponnelle T.	Not related with the investigated study	x
50.	10.1158/1078-0432.CCR-03-0817	Idenoue S.	Not related with the investigated study	x
51.	PMID: 15493578	Dabrowski A.	Not selected cancer type	x
52.	10.1016/S0002-9440(10)63407-4	Boman B.M.	SELECTED	Not analyzed. OS,OR/HR/AUC value was not included
53.	PMID: 9823313	Kawasaki H.	SELECTED	SELECTED

Pubmed

Key words: (TITLE-ABS-KEY(immunohistochemistry) AND TITLE-ABS-KEY(survivin) OR TITLE-ABS-KEY(BIRC5) AND TITLE-ABS-KEY ("colorectal cancer") AND TITLE-ABS-KEY (patient)) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (LANGUAGE, "English"))

S. No.	DOI	First Author	Results excluded with reasons	Selection/rejection reasons for metaanalysis
1.	10.1016/j.canlet.2016.08.008	Wang R.	Not releated with the investigated study	x
2.	10.1007/s00795-018-0204-0	Heidari Z.	SELECTED. Also in SCOPUS result	Not analyzed. OS value was not included
3.	10.4137/BIC.S11475	Zeestraten E.C.M.	Review	x
4.	10.1016/j.jsbmb.2019.03.017	Milczarek M.	Not releated with the investigated study	x
5.	10.1007/s00384-009-0725-z	Fang Y.J.	SELECTED. Also in SCOPUS result	SELECTED
6.	10.1007/s13277-016-5115-x	Rogers M.A.	Not related with the investigated study	x
7.	PMID: 19578769	Lima F.D.O	Not related with the investigated study	x
8.	10.4038/cmj.v63i3.8714	M Budak	Not related with the investigated study	x
9.	10.1002/ibd.21178	J Švec	Not related with the investigated study	x

Appendix 2 Articles selected/rejected with reasons from metaanalysis

S. No.	DOI	First author of metaanalysis	First author of selected article	Selected/Rejected from metaanalysis	Reason of rejection
1.	10.1371/journal.pone.0065338	Krieg A.	Kawasaki H.	Selected before metaanalysis	x
			Lin LJ.	Selected	Not analyzed. OS,OR/HR/AUC value was not included
			Knutsen	Rejected	Not selectal cancer type, rectal cancer
			Hsiao	Selected	Analyzed
			Liang	Rejected	HR value was not included
			Xiaouyan	Selected before metaanalysis	x
			Kallikmanis	Selected	Analyzed
			Xi	Selected before metaanalysis	x
			Chu	Rejected	HR value was not included
			Takasu	Rejected	Not selectal cancer type, rectal cancer
2.	10.1093/jjco/hyt103	Huang Y.J.	Fang	Selected before metaanalysis	x
			Kallikmanis	Selected	Analyzed
			Kawasaki	Selected before metaanalysis	x
			Lee	Rejected	Not related with the investigated study. Survivin low/high expression and OS correlation were evaluated
			Ponnelle	Rejected	Not related with the investigated study. Survivin localization and OS correlation were evaluated
			Qi	Rejected	Not related with the investigated study. Survivin localization and OS correlation were evaluated
			Sarela	Rejected	Not selected method for survivin
			Xi	Selected before metaanalysis	x
			Xiaoyuan	Selected before metaanalysis	x

*Overall Survival (OS) data, immunohistochemistry and colorectal cancer analysis were evaluated.