Systematic Review/Meta-analysis

Unique characteristics of *ARID1A* mutation and protein level in gastric and colorectal cancer: A meta-analysis

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Abstract

Background/Aim: Recently, *AT-rich interactive domain-containing 1A protein* (*ARID1A*) has been identified as a novel tumor suppressor gene in gastric cancer (GC) and colorectal cancer (CRC). However, the clinicopathologic value of *ARID1A* mutation or protein level in GC and CRC patients is controversial. Hence, we conducted a meta-analysis on the relationship between *ARID1A* aberrations and clinicopathologic parameters in GC and CRC.

Materials and Methods: Relevant published studies were selected from PubMed and EMBASE. The effect sizes of *ARID1A* mutation or level on the patient's clinicopathologic parameters were calculated by prevalence rate or odds ratio (OR) or hazard ratio (HR), respectively. The effect sizes were combined using a random-effects model.

Results: The frequency of *ARID1A* mutation and loss of *ARID1A* protein expression in GC patients was 17% and 27%, respectively. The loss of *ARID1A* protein expression of GC patients was significantly associated with advanced tumor depth (OR = 1.8, $P = 0.004$), lymph node metastasis (OR = 1.4, $P = 0.001$), and unfavorable adjusted overall survival (HR = 1.5, $P < 0.001$). *ARID1A* mutation of GC was significantly associated with microsatellite instability (MSI) (OR = 24.5, $P < 0.001$) and EBV infection (OR = 2.6, $P = 0.001$). The frequency of *ARID1A* mutation and *ARID1A* protein expression loss in CRC patients was approximately 12–13%. Interestingly, the loss of *ARID1A* protein expression in CRC patients was significantly associated with poorly differentiated grade (OR = 4.0, $P < 0.001$) and advanced tumor depth (OR = 1.8, $P = 0.012$).

Conclusion: Our meta-analysis revealed that *ARID1A* alterations may be involved in the carcinogenesis of GC by EBV infection and MSI. The loss of *ARID1A* protein expression may be a marker of poor prognosis in GC and CRC patients.

Keywords: *ARID1A*, colorectal cancer, gastric cancer, meta-analysis

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INTRODUCTION

Recent studies of gastric cancer (GC) and colorectal cancer (CRC) patients using next-generation sequencing have highlighted the new tumor suppressor gene, *AT-rich interactive domain-containing 1A protein* (*ARID1A*).[1-7] The prevalence of *ARID1A* mutation in GC and CRC ranged from 8–31% and 6–39%, respectively.[1-14] *ARID1A* encodes a large nuclear protein, which forms Switch/Sucrose nonfermentable chromatin remodeling complex and plays a critical regulatory role in cellular processes including development, differentiation, proliferation, and DNA repair.[15]

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The majority of *ARID1A* mutations are mostly insertion/deletion and nonsense mutations, which lead to protein truncation and consequent rapid degradation.[1,16] Therefore, loss of *ARID1A* protein expression is highly correlated with *ARID1A* mutation.[1,16] Several reports have indicated the loss of *ARID1A* protein expression in GC and CRC. [1,17-32] However, clinicopathologic significances of *ARID1A* mutation or protein expression loss in GC and CRC patients remains unclear.[1-4,17-32] Therefore, we conducted a meta-analysis to clarify the clinicopathologic characteristics of *ARID1A* mutation or protein expression loss in GC and CRC patients.

MATERIAL AND METHODS

Data collection and selection criteria for meta-analysis

The search was conducted according to the PRISMA (Preferred Reporting Items for Systemic Reviews and Meta-Analyses) guidelines.[33] We searched PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and EMBASE (www.embase.com) using the keywords: [(*ARID1A*) and (stomach cancer or gastric cancer) or (colorectal cancer or colon cancer or rectal cancer]. In addition, we manually explored the reference lists of identified articles. Duplicate data or overlapping articles were excluded by examining the authors' names and affiliations. When multiple articles were published by the same authors or group, the most informative or recent article was selected. Original articles reporting cases of *ARID1A* mutation or protein expression level in GC and CRC published before October 2016 were included. We excluded review articles without original data, conference abstracts, case reports, cell line studies, and articles lacking clinicopathologic data for meta-analysis. Geographic or language restrictions were not applied. Study quality was independently scored by two reviewers according to the Newcastle-Ottawa Scale,[34] which is frequently used for case-control studies with a maximum case-control score of 9. The selection process of the articles is shown in Figure 1.

Data pooling and statistics

A meta-analysis was performed as previously described.[35] Briefly, effect sizes for each study were calculated by prevalence rate or odds ratio (OR) or hazard ratio (HR), and the corresponding 95% confidence interval (CI) using the Mantel-Haenszel method or the Cohen method. The prevalence rate or OR or HR was combined using a random-effects model (DerSimonian-Laird method). Statistical heterogeneity among studies was evaluated using the Cochrane Q test and I^2 statistics. The I^2 statistic refers to the percentage of variation across studies due to heterogeneity rather than chance and does not inherently

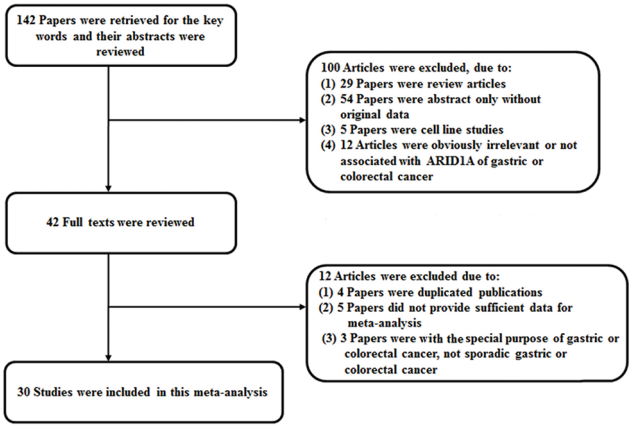

Figure 1: The flowchart of article selection for meta-analysis

depend on the number of studies considered [$I^2 = 100\% \times (Q - df)/Q$]. We clarified the cutoff of I^2 statistics for assignment of low (<25%), moderate (25–50%), and high (>50%) heterogeneities. If I^2 value was >25%, subgroup analysis was conducted. Sensitivity analyses were performed for influence of each study on the pooled prevalence rate, OR, or HR by serially omitting an individual study and pooling the remaining studies. The Publication bias was determined by funnel plots and Egger's tests for the degree of asymmetry. Publication bias was assumed as present if *P* value was <0.1. The pooled analysis was performed using Comprehensive Meta-analysis Software version 2.0 (Biostat, Englewood, NJ, USA).

RESULTS

Gastric cancer

ARID1A protein level

Thirteen studies reported the frequency of *ARID1A* protein level among 3948 cases of GC in 285 Caucasian and 3663 Asian patients [Table 1].[1,17-28] Pooled analysis indicated the loss of *ARID1A* protein expression in 26.7% of GC patients (95% CI: 14.8–43.1). Moreover, loss of *ARID1A* protein expression did not differ according to ethnicity ($P = 0.839$).

Ten studies described *ARID1A* protein level in GC patients according to gender.[1,17-24,26] *ARID1A* protein expression loss was observed in 522 of 2462 male and 234 of 1079 female GC patients. *ARID1A* protein level showed no association with gender (OR = 0.982, 95% CI: 0.797–1.209; $P = 0.862$, Q = 11.767, $I^2 = 23.515$).

Nine studies reported *ARID1A* protein level according to the histologic subtype of GC.[1,18-25] *ARID1A* protein expression loss was found in 285 of 1625 intestinal type and 219 of 1234 diffuse type GC patients. *ARID1A* protein

expression loss was not associated with the histologic subtype of GC (OR = 0.825, 95% CI: 0.671–1.014; $P = 0.068$, Q = 7.413, $I^2 = 0.000$).

Five studies presented *ARID1A* protein level according to the tumor depth.[18,20,21,23,24] *ARID1A* protein expression loss was observed in 71 of 637 early gastric cancer (EGC) and 324 of 1708 advanced gastric cancer (AGC) patients. The loss of *ARID1A* protein expression was significantly associated with AGC (OR = 1.813, 95% CI: 1.203–2.733; $P = 0.004$, Q = 8.030, $I^2 = 50.186$). Subgroup analysis revealed that the association between tumor depth and *ARID1A* protein level differed according to ethnicity [Table 2].

Ten studies presented *ARID1A* protein level according to the lymph node metastasis.[1,17-20,22-26] *ARID1A* protein expression loss was observed in 474 of 2085 cases with lymph node metastasis and 215 of 1275 cases without lymph node metastasis. The loss of *ARID1A* protein expression was significantly associated with lymph node metastasis (OR = 1.432, 95% CI: 1.158–1.772; $P = 0.001$, Q = 10.979, $I^2 = 18.026$) [Figure 2].

Five studies described *ARID1A* protein level according to the clinical stage.[1,21,22,25,26] *ARID1A* protein expression loss was observed in 175 of 742 of the stage III, IV and 136 of 720 of stage I, II GC patients. There was no significant association between stage and *ARID1A* protein expression loss (OR = 1.195, 95% CI: 0.861–1.658; $P = 0.287$, Q = 5.626, $I^2 = 28.901$). Subgroup analysis revealed that the association between stage and *ARID1A* protein level was not different according to the antibody type [Table 2].

Five[1,17,19,24,26] and four[17,20,24,26] studies presented the univariate unadjusted and multivariate adjusted survival outcomes of GC patients according to the *ARID1A* protein level. The number of patients in each study ranged from 109 to 489, for a total of 1355 and 1316 patients, respectively. The estimated unadjusted and adjusted HRs ranged from 0.511–1.981 and 1.36–1.663, respectively. The prognostic variables used in the multivariate survival model were patient's sex, histologic type, and clinical stage. The loss of *ARID1A* protein expression was significantly associated with unfavorable adjusted overall HR (HR = 1.508, 95% CI: 1.249–1.820; $P < 0.001$, Q = 0.834, $I^2 = 0.000$) [Figure 3], but not unadjusted overall HR (HR = 1.388, 95% CI: 0.937–2.055; $P = 0.102$, Q = 16.449, $I^2 = 75.683$). Subgroup analysis revealed that the kind of antibody used did not influence the relationship between *ARID1A* protein expression loss and unadjusted overall HR [Table 2].

Table 1: Characteristics of individual studies of *ARID1A* expression loss included in the meta-analysis

Study	Country of patients	Antibody	*ARID1A* expression negative/total (%)	Score
Gastric cancer				
Wang *et al*.[1]	Hong Kong	HPA005456	30/109 (27.5%)	7
Wang *et al*.[17]	China	3H2	115/224 (51.3%)	7
Abe *et al*.[18]	Japan	HPA005456	94/857 (11.0%)	6
Yan *et al*.[19]	China	n.c.	44/183 (24.0%)	6
Wiegand *et al*.[20]	Canada	HPA005456	55/253 (21.7%)	7
Han *et al*.[21]	Korea	PSG-3	88/417 (21.1%)	7
Kim *et al*.[22]	Korea	ab171870	62/191 (32.5%)	7
Aso *et al*.[23]	Japan	HPA005456	94/468 (20.1%)	7
Kim *et al*.[24]	Korea	HPA005456	65/350 (18.6%)	7
Lee *et al*.[25]	Korea	HPA005456	22/275 (8.0%)	7
Inada *et al*.[26]	Japan	HPA005456	109/489 (22.3%)	7
Kim *et al*.[27]	Korea	HPA005456	9/100 (9.0%)	6
I-V *et al*.[28]	Spain	HPA005456	8/32 (25.0%)	7
Colorectal cancer				
Lee *et al*.[25]	Korea	HPA005456	12/196 (6.1%)	7
Kim *et al*.[27]	Korea	HPA005456	8/100 (8.0%)	6
Xie *et al*.[29]	China	HPA005456	26/86 (30.2%)	7
Chou *et al*.[30]	Australia	HPA005456	110/1876 (5.9%)	7
Wei *et al*.[31]	China	PSG-3	54/209 (25.8%)	7
Lee *et al*.[32]	USA	HPA005456	49/552 (8.9%)	7

Score: Newcastle-Ottawa score; nc: Not commented

Table 2: Subgroup analysis

Category	No. of studies	Odd ratio (95% CI)	*P*
ARID1A protein level of gastric cancer			
Overall AGC predominance	5	1.813 (1.203-2.733)	0.004
Ethnicity			0.025
Asian	4	2.136 (1.580-2.886)	
Caucasian	1	0.785 (0.344-1.788)	
Used antibody			0.195
HPA005456	4	1.604 (1.036-2.484)	
PSG-3	1	3.101 (1.266-7.595)	
Overall stage association	5	1.195 (0.861-1.658)	0.287
Ab171870	1	1.180 (0.419-3.323)	0.719
HPA005456	3	0.955 (0.502-1.817)	
PSG-3	1	1.535 (0.589-4.003)	
Overall unadjusted hazard ratio	5	1.388 (0.937-2.055)	0.102
Used antibody			0.518
3H2	1	1.905 (0.693-5.239)	
HPA005456	3	1.117 (0.623-2.003)	
Not commented	1	1.981 (0.666-5.892)	
Overall EBV association	6	3.351 (2.156-5.210)	<0.001
Ethnicity			
Asian	5	3.310 (2.007-5.457)	0.873
Caucasian	1	3.804 (0.748-19.345)	
Used antibody			0.482
HPA005456	5	3.626 (2.165-6.073)	
PSG-3	1	2.354 (0.793-6.988)	
ARID1A protein level of colorectal cancer			
Overall histologic grade	5	3.952 (2.206-7.081)	<0.001
Ethnicity			
Asian	3	2.572 (1.283-5.158)	0.071
Caucasian	2	5.874 (3.336-10.344)	
Used antibody			0.118
HPA005456	4	5.093 (3.015-8.604)	
PSG-3	1	2.116 (0.802-5.582)	

No: Number; CI: Confidence interval; GC: Gastric AGC: Advanced gastric cancer; EBV: Epstein-Barr virus

Six studies reported *ARID1A* protein level according to Epstein-Barr virus (EBV) infection[1,18,20,21,23,24]. *ARID1A* protein expression loss was detected in 71 of 189 EBV-associated gastric cancer (EBVaGC) cases and 353 of 2258 non-EBVaGC cases. The loss of *ARID1A* protein expression was significantly associated with EBVaGC (OR = 3.351, 95% CI: 2.156–5.210; $P < 0.001$, Q = 8.301, $I^2 = 39.796$) [Figure 4]. Subgroup analysis revealed that the association between EBVaGC and *ARID1A* protein expression loss was not different according to the ethnicity and antibody type [Table 2].

ARID1A mutation

A total of 10 studies reported the frequency of *ARID1A* mutation among 1036 GC patients, of which 551 were Caucasian and 485 were Asian [Table 3].[1-5,8-12] Pooled analysis indicated *ARID1A* mutation in 16.8% of patients with GC (95% CI: 11.7–23.7). *ARID1A* mutation did not differ according to ethnicity ($P = 0.453$).

Four studies described *ARID1A* mutation in 325 cases with III or IV stage and 246 cases with I or II stage.[1-4] *ARID1A* mutation was observed in 70 of 325 stage III and IV cases and 69 of 246 stage I and II cases. The stage was not significantly associated with *ARID1A* mutation (OR = 0.782, 95% CI: 0.526–1.164; $P = 0.226$, Q = 1.309, $I^2 = 0.000$).

Four studies reported *ARID1A* mutation according to the microsatellite instability (MSI).[1-3,5] *ARID1A* mutation was found in 80 of 103 MSI GC cases and 55 of 422 stable MSI GC cases. *ARID1A* mutation was significantly associated with MSI (OR = 24.495, 95% CI: 13.633–44.012; $P < 0.001$, Q = 0.503, $I^2 = 0.000$). Three studies presented *ARID1A* mutation in EBVaGC.[1,3,4] *ARID1A* mutation was detected in 30 of 77 EBVaGC cases and 107 of 399 non-EBVaGC cases. *ARID1A* mutation was significantly associated with EBVaGC (OR = 2.572, 95% CI: 1.445–4.577; $P = 0.001$, Q = 0.530, $I^2 = 0.000$).

Colorectal cancer

Six studies reported the frequency of *ARID1A* protein level in 3019 CRC patients [Table 1].[25,27,29-32] Pooled analysis indicated the loss of *ARID1A* protein expression in 11.7% of CRC patients (95% CI: 6.1–21.4). Five studies presented the prevalence of *ARID1A* mutation in 776 CRC patients [Table 3].[6-8,13,14] Pooled analysis indicated *ARID1A* mutation in 13.0% of patients with CRC (95% CI: 6.4–24.6). *ARID1A* mutation and protein level did not differ with ethnicity ($P = 0.958$ and $P = 0.119$, respectively).

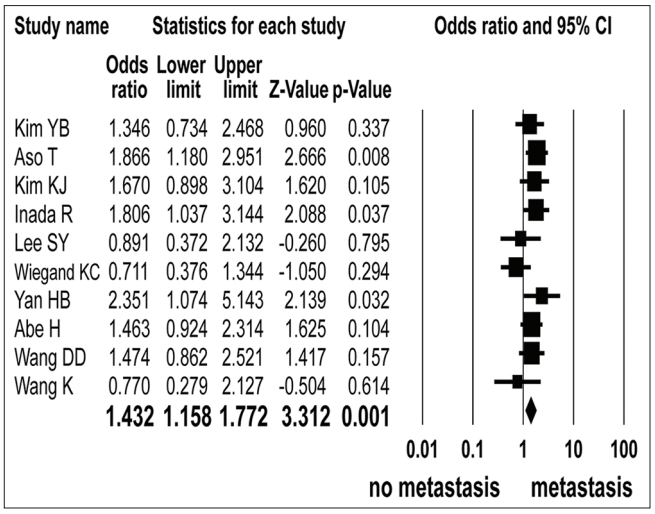

Figure 2: Odd ratios with corresponding 95% confidence intervals of individual studies and pooled data for the association between negative expression of *ARID1A* protein in gastric cancer patients and lymph node metastasis. Forest plot demonstrates the effect sizes and 95% CIs for each study and overall

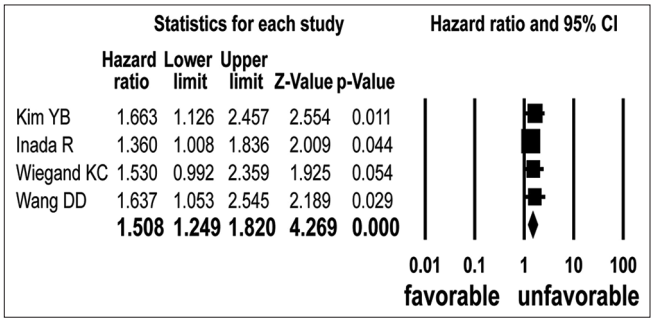

Figure 3: Hazard ratios and pooled data for overall survival according to *ARID1A* expression in multivariate analysis

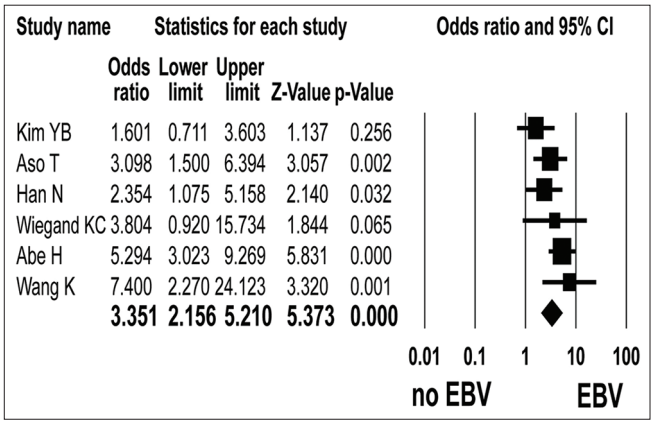

Figure 4: Forest plot of odds ratios with corresponding 95% confidence intervals for the association between negative expression of *ARID1A* protein and EBV associated gastric cancer

Five studies focused on *ARID1A* protein level in CRC by histologic grade.[25,29-32] *ARID1A* protein expression loss was found in 86 of 415 poorly differentiated and 139 of 2099 well to moderately differentiated CRC

Table 3: Characteristics of individual studies of *ARID1A* mutation included in the meta-analysis

Study	Country of patients	Method	*ARID1A* mutation Mutation/total (%)	Score
Gastric cancer				
Wang *et al*.[1]	Hong Kong	WES, S	32/109 (29.4%)	7
Zang *et al*.[2]	Singapore	WES, S	9/110 (8.2%)	6
Bass *et al*.[3]	USA	WES	90/289 (31.1%)	7
Chen *et al*.[4]	China	WES, S	15/78 (19.2%)	7
Kim *et al*.[5]	Korea	WES	4/17 (23.5%)	6
Jones *et al*.[8]	USA	S	10/100 (10.0%)	6
Chong *et al*.[9]	UK	WES, S	7/46 (15.2%)	7
Takeshima *et al*.[10]	Japan	TS	5/50 (10.0%)	7
Ali *et al*.[11]	USA	TS	28/116 (24.1%)	7
Kuboki *et al*.[12]	Japan	TS	10/121 (8.3%)	7
Colorectal cancer				
Muzny *et al*.[6]	USA	WES	25/224 (11.2%)	7
Cajuso *et al*.[7]	Finland	WES	18/46 (39.1%)	7
Jones *et al*.[8]	USA	S	12/119 (10.1%)	6
Kato *et al*.[13]	USA	TS	20/347 (5.8%)	7
Ling *et al*.[14]	China	S	5/40 (12.5%)	6

Score: Newcastle-Ottawa score; WES: Whole exome sequencing; S: Sequencing; TS: Target sequencing by next generation sequencing technique

patients. The loss of *ARID1A* protein expression was significantly associated with poorly differentiated CRC (OR = 3.952, 95% CI: 2.206–7.081; $P < 0.001$, Q = 9.440, $I^2 = 57.627$) [Figure 5].

Four studies described *ARID1A* protein level in CRC patients according to the tumor depth.[25,29,31,32] *ARID1A* protein expression loss was observed in 24 of 269 cases with T1,2 and 117 of 773 cases with T3,4 CRC patients. The loss of *ARID1A* protein expression was significantly associated with advanced tumor depth (OR = 1.849, 95% CI: 1.146–2.984; $P = 0.012$, Q = 0.793, $I^2 = 0.000$).

Four studies reported *ARID1A* protein level in CRC patients according to the stage.[25,29-31] The *ARID1A* protein expression loss was observed in 89 of 1118 cases with stage I, II and 112 of 1231 cases with stage III, IV CRC patients. Stage showed no significant association with *ARID1A* protein level (OR = 1.139, 95% CI: 0.837–1.550; $P = 0.409$, Q = 1.779, $I^2 = 0.000$).

Publication bias and sensitivity analysis

Funnel plots and the Egger's regression tests of pooled result of association between clinical stage of GC and *ARID1A* protein level indicated the possibility of publication bias. However, other pooled analyses showed no evidence of publication bias (data not shown).

Sensitivity analyses revealed that individual study affected the results of histologic subtype, tumor depth, stage, and unadjusted HR according to *ARID1A* protein level in GC. The study of Bass *et al*. influenced the result of EBV association.[3] However, other studies did not affect the OR or HR with the 95% CIs.

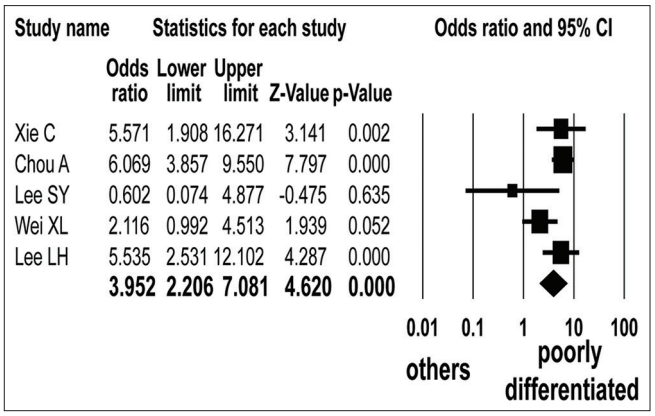

Figure 5: Forest plot of odds ratios with corresponding 95% confidence intervals for the association between negative expression of *ARID1A* protein and histologic grade of colorectal cancer

DISCUSSION

This pooled analysis using 1036 and 3948 GC patients confirmed that *ARID1A* mutation and *ARID1A* protein expression loss were detected in 17% and 27% cases, respectively. The loss of *ARID1A* protein expression in GC patients was significantly associated with advanced tumor depth, lymph node metastasis, and unfavorable overall survival. This meta-analysis confirmed that *ARID1A* mutation or protein expression loss was significantly associated with MSI and EBV infection of GC patients. In addition, the frequency of *ARID1A* mutation or loss of *ARID1A* protein expression occurred in 12–13% of CRC patients. The loss of *ARID1A* protein expression was significantly associated with poorly differentiated histologic grade CRC and advanced tumor depth.

To our knowledge, this is the first meta-analysis investigating the relationship between *ARID1A* mutation or protein expression loss and clinicopathologic parameters of GC and CRC patients. The role of *ARIDA1* aberration in individual GC and CRC patient is currently unclear due to the small sample size and heterogeneous patient population. Wang *et al*. claimed that *ARIDA1* alterations were associated with better prognosis in GC.[1] In contrast, some studies showed that loss of *ARID1A* protein expression was associated with poor prognostic factors.[17,21,22,26] The previous published data about the associations between *ARID1A* alteration and clinicopathologic parameters of CRC had not been consistent. The results of pooled analysis in our study indicated that the loss of *ARID1A* protein expression may be a marker of poor prognosis in individual GC and CRC patient.

The association between *ARIDA1* aberration and MSI is a very important issue. This meta-analysis revealed that *ARID1A* mutation causes dramatic increases in MSI GC patients. Thus, *ARID1A* may be a driver gene targeted by MSI pathway. Due to deficiency of data, we were unable to study the association between *ARIDA1* aberration and MSI of CRC.

Our meta-analysis indicated that *ARID1A* mutation or loss of its protein expression in GC was associated with EBVaGC. The *ARID1A* mutation or protein expression loss showed approximately three-fold increase in EBVaGC compared with non-EBVaGC patients. Histologically, EBVaGC is characterized by dense lymphocytic infiltration within or surrounding GC.[36] Interestingly, the lymphoid infiltration is one of the histologic features of GC with MSI.[37] The association between *ARID1A* mutation or its protein expression loss and subtype with lymphocytic infiltration is suggestive that *ARID1A* aberration may be related to the immune surveillance of this GC subtype.

Our study had a few limitations. First, the immunohistochemical results of *ARID1A* protein level vary with the kind of antibody used, tissue fixation time, and data interpretation. Second, the data of *ARID1A* alteration according to clinicopathologic parameters were insufficient. Lastly, we roughly classified patients into Caucasian and Asian groups, which could lead to discordance between the current result and original data.

Our meta-analysis indicated that GC or CRC with *ARID1A* alteration might be a marker of poor prognosis. The *ARID1A* alteration of GC may result from different epigenetic factors.

Acknowledgments

Young-Sik Kim and Hoiseon Jeong contributed equally to this work.

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Conflicts of interest

There are no conflicts of interest.

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