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Original Article

CD44 family proteins in gastric cancer: a meta-analysis and narrative review

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Abstract: With a meta-analysis and narrative review, we evaluated the clinical and prognostic role of all CD44 family proteins in gastric cancer (GC). Literatures published up to August 2014 were searched on PubMed. Among the 37 eligible studies (6606 patients), 34 were included in meta-analysis, and 10 were subjected to narrative review. With meta-analysis, standard CD44 (CD44s) was demonstrated to predict reduced overall survival (OS) (HR = 1.93, 95% CI: 1.58-2.34, P_{HR} = 0.0222) and disease free survival (HR = 3.13, 95% CI: 1.02-9.68, P_{HR} = 0.0469), advanced N-stage (RR = 1.12, 95% CI: 1.04-1.21, P_{RR} = 0.0019), and distant metastasis (RR = 2.14, 95% CI: 1.46-3.14, P_{RR} < 0.0001) of GC. CD44 variant 6 (CD44v6) in GC might influence OS (5 studies; HR = 1.27, 95% CI: 0.75-2.14, P_{HR} = 0.3783; 4 studies; HR = 1.52, 95% CI: 1.09-2.14, P_{HR} = 0.0139), while significantly associated with N-stage (RR = 1.23, 95% CI: 1.03-1.48, P_{RR} = 0.0240), M-stage (RR = 2.54, 95% CI: 1.08-6.00, P_{RR} = 0.0333), TNM-stage (RR = 1.72, 95% CI: 1.18-2.50, P_{RR} = 0.0045), Lauren type (RR = 0.67, 95% CI: 0.50-0.91, P_{RR} = 0.0106), lymphatic invasion (RR = 1.13, 95% CI: 1.04-1.23, P_{RR} = 0.0057), and liver metastasis (RR = 3.20, 95% CI: 1.94-5.27, P_{RR} < 0.0001) of the disease. Moreover, a narrative review was performed for CD44 isoforms, such as v3, v5, v7, v8-10, and v9, in GC. In conclusion, CD44s and CD44v6 as evaluated by immunohistochemistry, respectively, predicts the prognosis and disease severity of GC.

Keywords: CD44s, CD44 variants, gastric cancer, meta-analysis, narrative review, prognosis

Introduction

Gastric cancer (GC) is a major public health issue, as the fourth most common and the second most deadly human malignancy worldwide [1, 2]. Although great advances have been made for the diagnosis and therapy of the disease, the clinical outcome of patients is still poor [3-5]. Increasing evidence suggests that cancer stem cells (CSCs) within GC show the potential for the initiation and progression of cancer, such as inducing heterogeneity, metastasis, and therapeutic resistance of GC, and thus resulting in the poor prognosis of patients [6-8]. Furthermore, special biomarkers account for the particular property of CSCs [9-11]. Amongst the several stem cell surface markers of GC, the class I transmembrane glycoprotein CD44 family represents the novel and most robust surface marker for GC stem cells [9, 11]. CD44 family includes standard CD44 (CD44s) that expressed ubiquitously and CD44 splicing variants (CD44v) with specific distributions in keratinocytes (CD44v3-v10), epithelial cells (CD44v8-v10), and activated lymphocytes and macrophages (CD44v6) [12, 13]. Functionally, CD44 was initially identified as the receptor for the extracellular matrix component, hyaluronic acid, and involved in multiple physiological and pathological processes, like cancer development, angiogenesis, cell adhesion, wound healing and inflammation [14, 15]. Later studies suggested CD44 to be an important stem cell marker for multiple solid tumors including GC [9, 16]. Following the identification of various CD44 isoforms, the studies for CD44 became more broad and complex. Currently, it is revealed that CD44 family proteins mediate a variety of biological processes, such as epithelial-mesenchymal transition (EMT), DNA repair,

over expression of ABC transporters, chemo-radioresistance and invasiveness, in GC cells [5, 10, 17-19].

Although all of the aforementioned molecular functions of CD44 lead to the development and progress of cancer, the clinical studies evaluating the validity of CD44 as a therapeutic or diagnostic target in human GC are diversified, and the findings are also controversial. Mayer, B. et al first found that CD44 expression in GC independently predicted poor survival of patients [20], which were confirmed by some later studies [4, 6, 9, 12, 16, 21]. However, there were still some other studies showing the insignificant association between the presence of CD44 in GC and the poor clinical outcome of patients [22, 23]. Moreover, the reports on the clinical and prognostic role of CD44 variants in GC are also inconsistent [23-25]. To reveal the current research status, clarify the controversial issues and present some potential clues for the future research directions, we performed the meta-analysis and narrative review for the association of CD44 family proteins with the prognosis and clinicopathologic features in GC.

Methods

Publication search

In the PubMed database, publications were identified with the following search terms: "Stomach Neoplasms" or "gastric cancer" [Title/Abstract] or "gastric carcinoma" [Title/Abstract] or "gastric cancers" [Title/Abstract] or "gastric cancer*" [Title/Abstract] or "gastric carcinomas" [Title/Abstract] or "gastric carcinoma*" [Title/Abstract] or "gastric adenocarcinoma" [Title/Abstract] or "gastric adenocarcinomas" [Title/Abstract] or "gastric adenocarcinoma*" [Title/Abstract] or "stomach cancer" [Title/Abstract] or "stomach cancers" [Title/Abstract] or "stomach cancer*" [Title/Abstract] or "stomach carcinoma" [Title/Abstract] or "stomach carcinomas" [Title/Abstract] or "stomach carcinoma*" [Title/Abstract] or "stomach adenocarcinoma" [Title/Abstract] or "stomach adenocarcinomas" [Title/Abstract] or "stomach adenocarcinoma*" [Title/Abstract] or "gastric neoplasm" [Title/Abstract] or "gastric neoplasms" [Title/Abstract] or "gastric neoplasm*" [Title/Abstract] or "stomach neoplasm" [Title/Abstract] or "stomach neoplasms" [Title/Abstract] or "stomach neoplasm*" [Title/Abstract] or "cancer of the stomach" [Title/Abstract] or "cancer of stomach" [Title/Abstract], AND "Antigens, CD44" or "Hyaluronan-Binding Protein" [Title/Abstract] or "Hyaluronan Binding Protein" [Title/Abstract] or "CD44 Antigen" [Title/Abstract] or "Hyaluronan Receptor" [Title/Abstract] or "Hyaluronan Receptors" [Title/Abstract] or "Hyaluronic Acid Binding Protein" [Title/Abstract] or "CD44 Antigens" [Title/Abstract] or "MC56 protein" [Title/Abstract] or "homing-associated cell adhesion molecule" [Title/Abstract] or "MC56 drug-sensitivity marker protein" [Title/Abstract] or "HCAM protein" [Title/Abstract] or "CD44*" [Title/Abstract]. Articles included in the present analysis were published from 1991 through August 2014. The articles that detected CD44 by immunohistochemistry (IHC) method were included in the current study. To identify relevant articles, title/abstract scanning and full-text browsing were sequentially performed.

Inclusion criteria

The inclusion criteria for literatures were: (1) studies published as original research in English regardless of publication time; (2) studies presenting sufficient data for evaluating the impact of the expression of CD44 and its variants on the clinicopathological outcome in GC; (3) studies dealing with primary GC samples removed by surgery (not metastatic GC or GC adjacent tissue) and confirmed pathologically; (4) studies that is the newest or the most completed amidst duplicated reports on the same cohorts at different time, as checked out by references manager software EndNote (X7 version). Letters, case reports, reviews, conference abstracts and researches using animal or cell lines, and studies unrelated to our analysis were excluded.

Data extraction

With the standardized principle and tool for data extraction, two reviewers independently abstracted the data. The disagreements were resolved by consensus after referring to the original reports. Nonspecific-defined CD44 in the previous reports was regarded as CD44s, and CD44 isoforms were named as the original reports. The following information were collected from the eligible publications: name of first author, publication year, patients' country,

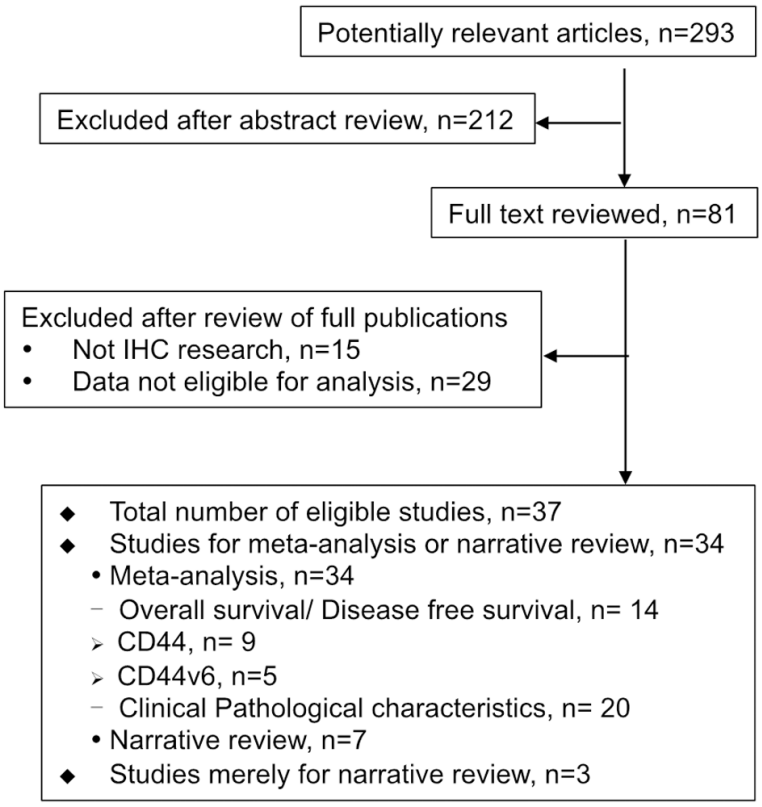

Figure 1. Flowchart for the selection of studies according to the predefined inclusion criteria in meta-analysis.

number of patients analyzed, research technique used, cut off value of CD44 family proteins, clinicopathological variables including cancer location, differentiation, Lauren type, lymphatic invasion, vascular invasion, liver metastasis, peritoneal metastasis, perineural metastasis, depth of invasion (T-stage), lymph node metastasis (N-stage), distant metastasis (M-stage), and TNM-stage. For ease of analysis, CD44 expression was categorized as high/positive and low/negative, and the following clinicopathological variables were combined into dichotomous categories: cardia and non-cardia location, well/moderate (WD/MD) and poor/undifferentiated (PD/UN) differentiation, intestinal and diffuse type, negative (-) and positive (+) lymphatic/vascular invasion, negative (-) and positive (+) liver/peritoneal/perineural metastasis, T1-2 and T3-4 stage, N0 and N1-3 stage, M0 and M1 stage, as well as I-II and III-IV TNM-stage. Hazard ratio (HR) and 95% confidence interval (CI) from univariate analysis was preferably taken if both univariate and multivariate analysis were reported. Calculation method was applied to extract HR and 95% CI where HR was not reported [26]. In those studies with only Kaplan-Meier (K-M) curve available, survival curves were read by Engauge Digitizer version 4.1 (downloaded from http://sourceforge.net), and HR, 95% CI, the significance as well as the orientation (favor protective or hazardous) were extracted from original publications as described by Parmar et al [27].

For the above categories, data reported not less than 3 times were meta-analyzed, and the others were subjected to narrative review. Additionally, data not shown in the primary articles were designated as "N/A (not available)" in our study. We did not request additional or unreported information of the primary studies. We also did not evaluate the studies with quality score, considering the quality score system in meta-analysis of observational studies is still controversial.

Statistical methods

R/meta software (R 3.0.2) was utilized to perform the statistical analysis. Unless specifically indicated, all statistic tests were two tailed with $P < 0.05$ as statistically significant. Heterogeneity of publications was calculated with the Chi-square-based Q statistic and inconsistency index (I2) statistic ($P < 0.10$ and I2 > 50% indicated substantial heterogeneity). A fixed-effect model was used if homogeneity was present, and a random-effect model was used if heterogeneity was demonstrated. Log HRs were used to make the forest plot in the survival analysis using R software, and 95% CI not overlap 0 was considered significant. Pooled HR and 95% CI were obtained from log HR by calculation, and a HR > 1 implied that CD44 high/positive expression predicted worse survival of patients. Risk ratio (RR) and 95% CI were utilized for the analysis of dichotomous data. It was considered as statistically signifi-

Table 1. Main characteristics of the eligible studies

Author	Year	Country	Cut off	Stage	Cancer	Cohort	Sample	Detection	Gene	Survival	HR Extraction
Cao, L.	2014	China	0	N/A	GC	203	FFPE	WTS-IHC	CD44	OS	Calculation
Qiu, Y.	2014	China	4 score	I-IV	GC	243	FFPE	TMA-IHC	CD44	N/A	
Hirata, K.	2013	Japan	3.55%	N/A	EGC	65	FFPE	WTS-IHC	CD44v9	DFS	Report-mul
Chen, S.	2013	China	65%	I-IV	GC	152	FFPE	WTS-IHC	CD44	OS	Report-mul
Jung, W. Y.	2013	Korea	N/A	I-IV	GC	430	FFPE	TMA-IHC	CD44	N/A	
Doventas, A.	2012	Turkey	0	I-IV	GC	48	FFPE	WTS-IHC	CD44	OS	SC
Wakamatsu, Y.	2012	Japan	10%	I-IV	GC	96	FFPE	WTS-IHC	CD44	CRS	Report-uni
Fanelli, M. F.	2012	Brazil	0	I-IV	GC	137	FFPE	TMA-IHC	CD44v6	OS	Calculation
Liang, Yi-Zhi	2012	China	5%	N/A	GC	59	FFPE	WTS-IHC	CD44v6	N/A	
Ryu, H. S.	2012	Korea	5%	I-IV	GC	276	FFPE	TMA-IHC	CD44	N/A	
Wang, T.	2011	Singapore	5 score	I-IV	GC	106	FFPE	TMA-IHC	CD44	OS	SC
Dhingra, S.	2011	United States	N/A	I-IV	GC	138	FFPE	WTS-IHC	CD44	N/A	
Kim, J. Y.	2009	Korea	10%	I-IV	GC	210	FFPE	TMA-IHC	CD44	OS	SC
Okayama, H.	2009	Japan	5%	I-III	GC	135	FFPE	WTS-IHC	CD44v6	N/A	
Songun, I.	2007	Netherlands	25%	N/A	R0 GC	286	FFPE	WTS-IHC	CD44v6	OS	Calculation
Kim, M. A.	2005	Korea	10%	I-IV	GC	729	FFPE	TMA-IHC	CD44	N/A	
Chen, X. Y.	2005	China	0	I-IV	GC	28	FFPE	TMA-IHC	CD44v6	N/A	
Chen, J. Q.	2004	China	10%	I-IV	D2/D3 GC	43	FFPE	WTS-IHC	CD44v6	N/A	
Polkowski, W. P.	2004	Poland	10%	II-IV	Cardia GC	49	FFPE	WTS-IHC	CD44v6	N/A	
Joo, M.	2003	Korea	10%	I-IV	GC	99	FFPE	WTS-IHC	CD44/CD44v6	N/A	
Yamaguchi, A.	2002	Japan	0	I-IV	AGC	201	FFPE	WTS-IHC	CD44v6	OS	SC
Xin, Y.	2001	Ireland	5%	I-IV	GC	155	FFPE	WTS-IHC	CD44v6	N/A	
Li, H.	2000	China	N/A	N/A	GC	74	Frozen	WTS-IHC	CD44v5/v6/v7/v8-10	N/A	
Yoo, C. H.	1999	Korea	5%	II/IIIA	GC	261	FFPE	WTS-IHC	CD44	OS	Report-mul
Saito, H.	1998	Japan	5%	I-IV	Diffuse GC	46	FFPE	WTS-IHC	CD44v6	OS	SC
Saito, H.	1998	Japan	5%	I-IV	Intestinal GC	71	FFPE	WTS-IHC	CD44v6	OS	SC
Kurozumi, K.	1998	Japan	30%	I-III	GC	98	FFPE	WTS-IHC	CD44v6	N/A	
Isozaki, H.	1998	Japan	10%	I-IV	GC	108	FFPE	WTS-IHC	CD44	N/A	
Yasui, W.	1998	Japan	5%	I-IV	GC	1074	FFPE	WTS-IHC	CD44v9	N/A	
Chong, J. M.	1997	Japan	N/A	N/A	GC	104	FFPE	WTS-IHC	CD44v6/v3-5	N/A	
Muller, W.	1997	Germany	5%	N/A	GC	418	FFPE	WTS-IHC	CD44v5	OS	Calculation
Ura, H.	1996	Japan	10%	N/A	GC	110	FFPE	WTS-IHC	CD44v6/v3	N/A	
Hong, R. L.	1995	China	0	N/A	GC	103	Frozen	WTS-IHC	CD44/CD44v6	OS/DFS	SC

Mirecka, J.	1995	Poland.	N/A	N/A	GC	112/105	FFPE	WTS-IHC	CD44v5/v6	N/A	
Yamaguchi, A.	1995	Japan	25%	I-IV	GC	194	FFPE	WTS-IHC	CD44v8-10	N/A	
Harn, H. J.	1995	China	N/A	N/A	GC	49	FFPE	WTS-IHC	CD44v5/v6	N/A	
Dammrich, J.	1995	Germany	N/A	N/A	GC	42	Frozen	WTS-IHC	CD44v6	N/A	
Mayer, B.	1993	Germany	N/A	N/A	GC	31	FFPE	WTS-IHC	CD44	CRS/DFS	Calculation

GC: gastric cancer; EGC: early gastric cancer; AGC: advanced gastric cancer; N/A: not available; FFPE: formalin-fixed, paraffin-embedded; WTS: whole tissue section; TMA: tissue microarray; IHC: immunohistochemistry; OS: overall survival; CRS: cancer related survival; DFS: disease free survival; HR: hazard ratio; SC: survival curve; mul: multivariate analysis; uni: univariate analysis.

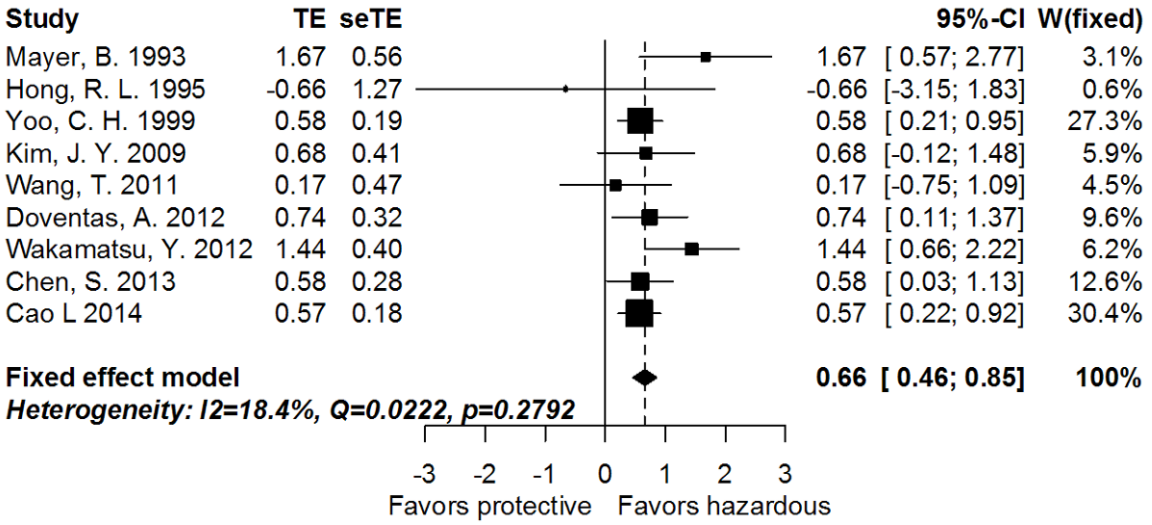

Figure 2. Forrest plot of log hazard ratio for the correlation between CD44s expression and overall survival.

Table 2. Meta-analysis of CD44s in gastric cancer

Stratification	Studies (N)	Patients (N)	Model	Log HR/RR (95% CI)	P_{HR}/P_{RR}	*P*	I2 (%)	P_{bias}
Overall survival	9	1210	Fixed	0.66 (0.46-0.85)	0.0222	0.2792	18.4	0.6264
Disease free survival	3	261	Random	1.14 (0.02-2.27)	0.0469	0.0168	75.5	0.6582
Location of cancer	7	1646	Fixed	0.95 (0.89-1.01)	0.1049	0.0791	47.0	0.7651
T-stage	11	1927	Random	0.97 (0.85-1.11)	0.6909	0.0008	66.7	0.0297
N-stage	13	2336	Fixed	1.12 (1.04-1.21)	0.0019	0.5891	00.0	0.9071
M-stage	4	426	Fixed	2.14 (1.46-3.14)	< 0.0001	0.6093	00.0	0.5477
TNM-stage	10	2103	Fixed	1.09 (0.99-1.20)	0.0854	0.0536	46.1	0.3935
Lymphatic invasion	7	1105	Fixed	1.09 (0.97-1.22)	0.1529	0.7111	00.0	0.5177
Vascular invasion	4	693	Fixed	1.07 (0.85-1.33)	0.5677	0.9133	00.0	0.6898
Degree of differentiation	9	1479	Random	1.12 (0.97-1.29)	0.1122	0.0144	58.1	0.6852
Lauren type	7	852	Random	0.96 (0.71-1.30)	0.7923	0.0070	66.1	0.9145
Perineural metastasis	3	598	Fixed	0.98 (0.78-1.25)	0.8972	0.6098	00.0	0.5374

HR: hazard ratio; RR: risk ratio; N: number of studies or patients; CI: confidence interval; P_{HR}: significance of HR; P_{RR}: significance of RR; *P*: significance for heterogeneity of publications; P_{bias}: significance for publication bias.

cant if the 95% CI for RR did not overlap 1. To assess the stability of the results, we conducted sensitivity analysis, which means to delete one at a time to check the influence of the individual data set on the pooled RR (or HR). Egger's regression tests were performed to evaluate the publication bias.

Results

Description of studies

Figure 1 showed the detailed search steps. A total of 293 studies were retrieved with the search strategy described above. After title/abstract scanning, 81 studies were considered relevant and further evaluated by reviewing full text in detail. Of these publications, 44 were excluded: 15 were not immunohistochemical research for CD44, and 29 were with non-extractable data for analysis. Finally, there were totally 37 eligible studies involving 38 cohorts. Thirty-four studies including 35 observational cohorts (totally 5450 patients, ranging from 28 to 729 patients per cohort) were included in meta-analysis, and 7 of them were also subjected to narrative review. The other 3 studies were merely analyzed by narrative review. **Table 1** showed the major characteristics of the eligible studies.

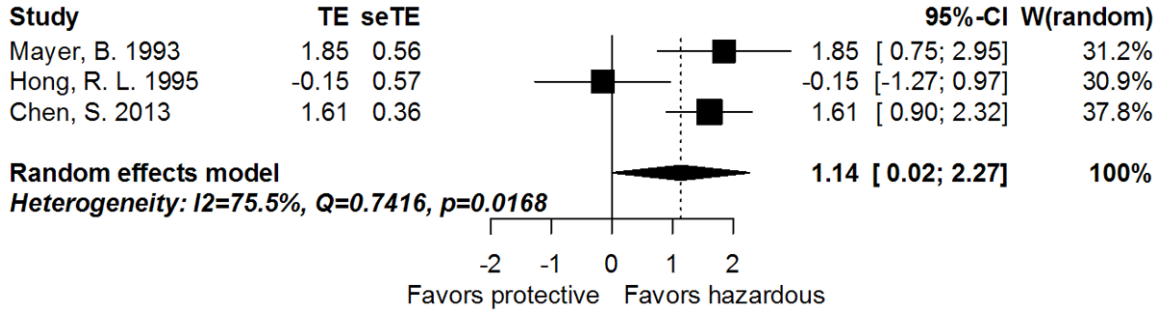

Figure 3. Forrest plot of log hazard ratio for the correlation between CD44s expression and Disease free survival.

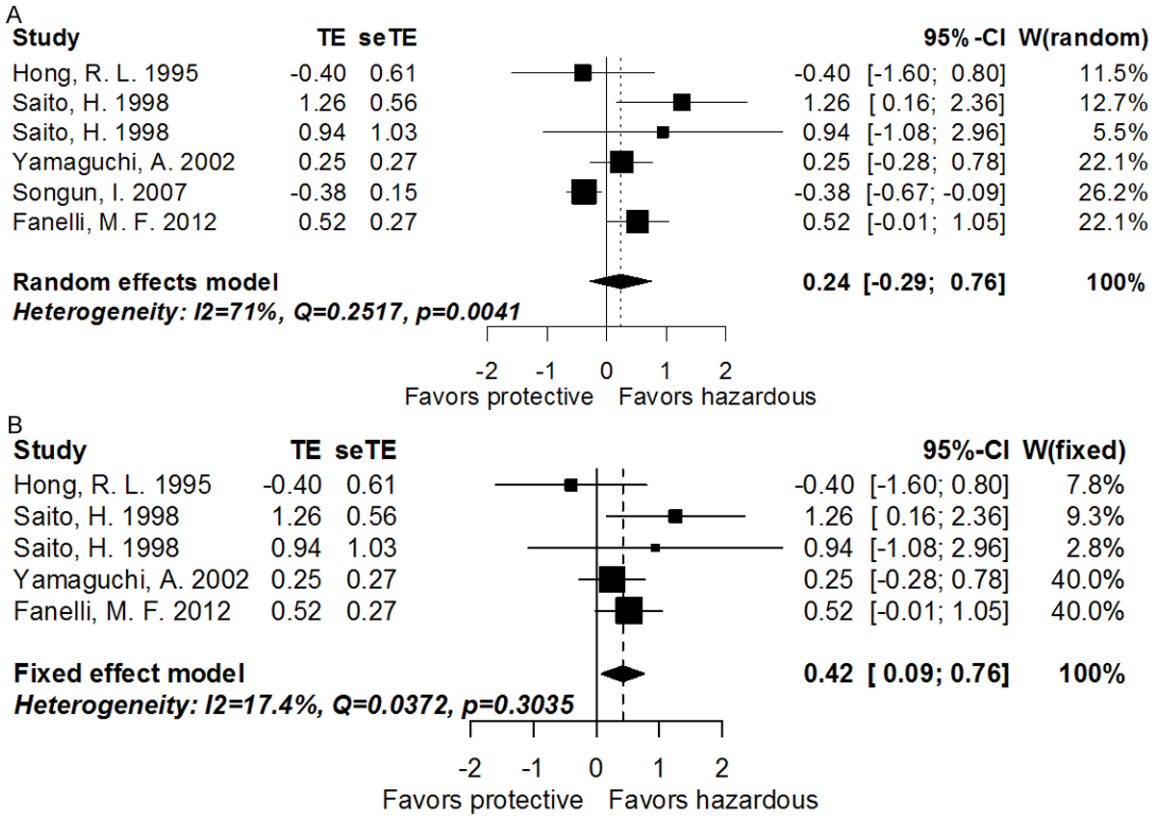

Figure 4. A. Forrest plot of log hazard ratio for the correlation between CD44v6 expression and overall survival. B. Forrest plot of log hazard ratio for the correlation between CD44v6 expression and overall survival after omitting the study by Dr. Songun, I.

Meta-analysis for CD44s expression in GC

The correlation between CD44s and OS of GC patients was illustrated in **Figure 2**. For the systematic evaluation of 9 eligible studies (1210 patients), the pooled HRs were got directly (3 studies) or extracted (6 studies) with the aforementioned methods (**Table 1**). In a fixed-effect model (I2 = 18.4%, P = 0.2792), the presence of CD44s highly indicated reduced OS (pooled HR = 1.93, 95% CI: 1.58-2.34, transformed from log HR and its 95% CI indicated in **Figure 2** and **Table 2**; P_{HR} = 0.0222). Moreover, CD44s expression tended to associate with poorer disease free survival (DFS) in GC (random effect; pooled HR = 3.13, 95% CI: 1.02-9.68, transformed from log HR and its 95% CI indicated in **Figure 3** and **Table 2**; P_{HR} = 0.0469). Thirteen studies (2336 patients) evaluated the correlation of CD44s expression with lymph node metastasis of cancer (**Table 2**). The pooled RR was 1.12 (95% CI: 1.04-1.21, P_{RR} = 0.0019,

Table 3. Meta-analysis of CD44v6 in gastric cancer

Stratification	Studies (N)	Patients (N)	Model	Log HR/RR (95% CI)	P_{HR}/P_{RR}	*P*	I2 (%)	P_{bias}
Overall survival	6	844	Random	0.24 (-0.29-0.76)	0.3783	0.0041	71.0	0.1738
*Subgroup overall survival	5	558	Fixed	0.42 (0.09-0.76)	0.0139	0.3035	17.4	0.7620
Location of cancer	3	248	Fixed	0.99 (0.88-1.12)	0.8813	0.3534	3.9	0.3638
T-stage	10	1295	Random	1.18 (0.97-1.44)	0.1002	0.0261	52.4	0.5069
N-stage	14	1716	Random	1.23 (1.03-1.48)	0.0240	0.0002	67.1	0.2888
M-stage	3	299	Fixed	2.54 (1.08-6.00)	0.0333	0.7393	00.0	0.9129
TNM-stage	3	277	Fixed	1.72 (1.18-2.50)	0.0045	0.2265	32.7	0.2250
Lymphatic invasion	8	1270	Fixed	1.13 (1.04-1.23)	0.0057	0.1242	38.3	0.3916
Vascular invasion	7	1172	Random	1.08 (0.90-1.30)	0.3839	0.0479	52.8	0.7268
Peritoneal metastasis	3	361	Fixed	0.85 (0.58-1.24)	0.3994	0.5619	00.0	0.1358
Liver metastasis	4	509	Fixed	3.20 (1.94-5.27)	< 0.0001	0.8192	00.0	0.6360
Degree of differentiation	8	895	Random	0.98 (0.76-1.26)	0.8661	0.0004	73.8	0.4538
Lauren type	8	1166	Random	0.67 (0.50-0.91)	0.0106	0.0002	75.5	0.2197

*: Subgroup assay for overall survival after omitting the study by Songun.I, et cl. HR: Hazard ratio; RR: risk ratio; N: number of studies or patients; CI: confidence interval; P_{HR}: significance of HR; P_{RR}: significance of RR; *P*: significance for heterogeneity of publications; P_{bias}: significance for publication bias.

fixed-effect), and there was no significant heterogeneity (I2 = 00.0%, *P* = 0.5891), indicating that presence of CD44s was highly related with advanced N-stage of GC. Furthermore, CD44s expression was significantly associated with distant metastasis (**Table 2**, 4 studies, 426 patients; pooled RR = 2.14, 95% CI: 1.46-3.14, P_{RR} < 0.0001, fixed-effect) with no obvious heterogeneity observed (I2 = 00.0%, *P* = 0.6093). As shown in **Table 2**, there was no statistically significant association between CD44s expression and other parameters such as cancer location, T-stage, TNM-stage, differentiation, Lauren type, lymphatic invasion, vascular invasion, and perineural metastasis.

Meta-analysis for CD44v expression in GC

Five studies including 6 cohorts evaluated the impact of CD44 variant 6 (CD44v6) on OS of GC. The pooled HR was 1.27 (95% CI: 0.75-2.14, transformed from log HR and its 95% CI indicated in **Figure 4A** and **Table 3**; P_{HR} = 0.3783, random effect) and the heterogeneity was significant (I2 = 71.00%, *P* = 0.0041). However, CD44v6 could predict poorer OS while the study by Songun was omitted according to the sensitivity assay (pooled HR: 1.52, 95% CI: 1.09-2.14, transformed from log HR and its 95% CI indicated in **Figure 4B** and **Table 3**; P_{HR} = 0.0139, I2 = 17.4%, *P* = 0.3035, fixed-effect). In the further analysis for clinicopathological variables (**Table 3**), CD44v6 was significantly correlated with N-stage (14 studies, 1716 patients; pooled RR = 1.23, 95% CI: 1.03-1.48, P_{RR} = 0.0240, I2 = 67.1%, *P* = 0.0002, random-effect), M-stage (3 studies, 299 patients; pooled RR = 2.54, 95% CI: 1.08-6.00, P_{RR} = 0.0333, I2 = 00.0%, *P* = 0.7393, fixed-effect), TNM-stage (3 studies, 277 patients; pooled RR = 1.72, 95% CI: 1.18-2.50, P_{RR} = 0.0045, I2 = 32.7%, *P* = 0.2250, fixed-effect), Lauren type (8 studies, 1166 patients; pooled RR = 0.67, 95% CI: 0.50-0.91, P_{RR} = 0.0106, I2 = 75.5%, *P* = 0.0002, random-effect), lymphatic invasion (8 studies, 1270 patients; pooled RR = 1.13, 95% CI: 1.04-1.23, P_{RR} = 0.0057, I2 = 38.3%, *P* = 0.1242, fixed-effect), and liver metastasis (4 studies, 509 patients; pooled RR = 3.20, 95% CI: 1.94-5.27, P_{RR} < 0.0001, I2 = 00.0%, *P* = 0.8192, fixed-effect), whereas exhibited no impact on cancer location, T-stage, differentiation, vascular invasion, or peritoneal metastasis. Additionally, the expression of CD44 variant 5 (CD44v5) had no relationship with GC differentiation in the systematic review of 4 studies (652 patients; pooled RR = 0.93, 95% CI: 0.66-1.31, P_{RR} = 0.6852, I2 = 79.4%, *P* = 0.0022, random-effect; Table S1).

Egger's test and sensitivity assay

Egger's test was performed to evaluate the publication bias of the eligible studies (**Tables 2**, **3**, S1). The results indicated no publication bias for most subgroup assays, except for the depth of invasion for the CD44 subgroup (P_{bias} = 0.0297). In addition, most sensitivity analysis

did not reveal significant variation on the pooled RR (or HR) after omitting any single study at a given time, except that for OS and distant metastasis for the CD44v6 analysis, and DFS for the CD44s analysis (Table S2).

Narrative review for CD44 family proteins in GC

As shown in Table S3, CD44v5 phenotype was demonstrated to indicate poorer OS of GC by Dr. Muller, W [28] (HR = 1.36, 95% CI: 1.00-1.84, P_{HR} = 0.049), whereas neither CD44v5 (HR = 0.97, 95% CI: 0.74-1.28, P_{HR} = 0.840) nor CD44 variant 9 (CD44v9; HR = 1, 95% CI: 0.76-1.31, P_{HR} = 0.230) could predict OS as shown by Dr. Songun, I [25]. Moreover, DFS of GC was significantly related with CD44v9 [29] (HR = 21.8, 95% CI: 5.71-83.1, P_{HR} < 0.001), but not CD44v6 [23] (HR = 0.77, 95% CI: 0.28-2.12, P_{HR} = 0.610). Table S4 summarizes the review of clinicopathological parameters. Dr. Muller, W. reported that CD44v5 significantly predicted Lauren classification (P_{report} = 0.001), differentiation (P_{report} = 0.001), T-stage (P_{report} = 0.001), vascular invasion (P_{report} = 0.004), and lymphatic invasion (P_{report} = 0.001) [28]. However, Dr. Mirecka, J. failed to demonstrate the association of CD44v5 with T-stage and differentiation of GC [30]. CD44 variant 8-10 (CD44v8-10) was associated with vascular invasion (P_{report} = 0.032) and liver metastasis (P_{report} = 0.015) [31], but not T-stage, N-stage, TNM-stage, lymphatic invasion, peritoneal invasion [31] or differentiation [32]. In addition, CD44s significantly predicted hepatic metastasis (P_{report} = 0.0002) [33] and tumor relapse (P_{report} = 0.025) [4]; CD44 variant 3-5 (CD44v3-5) was related with lymphatic invasion (P_{report} < 0.050) and N-stage (P_{report} < 0.050) [34]; CD44 variant 7 (CD44v7) could predict poorly differentiation (P_{report} < 0.010) [32]; and CD44 variant 9 (CD44v9) was correlated with T-stage (P_{report} < 0.010), N-stage (P_{report} < 0.010), TNM-stage (P_{report} < 0.050), and differentiation (P_{report} < 0.010) [35], but not location of GC [29]. Moreover, CD44 variant 3 (CD44v3) had no relationship with either liver metastasis or N-stage in GC [36].

Discussion

Since the indicative significance of CD44 family phenotype in GC is controversial and the related studies are diversified, a quantitative meta-analysis and comprehensive narrative review of the previous studies is warranted. Currently, CD44s is shown to associate with poor OS by combining 1210 patients from 9 studies, and with reduced DFS in 261 patients from 3 studies (**Figures 1-3**; **Table 2**). Moreover, CD44s expression significantly predicts lymph node and distant metastasis of GC (**Table 2**). As for CD44 splicing variants, CD44v6 shows distinct impact on OS in the meta-analysis of 5 (6 cohorts; 844 patients) and 4 studies (5 cohorts; 558 patients) (**Figure 4**; **Table 3**), whereas statistically relates with Lauren type, lymphatic invasion, liver metastasis, and N-, M- and TNM-stage of GC. CD44v3-5, v5, v7, v8-10, and v9 show the potential to influence disease severity and outcome of GC in the narrative review (Tables S3, S4). As far as we know, this is the first study to simultaneously assess the predictive value of standard CD44 and CD44 variants for the clinicopathological characteristics and survival status of GC.

As the principal cell surface receptor for hyaluronic acid, CD44 family exerts important functions in cell survival, proliferation, motility, and extracellular matrix adherence and degradation [11, 13, 14]. Some researchers have reported the prognostic value of CD44 family for GC and the results show that CD44 could be used as a novel marker for the characteristics and management of GC [4, 20]. In our study, there was no association between CD44s expression and cancer location, differentiation, Lauren type, vascular invasion, lymphatic invasion, depth of invasion, TNM-stage, or perineural metastasis. On the contrary, our meta-analysis demonstrated that CD44s phenotype was positively correlated with lymph node and distant metastasis, and poorer outcome of GC patients (**Table 2**; **Figures 2**, **3**), suggesting the potential value of this marker for clinical applications.

As for CD44 variants, CD44v6 in GC could be meta-analyzed in the current study. Previously, the only one meta-analysis about CD44 family proteins in GC was about the clinical and survival validity of CD44v6 by Dr. Chen Jing [37]. Although both reports included 5 studies for the analysis of OS and CD44v6, great differences were shown as follows. First, unlike the previous report that focused on Asian cohorts, the current study did not set limitation for ethnology, because there is no evidence so far to

show that CD44 family proteins exert ethnology-related functions. Second, the previous report included the Korean study by Dr. Eom, D. W. and indicated the data for analysis was reported in the text of the original report [37]. However, we could not find the necessary data in the original article, thus excluded the article for further analysis. Third, the 2 Chinese of totally 5 Asian studies included by the previous report were published in Chinese, while the current analysis excluded the publications in Chinese and the included Chinese study was published in English. Fourth, the previous report demonstrated CD44v6 to be the predictor of higher risk of death (767 patients) [37]. Presently, the correlation between CD44v6 and OS (**Figure 4**; **Table 3**) shifted from insignificance (844 patients, significant heterogeneity) to significance (558 patients, no heterogeneity) after omitting the heterogeneous study that used relatively higher cutoff (25%) comparing with the others (0-5%, **Table 1**). Furthermore, we failed to get the significant relationship shown by Dr. Chen [37] between CD44v6 and T-stage, vascular invasion, and histological differentiation; while found the influence of CD44v6 on Lauren type, lymphatic invasion, and liver metastasis (**Table 3**). The current report included the data from the whole world including those from Asian and published more recently, and updated the previous report about the prognostic and clinical pathological role of CD44v6 in GC. Moreover, the difference between the current and the previous report suggested the necessity of further research about the topic.

To interpret the results of the meta-analysis, certain limitations in the present meta-analysis should be concerned. First, publication bias should be taken into account, although most of our obtained statistical results are insignificant. The power of detecting publication bias could be reduced by the small number of eligible studies. Additionally, we excluded some studies from our analysis, for reasons of language restriction, non-extractable or insufficient survival data [5, 38, 39]. The missing data, especially those reported "negative" or more conservative correlation of CD44 with prognosis [5, 38, 39], might affect the significance of CD44 phenotype as an indicator of disease severity and patients outcome. Second, the size of included studies for analysis is not large (248-2336 patients), the patient populations are not uniform, and the length of follow-up varies. Yoo *et al.* focused on patients with stage II and IIIA GC [21], and the median follow-up duration ranged from 9.5 to 137 months [22, 23]. All these might influence the significance of the clinical outcome in the current analysis. Third, the survival data are achieved directly, calculated from the available data, or extracted from the K-M curves in the articles (**Table 1**). The latter two methods are less reliable than direct analysis of primary data [26]. Fourth, the methods for CD44 evaluation, such as the cutoff scores, are not unified between the studies (**Table 1**), and could affect the conclusion.

In summary, we firstly evaluate the prognostic and clinical pathological role of all CD44 family proteins in GC with systematic or narrative review, and update the previous report for CD44v6 in GC. CD44s and CD44v6 might indicate reduced survival and the potential of metastasis and invasion of GC. The detection of CD44 family by IHC would be helpful to predict the severity of disease, and the development of treatment strategy against subset of CD44 proteins could be novel therapeutic choice in clinical settings. Given the variety of molecular function and clinical validity of CD44 family proteins in GC, further large-sample studies are required.

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Disclosure of conflict of interest

None.

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Table S1. Meta-analysis of CD44v5 in gastric cancer

Stratification	Studies (N)	Patients (N)	Model	RR (95% CI)	P_{RR}	*P*	I2 (%)	P_{bias}
Degree of differentiation	4	652	Random	0.93 (0.66-1.31)	0.6852	0.0022	79.4	0.0811

RR: risk ratio; N: number of studies or patients; CI: confidence interval; P_{RR}: significance of RR; *P*: significance for heterogeneity of publications; P_{bias}: significance for publication bias.

Table S2. Sensitivity analysis of CD44 family proteins in gastric cancer

	CD44v6				CD44s	
	Overall survival		M-stage		Disease free survival	
Stratification	Log HR (95% CI)	P_{HR}	RR (95% CI)	P_{RR}	Log HR (95% CI)	P_{HR}
Omitting Songun, I. 2007	0.43 (0.03-0.83)	0.0340	-	-		
Omitting Hong, R. L. 1995	-	-	1.92 (0.66-5.63)	0.2341	1.68 (1.09-2.27)	< 0.0001
Omitting Xin, Y. 2001	-	-	3.16 (0.98-10.13)	0.0534		

HR: Hazard ratio; RR: risk ratio; CI: confidence interval; P_{HR}: significance of HR; P_{RR}: significance of RR.

Table S3. Narrative review for the survival and CD44 family proteins

Survival	Author	Year	Country	Cut off	Stage	Cancer	Cohort	Sample	Detection	Gene	HR	95% CI	HR Extraction
OS	Muller, W.	1997	Germany	5%	N/A	GC	418	FFPE	WTS-IHC	CD44v5	1.36	1.00-1.84	Calculation
OS	Songun, I.	2005	Netherlands	5%	N/A	R0 GC	286	FFPE	WTS-IHC	CD44v9	1.00	0.76-1.31	Calculation
OS	Songun, I.	2006	Netherlands	0	N/A	R0 GC	286	FFPE	WTS-IHC	CD44v5	0.97	0.74-1.28	Calculation
DFS	Hirata, K.	2013	Japan	3.55%	N/A	EGC	65	FFPE	WTS-IHC	CD44v9	21.8	5.71-83.1	Report-mul
DFS	Hong, R. L.	1995	China	0	N/A	GC	78	Cryostat section	WTS-IHC	CD44v6	0.77	0.28-2.12	Calculation

OS: overall survival; DFS: disease free survival; GC: gastric cancer; EGC: early gastric cancer; R0 GC: R0 resection for gastric cancer; FFPE: formalin fixed paraffin embedded; WTS-IHC: whole tissue section-immunohistochemistry; mul: multivariate.

Table S4. Narrative review for the clinicopathological characteristics and CD44 family proteins

Clinicopathological Event	Author	Year	N-high	Event-high	N-low	Event-low	N-total	Event-total	Detection	Gene
Location (Non-cardia)	Chong, J. M.	1997	80	63	24	19	104	82	WTS-IHC	CD44v3-5
Location (Non-cardia)	Hirata, K.	2013	13	13	52	51	65	64	WTS-IHC	CD44v9
T-stage (3-4)	Muller, W.	1997	273	92	145	41	418	133	WTS-IHC	CD44v5
T-stage (3-4)	Mirecka, J.	1995	70	24	42	15	112	39	WTS-IHC	CD44v5
T-stage (3-4)	Yasui, W.	1998	46	20	77	13	123	33	WTS-IHC	CD44v9
T-stage (3-4)	Yamaguchi, A.	1995	65	36	129	71	194	107	WTS-IHC	CD44v8-10
N-stage (1-3)	Ura, H.	1996	22	16	88	50	110	66	WTS-IHC	CD44v3
N-stage (1-3)	Chong, J. M.	1997	80	42	24	17	104	59	WTS-IHC	CD44v3-5
N-stage (1-3)	Muller, W.	1997	273	159	145	70	418	229	WTS-IHC	CD44v5
N-stage (1-3)	Yasui, W.	1998	46	20	77	11	123	31	WTS-IHC	CD44v9
N-stage (1-3)	Yamaguchi, A.	1995	65	53	129	104	194	157	WTS-IHC	CD44v8-10
TNM-stage (III-IV)	Yasui, W.	1998	77	20	46	9	123	29	WTS-IHC	CD44v9
TNM-stage (III-IV)	Yamaguchi, A.	1995	65	52	129	99	194	151	WTS-IHC	CD44v8-10
Lymphatic invasion (+)	Chong, J. M.	1997	80	54	24	18	104	72	WTS-IHC	CD44v3-5
Lymphatic invasion (+)	Muller, W.	1997	273	147	145	52	418	199	WTS-IHC	CD44v5
Lymphatic invasion (+)	Yamaguchi, A.	1995	65	57	129	113	194	170	WTS-IHC	CD44v8-10
Vascular invasion (+)	Chong, J. M.	1997	80	50	24	18	104	68	WTS-IHC	CD44v3-5
Vascular invasion (+)	Muller, W.	1997	273	78	145	23	418	101	WTS-IHC	CD44v5
Vascular invasion (+)	Yamaguchi, A.	1995	65	48	129	75	194	123	WTS-IHC	CD44v8-10
Peritoneal invasion (+)	Isozaki, H.	1998	47	5	61	6	108	11	WTS-IHC	CD44s
Peritoneal invasion (+)	Yamaguchi, A.	1995	65	16	129	49	194	65	WTS-IHC	CD44v8-10
Liver metastasis (+)	Isozaki, H.	1998	47	29	61	15	108	44	WTS-IHC	CD44s
Liver metastasis (+)	Ura, H.	1996	22	8	88	22	110	30	WTS-IHC	CD44v3
Liver metastasis (+)	Yamaguchi, A.	1995	65	15	129	13	194	28	WTS-IHC	CD44v8-10
Differentiation (PD/UN)	Mirecka, J.	1995	70	41	41	28	111	69	WTS-IHC	CD44v5
Differentiation (PD/UN)	Li, H.	2000	17	12	57	41	74	53	WTS-IHC	CD44v7
Differentiation (PD/UN)	Li, H.	2000	4	4	70	49	74	53	WTS-IHC	CD44v8-10
Differentiation (PD/UN)	Yasui, W.	1998	328	81	746	258	1074	339	WTS-IHC	CD44v9
Lauren type (Diffuse)	Chong, J. M.	1997	80	43	24	18	104	61	WTS-IHC	CD44v3-5
Lauren type (Diffuse)	Muller, W.	1997	273	60	145	94	418	154	WTS-IHC	CD44v5
Cancer recurrence (+)	Chen, S.	2013	27	10	125	22	152	32	WTS-IHC	CD44s

PD: poorly differentiated; UN: undifferentiated; WTS-IHC: whole tissue section-immunohistochemistry.