



Prognosis and Biological Behavior of Gastric Signet-Ring Cell Carcinoma Better or Worse: A Meta-Analysis

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Background: The clinical pathology of gastric signet-ring cell carcinoma (SRC) is still unclear. This meta-analysis was performed to evaluate the difference in biological behavior and prognosis between SRC and non-signet ring cell carcinoma (NSRC).

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Zhao S, Lv L, Zheng K, Tian Y, Zheng J-C and Jiang C-G (2021) Prognosis and Biological Behavior of Gastric Signet-Ring Cell Carcinoma Better or Worse: A Meta-Analysis. Front. Oncol. 11:603070. doi: 10.3389/fonc.2021.603070 **Methods:** A total of 58 eligible studies were analyzed using RevMan and other auxiliary software. Biological behaviors were compared based on odds ratio (OR) and mean difference (MD). Hazards ratio (HR) was calculated for prognosis based on Kaplan–Meier curves.

Results: Totally, 28,946 SRC patients were compared with 81,917 NSRC patients. Compared with NSRC patients, lower male: female ratio (OR = 0.53, P < 0.01), younger age (MD = -4.89, P < 0.01), more middle location (OR = 1.64, P < 0.01), more depressed type at early stage (OR = 1.31, P < 0.05), higher incidence of Borrmann type IV (OR = 1.96, P < 0.01), less lymph node metastasis at early stage (OR = 0.78, P < 0.05), better prognosis at early stage (HR = 0.59, P < 0.01), and worse prognosis at advanced stage (HR = 1.19, P < 0.01) were associated with SRC patients.

Conclusion: The prognosis of SRC at early stage is better than other types of gastric cancer, while that of SRC at advanced stage is relatively poorer.

Keywords: gastric neoplasm, signet-ring cell carcinoma, prognosis, meta-analysis, biological behavior

INTRODUCTION

Signet-ring cell carcinoma (SRC) is associated with unique histological features based on microscopic observation of the tumor cells rather than on biological behavior. Gastric SRC has been categorized as the "undifferentiated type" by Sugano et al. (1), the "diffused type" by Lauren et al. (2), the "infiltrative type" by Ming et al. (3), and "high grade type" by UICC. Several studies have shown that SRC is associated with a high rate of peripheral metastasis and poor prognosis (4–9); however, a few studies have indicated that SRC has a better outcome than other types of gastric cancer (GC) (10, 11). Meanwhile, several studies have demonstrated that the difference in survival

Abbreviations: SRC, signet-ring cell carcinoma; NSRC, non signet-ring cell carcinoma; OR, odds ratio; HR, hazard ratio; CI, confidence interval; UICC, Union for International Cancer Control; GC, gastric cancer; EGC, early gastric cancer; AGC, advanced gastric cancer; LNM, lymph node metastasis.

rates between SRC and non-signet ring cell carcinoma (NSRC) is statistically insignificant (12, 13). Additionally, multiple studies have also indicated that early stage gastric SRC has a higher fiveyear survival rate than NSRC (14, 15). Here, we aimed to elucidate the difference in biological behavior between SRC and NSRC.

This meta-analysis compared the biological behavior and prognosis between SRC and NSRC patients, including gender, tumor location, lymph node metastasis (LNM), age, chemotherapy, tumor size, macroscopic type, and overall survival.

METHODS

Population

All patients were diagnosed with GC.

Intervention and Comparator

Exposure Group

Patients who were diagnosed with SRC based on pathological analyses.

Control Group

Patients who were diagnosed with NSRC based on pathological analyses.

Outcomes

Biological behavior and prognosis.

Study Design

This meta-analysis complied with the PRISMA statement. All the included studies were primary research studies. There were no language restrictions.

Search Strategy

The Web of Science, PubMed, and Embase databases were searched from initiation until November 2020 as follows: "(("gastric" [Title/Abstract] OR "stomach" [Title/Abstract]) AND ((("cancer" [Title/Abstract] OR "tumor" [Title/ Abstract]) OR "carcinoma" [Title/Abstract]) OR "neoplasm" [Title/Abstract])) AND (("signet ring cell" [Title/Abstract] OR "signet-ring cell" [Title/Abstract]) OR "signet cell" [Title/ Abstract])", including both published and unpublished articles. There were no language restrictions. The articles were retrieved by more than three independent investigators and compiled.

Inclusion and Exclusion Criteria

The criteria for study enrollment were as follows: [1] Based on the WHO classification, SRC was classified when more than 50% cancer cells were predominantly SRC. [2] All studies related to the prognosis and biological behavior of gastric SRC were included. [3] All studies that showed differences in the biological behavior and prognosis between SRC and NSRC were included. [4] All the included studies were primary research articles. [5] If the same research team reported multiple studies during the same time period, only the latest article or that with complete data was included.

Studies without full text or efficacious data were excluded. Additionally, case reports and editorials were not included.



FIGURE 1 | Schematic of the search and selection of the studies.

TABLE 1 | Information of the included studies.

Author	Year	Country	Research stage	Total	SRC	NSRC	NOS
Aihara (16)	2006	Japan	Early stage	150	76	74	6
Anh (17)	2020	Korea	Whole period	460	200	260	6
Bozkaya (18)	2017	Turkey	Whole period	193	142	51	6
Cai (19)	2017	China	Whole period	2,980	133	2,847	6
Chen J (20)	2018	China	Whole period	241	62	179	6
Chen JN (21)	2020	China	Early stage	1.107	203	904	7
Chiu (12)	2011	China	Whole period	2 439	505	1 934	8
Chon (22)	2017	Korea	Whole period	7 667	1 646	6.021	7
Cui (23)	2015	China	Farly stage	1 447	288	1 159	7
Gronnier (24)	2013	France	Early stage	/01	104	317	7
	2015	China	Early stage	720	104	522	6
Guo S (26)	2010	China	Whole period	16 / 82	2715	10 767	7
Guo 3 (20)	2019	Crima		6.41	000	12,707	7
Ha(14)	2008	Norea Obiela	Early stage	041	300	203	7
Huang (27)	2020	China	vvnole period	441	181	260	/
Hun (28)	2013	Korea	Early stage	720	198	522	6
Hyung (29)	2002	Korea	Early stage	933	263	670	1
Imamura (30)	2016	Japan	Early stage	746	190	556	7
Jiang (13)	2011	China	Whole period	2,315	211	2,104	7
Jin (31)	2015	Korea	Early stage	1,105	227	878	7
Kao (32)	2019	China	Whole period	2,152	570	1,582	7
Kim BS (33)	2014	Korea	Early stage	2,050	345	1,705	7
Kim DY (34)	2004	Korea	Whole period	2,358	204	2,154	8
Kim HM (35)	2011	Korea	Early stage	707	419	288	6
Kim JP (36)	1994	Korea	Whole period	3,399	450	2,949	7
Kim YH (37)	2016	Korea	Early stage	1,471	1,046	425	6
Kong (38)	2016	China	Whole period	480	90	390	7
Kunisaki (39)	2004	Japan	Whole period	1,113	174	939	8
Kwon (40)	2014	Korea	Whole period	769	108	661	6
Lai (41)	2016	China	Early stage	2.873	745	2,128	7
Lee HH (10)	2012	Korea	Whole period	1.322	320	1.002	7
Lee IS (42)	2017	Korea	Early stage	1 161	652	509	6
Lee .IH (43)	2010	Korea	Whole period	1,362	448	914	7
Lee SH (44)	2015	Korea	Farly stage	696	114	582	7
	2007	Korea		4 759	662	1 097	7
	2007	China	Farly stage	91	7	4,007	6
Liu (5)	2010	China	Whole period	1 464	129	1 226	7
Liu (0)	2013	China		1,404	150	1,020	7
LU (47)	2016	Unina		2,199	304	1,840	/
Naenara (11)	1992	Japan	vvnole period	1,500	51	1,449	8
Nakamura (48)	2019	Japan	Early stage	314	209	105	6
Nam (49)	2010	Korea	Early stage	2,518	720	1,798	1
Otsuji (50)	1998	Japan	Whole period	1,498	154	1,344	7
Park (51)	2008	Korea	Whole period	2,275	251	2,024	7
Piessen (6)	2009	France	Whole period	159	59	100	7
Postlewait (7)	2015	America	Whole period	768	312	456	6
Shim (52)	2014	Korea	Whole period	2,643	377	2,266	7
Taghavi (53)	2012	America	Whole period	10,246	2,666	7,580	8
Tang (54)	2020	China	Whole period	6,017	5,265	752	7
Tong (55)	2011	China	Early stage	422	102	320	7
Voron (8)	2016	France	Whole period	1,799	899	900	7
Wang JM (56)	2010	China	Early stage	103	38	65	7
Wang Z (15)	2015	China	Early stage	334	115	219	7
Yokota (9)	1998	Japan	Whole period	683	93	590	7
Yoon (57)	2016	Korea	Early stage	3,058	930	2,128	7
Zhang (58)	2010	China	Whole period	1,439	218	1.221	8
Zhao (59)	2020	China	Whole period	1 891	235	1,656	R
Zhu (60)	2020	China	Farly stage	508	278	230	6
Zou (61)	2020	China	Early stage	303	154	160	6
Zu (62)	2020	China	Lany sidye	JZJ 7/1	104	607	U
∠u (0∠)	2014	Unina	Auvanceu stage	741	44	097	Ö

NOS, Newcastle-Ottawa scale.

Data Extraction and Quality Assessment

The following data were extracted from the included studies: publication year, name of the first author, country of author,

sample size, and clinicopathological features (*e.g.*, sex ratio, mean age, tumor location, tumor size, chemotherapy, macroscopic type, LNM, and overall survival). However,

owing to insufficient data, other variables of clinicopathological features (*e.g.*, venous invasion, peritoneal dissemination, and ulceration) were not extracted or analyzed.

Engauge Digitizer 4.1 was employed to distinguish the survival curve and extract hazard ratio (HR) of overall survival (data not shown).

4	SRC	_	NSR	c_		Odds Ratio	Odds Ratio	
Study or Subarouo	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	<u>M-H, Random, 95% C</u>	1
Anh 2020	100	200	184	286	3.4%	0.55[038,0.80]		
Dozkaya 2017 Cai 2017	81	142	35	51 2047	1.5%	0.51 [0.31, 1.20]	_ _	
Chiu 2011	256	505	2244	204/	5.4%	0.57 [0.35, 0.73]	_ - _	
Chon 2017	813	1646	4246	6021	6.8%	0.41[0.36.0.46]	-	
Cui 2015	163	288	842	1159	4.6%	0.49[0.38, 0.64]	- - -	
Guo S 2019	1954	3715	8785	12767	7.2%	0.50 [0.47, 0.54]	•	
Huang 2020	108	181	203	260	2.9%	0.42 [0.27, 0.63]		
Kim DY 2004	120	204	1456	2154	4.3%	0.68 [0.51, 0.92]		
Kong 2016	64	90	285	390	2.3%	0.91 [0.55, 1.51]		
Lee IH 2012	225	320	689	914	4.8%	0.32[0.71, 1.19]	- -	
Liu 2015	81	138	941	1326	3.5%	0.58[0.41.0.83]		
Lu 2016	196	354	1409	1845	5.0%	0.38[0.30, 0.49]		
Maehara 1992	22	51	984	1449	1.9%	0.36 [0.20, 0.63]	_ .	
Otsuji 1998	84	154	906	1344	3.7%	0.58 [0.41, 0.81]		
Park 2008	143	251	1348	2024	4.6%	0.66 [0.51, 0.87]		
Piesson 2009 Postlewaji 2015	39 147	312	280	456	4.3%	0.72[0.36, 1.45]		
Shim 2014	191	337	1573	2266	5.1%	0.58 [0.46, 0.73]		
Taghavi 2012	1405	2866	5207	7580	7.1%	0.51 [0.46, 0.56]	•	
Tang 2020	2810	5265	522	752	6.1%	0.50 [0.43, 0.59]	-	
Voron 2016	539	899	618	900	5.6%	0.68 [0.56, 0.83]		
Total (95% CI)		18358		10827	100.0%	0 53 [0 49 0 59]	•	
Total events	9815	10300	34720	49021	100.0 %	0.55 [0.49, 0.56]	· ·	
Heterpgeneity: Tau ² =	0.03; Chl ²	= 82.40	, df = 22	P < 0.0	0001); l ² =	= 73%		1
Test for overall effect	: Z = 13.49	P < 0.0	0001)				Eavours SRC Favours N	SRC
В	SRC		NSR	с		Odds Ratio	Odds Ratio	
Study or Subarouo	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H. Random. 95% C	
Aihara 2006	32	76	53	74	3.0%	0.29 [0.15, 0.57]		
Chen J 2018	12	28	51	84	2.4%	0.49 [0.20, 1.16]		
Chen JN 2020	124	203	614	904	4.4%	0.74[0.54, 1.02]	-	_
Gronmer 2013	64	149	228	317	3.8%	0.62[0.39.0.99]		
Guo CG 2015	100	198	347	522	4.3%	0.51 [0.37, 0.72]		
Ha 2008	190	388	170	253	4.3%	0.47 [0.34, 0.65]	_ - _	
Huang 2020	9	30	22	37	2.0%	0.29 [0.11, 0.81]		
Huh 2013	288	540	1101	1512	4.7%	0.43 [0.35, 0.52]		
Hyung 2002	140	263	466	670	4.5%	0.50[0.37, 0,67]		
Jiang 2011	34	54	169	215	4.3%	0.46[0.24, 0.88]		
Kao 2019	96	185	472	634	4.3%	0.37 [0.26, 0.52]	_ - -	
Kim DY 2004	58	94	314	467	3.9%	0.79 [0.50, 1.24]		
Kim HM 2011	228	419	173	288	4.4%	0.79 [0.59, 1.08]		
Kim JP 1994	105	185	419	581	4.3%	0.51 [0.36, 0.71]		
Kim YH 2016 Kupicaki 2004	507	1046	279	425	4.7%	0.49[0.39, 0.62]	_	
Kwon 2014	26	51	283 187	275	3,3%	0.49 [0.27, 0.90]		
Lai 2016	391	745	1509	2128	4.8%	0.45[0.38, 0.54]		
Lee SH 2015	58	114	413	582	4.0%	0.42 [0.28, 0.64]	— —	
Maehara 1992	12	28	245	356	2.7%	0.34 [0.16, 0.74]	— - –	
Otsuji 1998	52	94	342	474	3.9%	0.48 [0.30, 0.75]		
Tong 2011	68	102	249	320	3.7%	0.57 [0.35, 0.93]		
7hao 2020	73	54	128	∠19 225	3.8%	0.3710.20.0.691		
	23	54		220	0.270	0.01 [0.20, 0.00]	.	
Total (95% CI)		5575		12941	100.0%	0.55 [0.45, 0.66]	◆	
Total events	2922	- 467 -	8875	(n				
Test for overall effect	• U.18; Chl ^z • 7 = 6 35 /	= 157.7	9, df = 2	0 > א) כ	.00001); l	= 04%	0.2 0.5 1 2	5
		0.00		~		Odde Datia	Favours SRC Favours N	SRC
Study or Subarous	SRC	Total	NSR Evente	Total	Weight	M-H. Random 95% Cl	M-H Random 95% C	
Chen J 2018	21	34	66	95	5.4%	0.71 [0.31. 1.61]		
Chiu 2011	188	356	1008	1504	8.2%	0.55 [0.44, 0.70]	- - -	
Huang 2020	99	151	181	223	7.1%	0.44 [0.27, 0.71]		
Jiang 2011	90	157	1403	1889	7.8%	0.47 [0.33, 0.65]		
Kao 2019	346	570	1311	1582	8.2%	0.32 [0.26, 0.40]		
Kim DY 2004	62	110	1142	1687	7.5%	0.62 [0.42, 0.91]		
Kim JP 1994 Kupleaki 2004	146	265	1586	2368	8.1%	0.60 [0.47, 0.78]		
Kunisaki 2004 Kwon 2014	28	57	384	386	6.7%	0.45 [0.26, 0.80]		
Li C 2007	456	662	2757	4097	8.3%	1.08[0.90 1.28]	_ + _	
Maehara 1992	10	23	739	1093	5.3%	0.37 [0.16, 0.85]		
Otsuji 1998	32	60	564	870	6.9%	0.62 [0.37, 1.05]		
Zhao 2020	114	161	1317	1431	7.7%	0.15 [0.10, 0.21]		
Zu 2014	32	44	531	697	6.1%	0.83 [0.42, 1.66]		
		2724		18468	100.0%	0.4910 36 0.671	•	
Total (95% CI)					/0	0.40 [0.00, 0.07]	-	
Total (95% CI) Total events	1647		13242				I	
Total (95% CI) Total events Heterpgeneity: Teu'=	1647 = 0.30; Chl²	= 141.1	13242 2, df = 1	3 (P < 0	.00001): I	² = 91%		
Total (95% CI) Total events Heterpgeneity: Teu ² = Test for overall effect	1647 = 0.30; Chl ² t: Z = 4.49 (F	= 141.1 > < 0.00	13242 2, df = 1 001)	3 (P < 0	.00001); I	² = 91%	0.1 0.2 0.5 1 2 Execute SPC Execute N	5 1

FIGURE 2 | Forest plot displaying the results of the meta-analysis. (A) Odds ratio for the male ratio of patients with SRC and NSRC. (B) Odds ratio for male ratio at early stage. (C) Odds ratio for male ratio at advanced stage.

A	SRC		NSRC			Mean Difference		Mean Di	ference	
Study or Subgroup	Mean SD	Total Me	in SD	Total	Weight	IV. Random. 95% CI		IV. Rando	m. 95% Cl	
Anh 2020	56.5 12.8	200 59	9 13.3	286	5.8%	-3.40 [-5.75, -1.05]				
Chiu 2011	58.4 13.7	505 64	2 12.6	1934	7.6%	-5.80 [-7.12, -4.48]				
Chon 2017	51.8 12	1646 58	.4 11.4	6021	8.6%	-6.60 [-7.25, -5.95]		•		
Cui 2015	57 12	288	51 11	1159	7.3%	-4.00 [-5.52, -2.48]		-		
Guo S 2019	60 12.2	3715 64	2 10.6	12767	8.8%	-4.20 [-4.63, -3.77]				
Kim DY 2004	50.1 11.9	204 56	5 10.8	2154	7.0%	-6.40 [-8.10, -4.70]				
Kong 2016	57.1 10.6	90 57	7 11.7	390	5.6%	-0.60 [-3.08, 1.88]		-	_	
Lee HH 2012	52.4 12	320 54	.6 12.8	1002	7.3%	-2.20 [-3.74, -0.66]		-		
Maehara 1992	51.5 12.8	51 58	2 12.3	1449	4.0%	-6.70 [-10.27, -3.13]				
Park 2008	50.2 12.5	251 55	.8 11.5	2024	7.1%	-5.60 [-7.23, -3.97]				
Postlewait 2015	61 13	312	57 12	456	6.8%	-6.00 [-7.81, -4.19]		-		
Taghavl 2012	61.9 14.8	2666 68	7 13.2	7580	8.6%	-6.80 [-7.44, -6.16]		•		
Yokota 1998	55.9 1.2	93 62	.9 0.4	590	8.9%	-7.00 [-7.25, -6.75]		•		
Zhang 2010	56.2 12.4	218 57	.9 11.3	1221	6.8%	-1.70 [-3.46, 0.06]		-		
Total (95% CI)		10559		39033	100.0%	-4.89 [-5.85, -3.94]		٠		
Heterpgeneity: Teu'	2.68; Chl ² = 21	2.46, df = 1	(P < 0.0	0001); l ² =	= 94%			1		
Test for overall effect	: Z = 10.02 (P < 1	0.00001)					-20	-10 U	Favours NSP	20
B	SPC		NSRC			Mean Difference		Mean Di	ference	·
Study or Subgroup	Mean SD	Total Mea	n SD	Total V	Neight	IV Random 95% CI		IV. Rando	m. 95% Cl	
Chen . J 2018	50.18 1.918	28 60.1	5 1.248	84	8.5%	-9 97 [-10 73 -9 21]		-		
Chiu 2011	56.3 11.8	149 59	3 14.3	356	7.0%	-3 00 [-5 41 -0 59]				
Guo CG 2015	49.9 11.5	198 64	5 11.4	522	7.6% -	14.60 [-16.4812.72]	-			
Huh 2013	51.2 11.7	540 59	1 10.6	1512	8.3%	-7.90 [-9.02, -6.78]		-		
Jiang 2011	50.74 11.02	54 55.2	9 12.18	215	5.9%	-4.55 [-7 91, -1.19]				
Kim BS 2014	48.81 11.43	345 55.9	7 11.17	1705	8.1%	-7.16 [-8.48, -5 84]		-		
Kim DY 2004	49.01 11.2	94 56	3 10	467	6.9%	-7.29 [-9.73, -4.85]				
Kim YH 2016	52.2 11.3	1046 57	2 11.3	425	8.1%	-5.00 [-6.27, -3.73]		-		
Kunisaki 2004	51.8 11.9	120 58	8 12.2	393	6.9%	-7.00 [-9.45, -4.55]		-		
Kwon 2014	55.5 11.5	51 61	2 11.6	275	5.8%	-5.70 [-9.14, -2.26]				
Lai 2016	49.1 12	745 57	2 10.8	2128	8.4%	-8.10 [-9.08, -7.12]		+		
Lee SH 2015	53.9 12.5	114 63	5 9.9	582	6.9%	-9.60 [-12.03, -7.17]				
Maehara 1992	50.6 10.8	28 58	4 12.1	356	5.0%	-7.80 [-11.99, -3.61]				
Tong 2011	52.8 11.8	102 56	1 12.6	320	6.7%	-3.30 [-5.97, -0.63]				
Total (95% CI)		3614		9340 1	100.0%	-7 34 1-8 76 -5 921		٠		
Heterogeneity: Teu ² =	6.02: Chl ² = 132	61 df = 13	(P<0.00	001): 12 =	90%	1.04[-0.10,-0.02]	H			
Test for overall effect	Z = 10.13 (P < 0	0.00001)	(,,			-20	-10	10	20
c	SPC	,	NEDC			Maan Difference		Favours SRC	Favours NSR	
Study or Subgroup	Mean SD	Total Mer	n SD	Total	Weight	W Random 95% Cl		Weah D	m 95% Cl	
Chen 12018	57.65 2.107	34 65	6 1 107	- QE	14 5%	-7 61 [.8 36 _6 96]		TV. Rando	111. 30 /0 CI	
Chiu 2010	59.3 14.2	356 64	2 12 0	1504	13 9%	-4 90 [-6 52 -2 29]		-		
liana 2011	54.5 12.62	157 57	1 10.00	1880	13.5%	-3 31 [-5 35 -1 27]				
Kim DY 2004	513 12.03	110 50	5 10.80	1687	13 1%	-5 20 [-7 57 -2 92]		_		
Kunicaki 2004	54.1 11.9	54 60	1 12	546	11 0%	6 00 [9 33 2 67]		_		
Kwop 2014	59.2 15.9	57 61	0 12 4	296	10.6%	-3.60[-7.99.0.69]			-	
Lic 2007	55.5 12.1	662 56	0 12.4	4007	14 3%	0.40[-1.30, 0.50]				
Maehara 1992	52.7 15.1	23 58	1 12.4	1093	8.2%	-5.40[-11.61.0.81]			-	
	54.1 10.1	20 00		1000	0.270					
Total (95% CI)		1453		11297	100.0%	-4.51 [-7.18, -1.83]		•		
Heterpgeneity: Teu ² =	12.71; Chl ² = 1	33.77, df = 7	(P < 0.00	001); l ² =	95%		-20	10	10	20
Test for overall effect	: Z = 3.30 (P = 0.	.0010)					-20	Favours SRC	Favours NSP	20
								arouls and	i arouls NoR	•

at early stage. (C) Mean difference for mean age at advanced stage.

~	SR	С	NS	SRC			Mean Difference		Mean Difference		
Study or Subgroup	Mean S	D Total	Mean	SD	Total W	eight	IV. Random. 95% Cl		IV. Random. 95% Cl		-
Anh 2020	43.2 37	.1 200	43.7 3	0.4	260	9.7%	-0.50 [-6.83, 5.83]				
Chiu 2011	44	34 505	44	28	1934 1	0.3%	0.00 [-3.22, 3.22]		+		
Cui 2015	58	36 288	56	30	1159 1	0.1%	2.00 [-2.50, 6.50]				
Kim DY 2004	38 26	.5 204	50 3	1.1	2154 1	0.2% .	-12.00 [-18.87, -8.13]		-		
Lee HH 2012	48	32 320	57	37	1002 1	0.2%	-9.00 [-13.19, -4.81]				
Maehara 1992	59	36 51	70	40	1449	86%	-11.00 [-21.09, -0.91]				
Park 2008	46	33 251	47	27	2024 1	0.2%	-1.00 [-5.25, 3.25]		-		
Postlewait 2015	53	40 312	46	31	456 1	0.0%	7.00 [1.73, 12.27]				
Yokota 1998	62	5 93	50	1	590 1	0.6%	12.00 [10.98, 13.02]				
Zhang 2010	61	29 218	67	32	1221 1	0.2%	-6.00 [-10.25, -1.75]		-		
Total (95%, CI)		2442		1	2249 10	0.0%	-1.68 [-8.45, 5.11]				
Heterogeneity: Tau*	= 113.51; Ch	* = 331.30	, df = 9(F	< 0.0	0001); I ²	= 97%	-5	0	-25 0 25	50	
Test for overall effect	: Z = 0.49 (P	= 0.63)							FavoursSRC Favours NSRC		
В	SE	c	N	ISRC			Mean Difference		Mean Difference		
Study or Subgroup	Mean	SD Total	Mean	SD	Total V	Neight	IV. Random, 95% CI		IV. Random, 95% Cl		_
Chiu 2011	20	12 149	22	16	430	9.8%	-2.00 [-4.45, 0.45]		.0		-
Guo CG 2015	26.4 1	5.5 198	26.7	16.2	522	9.3%	-0.30 [-2.87, 2.27]		+		
Huh 2013	24 1	5.4 540	23.2	15.6	1512	13.7%	0.80 [-0.72, 2.32]		+		
Jiang 2011	34.8 1	7.8 54	31.8	17.3	215	3.6%	3.00 [-2.28, 8.28]		+		
Kim BS 2014	31.7 19	.21 345	30.05	18.72	1705	10.7%	1.65 [-0.56, 3.86]		•		
Kim DY 2004	20.9	13 94	24	17	215	6.6%	-3.10 [-6.57, 0.37]				
Kim YH 2016	23.3 1	4.7 1046	23.3	18.4	425	11.7%	0.00 [-1.96, 1.96]		ŧ		
Kunlsaki 2004	36.6 2	3.7 120	30.5	18.4	393	4.5%	6.10[1.49.10.71]				
Kwon 2014	28.4 2	5.1 51	21.4	15.2	275	2.2%	7.00 [-0.12, 14, 12]				
Lee SH 2015	26.8 1	9.1 114	25.9	16.7	582	6.0%	0.90 [-2.86, 4.66]		+		
Maehara 1992	47	28 28	37	22	356	1.1%	10.00 [-0.62, 20.62]				
Tong 2011	32	18 102	30.7	16.7	320	5.6%	1.30 [-2.64, 5.24]				
Yoon 2016	24.3 1	4.9 930	24.8	16.5	2128	15.2%	-0.50 [-1.69, 0.69]		+		
Total (95%, CI)		3771			9078 1	100.0%	0.55 [-0.58, 1.67]		•		
Heterogeneity: Tau ² :	= 1.80; Chi ² =	24.90, df	= 12(P =	0.02)	12 = 52%		,				
Test for overall effect	: Z = 0.96 (P	= 0.34)						-50	-25 U 25	50	
c		•	NI	PPC			N		Pavours SRC Pavours NSRC		
Churden and Carls and and	SK	C		on	Total M	Inlash4	Mean Difference		Mean Difference		
Study of Subgroup	mean :	SD Total	Mean	50	Total W	reight	IV. Random. 95% CI		IV. Random. 95% CI		-
Chiu 2011	53	36 356	50	28	1504	19.4%	3.00 [-1.00, 7.00]		-		
Jiang 2011	67.2 30	0.6 157	60.9 2	9.3	1889	17.5%	6.30 [1.33, 11.27]				
Kim DY 2004	52.6	26 110	56.9	30	1687	17.3%	-4.30 [-9.37, 0.77]				
Kunisaki 2004	55.3 33	1.5 54	57.5	31.1	546	10.3%	-2.20 [-11.51, 7.11]				
Kwon 2014	63.5 40	0.1 57	52.9 3	33.1	386	8.5%	10.60 [-0.32, 21.52]				
Li C 2007	58	31 662	54	29	4097	22.0%	4.00 [1.48, 6.52]			_	
Maehara 1992	75	39 23	50	28	1093	4.9%	25.00 [8.98, 41.02]			100	
T-1-1 (059/ 00						00.00/					
Total (95%, CI)		1419	1011 - 101124F	1	1202 1	00.0%	3.71 [-0.24, 7.67]		· · · · · · · · · · · · · · · · · · ·		
Heterogeneity: Tau*	= 16.81; Chi	= 20.47, c	If = 6 (P =	= 0.002	2); 1 = 71	%	5	50	-25 0 25	50	
Test for overall effect	: Z = 1.84 (P	= 0.07)							Favours SRC Favours NSRC		

FIGURE 4 | Forest plot displaying the results of meta-analysis. (A) Mean difference for tumor size of patients with SRC and NSRC. (B) Mean difference for tumor size at early stage. (C) Mean difference for tumor size at advanced stage.

~	SRC		NSR	C		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random. 95% CI	M-H. Random. 95% Cl
Anh 2020	88	200	84	260	4.4%	1.65 [1.12, 2.41]	
Bozkaya 2017	53	142	12	51	2.0%	1.94 [0.93, 4.02]	
Cal 2017	26	133	513	2847	3.9%	1.11 [0.71, 1.71]	
Chiu 2011	133	505	317	1934	6.2%	1.82 [1.45, 2.30]	
Chon 2017	648	1646	1766	6021	7.5%	1.56 [1.40, 1.75]	-
Cui 2015	31	288	95	1159	4.0%	1.35 [0.88, 2.07]	
Guo S 2019	402	3715	1088	12767	7.4%	1.30 [1.15, 1.47]	
Huang 2020	76	181	70	260	4.2%	1.96 [1.31, 2.94]	
Kim DY 2004	65	204	554	2154	5.2%	1.35 [0.99, 1.84]	
Kong 2016	28	90	103	390	3.4%	1.26[0.76, 2.07]	
Lee HH 2012	141	204	392	1002	5.1%	3.48 [2.52, 4.81]	_
Lee JH 2010	184	440	247	1226	0.1%	1.88 [1.48, 2.39]	
Liu 2015	129	354	432	1946	6 1%	1.70[1.12, 2.37]	
Maehara 1992	26	51	432	1440	2 9%	2 82 [1.45, 2.30]	
Otsuii 1998	54	154	535	1344	4.8%	0.82[0.58, 1.16]	+
Park 2008	118	251	703	2024	5.8%	1.67 [1.28, 2.17]	
Shim 2014	156	377	573	2266	6.3%	2.09[1.66, 2.61]	
Tang 2020	582	5265	63	752	5.7%	1.36 [1.04, 1.78]	
Zhang 2010	51	218	192	1221	4.8%	1.64 [1.15, 2.32]	——
Total (95% CI)		14564		41986	100.0%	1.64 [1.45, 1.85]	•
Total events	3024		8343				
Heterogeneity: Tau ² =	0.05; Chi ² :	= 69.56	, df = 19	(P < 0.0	0001); I ² = 7	73%	0.1 0.2 0.5 1 2
Test for overall effect:	Z = 8.04 (P	v < 0.00	001)				Favours SRC Favours NSRC
В	SRC		NSR	с		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random. 95% CI	M-H. Random. 95% Cl
Alhara 2006	53	76	52	74	2.3%	0.97 [0.48, 1.96]	-+
Chen J 2018	10	28	16	84	1.4%	2.36 [0.92, 6.08]	
Chen JN 2020	58	203	212	904	5.0%	1.31 [0.93, 1.84]	
Chiu 2011	59	149	82	430	4.3%	2.78 [1.85, 4.18]	
Guo CG 2015	25	198	72	522	3.6%	0.90 [0.55, 1.47]	
Ha 2008	173	388	92	253	5.2%	1.41 [1.02, 1.95]	_
Huang 2020	20	30	14	37	1.3%	3.29 [1.20, 9.01]	
Huh 2013	328	540	681	1512	6.6%	1.89 [1.55, 2.31]	
Hyung 2002	126	263	266	670	5.6%	1.40 [1.05, 1.86]	
Jiang 2011	16	54	52	215	2.5%	1.32 [0.68, 2.56]	
Kao 2019	107	185	245	634	5.1%	2.18 [1.56, 3.04]	
KIM BS 2014 Kim DX 2004	136	345	490	1/05	0.1%	1.61 [1.27, 2.05]	
Kim DY 2004 Kim UM 2011	32	94	135	467	3.7%	1.27 [0.79, 2.03]	
Kim IP 1004	101	419	210	200 501	5.0%	1.00 [0.77, 1.44]	Ĺ
Kim YH 2016	570	10/6	219	125	6.3%	0.94 [0.75 1.92]	
Kunisaki 2004	610	120	174	302	4 2%	1 70 [1 13 2 57]	_ _
Kwon 2014	26	51	83	275	2.8%	2 41 [1 31 4 41]	
Lai 2016	410	745	957	2128	6.9%	1.50 [1.27, 1.77]	
Lee SH 2015	72	114	243	582	4.2%	2.39 [1.58. 3.62]	— —
Maehara 1992	18	28	157	356	1.9%	2.28 [1.02, 5.08]	·
Otsuji 1998	53	94	223	474	3.9%	1.45 [0.93, 2.27]	⊢
Tong 2011	30	102	79	320	3.5%	1.27 [0.77, 2.09]	- -
Wang Z 2015	30	115	49	219	3.3%	1.22 [0.73, 2.07]	-+
-							.
Total (95% CI)		5572		13548	100.0%	1.51 [1.34, 1.72]	◆
Total events	2675		4942				
Heterogeneity: Tau ² =	0.05; Chi*	= 60.79	9, df = 29	(P<0.0	001); I ² = 6	2%	0.1 0.2 0.5 1 2
Test for overall effect:	Z = 6.49 (F	- < 0.00	0001)				Favours SRC Favours NSRC
С	SRC		NSR	с		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random. 95% CI	M-H. Random. 95% Cl
Chen J 2018	9	34	24	95	2.5%	1.06 [0.44, 2.60]	
Chiu 2011	74	356	235	1504	11.0%	1.42 [1.06, 1.90]	
Huung 2020	56	151	56	223	7.1%	1.76 [1.12, 2.75]	
Jiang 2011	46	157	529	1889	9.2%	1.07 [0.74, 1.52]	- !-
Kao 2019	223	570	451	1582	13.9%	1.61 [1.32, 1.97]	
Kim DY 2004	33	110	419	1687	7.7%	1.30 [0.85, 1.98]	
Kim JP 1994	129	265	820	2368	12.1%	1.79 [1.39, 2.31]	
Kunisaki 2004	27	54	167	546	5.3%	2.27 [1.29, 3.99]	
Kwon 2014	20	57	106	386	5.0%	1.43 [0.79, 2.57]	
Li C 2007	287	662	1657	4097	15.0%	1.13 [0.95, 1.33]	-
Maehara 1992	8	23	233	1093	2.7%	1.97 [0.82, 4.70]	
	18	60	332	870	5.2%	0.69 [0.39, 1.23]	
Otsuji 1998	9	44	112	697	3.3%	1.34 [0.63, 2.87]	
Otsuji 1998 Zu 2014		05/0		47007	100 000	4 20 14 40 4 600	
Otsuji 1998 Zu 2014		-1642		17037	100.0%	1.39 [1.19, 1.62]	▼
Olsuji 1998 Zu 2014 Total (95% CI)		2343					
Otsuji 1998 Zu 2014 Total (95% CI) Total events	939	- 04 0	5141	(D = 0 -	0). 12 - 500	,	
Olsuji 1998 Zu 2014 Total (95% CI) Total events Heterogeneity: Tau ² =	939 0.03; Chi ²	= 24.83	5141 3, df = 12	(P=0.0	2); I ² = 52%	6	0.1 0.2 0.5 1 2
Olsuji 1998 Zu 2014 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	939 0.03; Chi ² Z = 4.23 (F	= 24.83 P < 0.00	5141 3, df = 12)01)	(P=0.0	02); I² = 52%	6	0.1 0.2 0.5 1 2 S Favours SRC Favours NSRC

Statistical Analysis

All data were analyzed using Review manager 5.3 and Stata 12.0. Heterogeneity was detected by chi-square test. *P*-value >0.10 was considered as homogeneous, otherwise as heterogeneous. Moreover, the I^2 index was used to assess heterogeneity, and $\rm I^2$ >50% was considered as statistically significant. For homogeneous affirmation, the fixed effects model was selected; otherwise, a random effects model was adopted. The odds ratio (OR), mean difference (MD), and hazard ratio (HR) were calculated, and publication bias was assessed by Egger's test.

RESULT

Search Result

A total of 4,093 studies were retrieved from PubMed, Web of Science, and Embase. After reading the abstracts, we further assessed the full text of 80 studies; we could not obtain the full text for nine studies; 13 contained no usable and reliable data. Finally, 58 eligible studies (5–62) were included in this metaanalysis (**Figure 1**), among which 31 reported the entire period of patients with SRC or NSRC, 25 focused on early GC, and two reported advanced GC regarding both SRC and NSRC (**Table 1**). The study population of SRC (28,946) was much smaller than that of NSRC (81,917).

Quality assessment was conducted with Newcastle–Ottawa scale based on three indexes (a maximum of nine points): selection, comparability, and exposure. Among the 58 included studies, 17 scored six points, 34 scored seven points, and seven scored eight points. Based on the threshold of six points, all the studies were eligible.

Clinicopathological Characteristics

The percentage of male patients of SRC was substantially less than that of NSRC (OR = 0.53, 95%CI = 0.49–0.58, P < 0.01; **Figure 2**). The mean age of SRC patients was substantially younger than that of NSRC patients, at both early and advanced stages (MD = -4.89, 95%CI = -5.85–3.94, P < 0.01; **Figure 3**). No statistical difference in tumor size of SRC between SRC and NSRC was observed, irrespective of early GC (EGC) or advanced GC (AGC) (total: MD = -1.68, 95%CI = -8.48–5.11, P = 0.63; EGC: MD = 0.55, 95%CI = -0.58–1.67, P = 0.34; AGC: MD = 3.71, 95%CI = -0.24–7.67, P = 0.07; **Figure 4**). SRC was

found to potentially occur at the middle location of the stomach, irrespective of EGC or AGC (OR = 1.64, 95%CI = 1.45-1.85, P < 0.01; Figure 5). Microscopic analysis found that early stage SRC was associated with more depressed type than NSRC (OR = 1.31, 95%CI = 1.03–1.66, *P* < 0.05; Figure 6A). Moreover, an increased number of incidences with Borrmann type IV at the advanced stage was noted in SRC patients than that in NSRC patients (OR = 1.96, 95%CI = 1.45–2.66, *P* < 0.01; Figure 6B). However, no marked difference in LNM among advanced-stage SRC and NSRC was found (OR = 1.15, 95%CI = 0.74-1.80, P = 0.53, Figure 7C); while in all the GC cases or EGC cases, SRC was associated with less LNM, in comparison with NSRC (total: OR = 0.78, 95%CI = 0.63-0.96, P < 0.01; EGC: OR = 0.64, 95%CI = 0.52-0.79, P < 0.01; Figures 7A, B). Moreover, 10 studies employed chemotherapy, while no marked difference in the chemotherapy rate was found between SRC and NSRC (OR = 0.95, 95%CI = 0.70-1.27, P = 0.85; Figure 8).

Prognosis

No statistically significant difference was noted in the overall survival between SRC and NSRC patients (HR = 1.07, 95%CI = 0.94–1.22, P = 0.285; **Figure 9A**). Early stage SRC exhibited better prognosis than NSRC (HR = 0.59, 95%CI = 0.45–0.79, P < 0.01; **Figure 9B**), while advanced-stage SRC exhibited poorer prognosis than NSRC (HR = 1.19, 95%CI = 1.13–1.27, P < 0.01; **Figure 9C**).

Publication Bias

No noticeable publication bias was observed based on the results of Egger's test (P = 0.416; **Figure 10**).



Borrmann IV at advanced stage. (DT, depressed type; B-4, Borrmann IV).

Study or Subarcus	Evente	Total	Evente	Total	Weight	M-H Pandom 95% Cl	M-H Random 95% Cl
Study or Subgroup	Events	iotal	Events	octal	weight	м-п. капdom. 95% C	M-n. Kanuom. 95% GI
Cai 2017	92	133	1769	2847	6.2%	1.37 [0.94, 1.99]	
Chiu 2011	271	505	1158	1934	7.3%	0.78 [0.64, 0.95]	_
Chon 2017	424	1646	2335	6021	7.6%	0.55 [0.48, 0.62]	
Cui 2015	195	288	/31	1159	6.9%	1.23 [0.93, 1.62]	
Guo S 2019	3090	3/15	10409	12/67	1.7%	1.12 [1.02, 1.23]	ľ
Lee HH 2012	119	320	580	1002	7.0%	0.43 [0.33, 0.56]	
Lee JH 2010	48	448	82	914	6.2%	1.22 [0.84, 1.77]	
Liu 2015	96	138	867	1326	6.2%	1.21 [0.83, 1.77]	
Maehara 1992	17	51	884	1449	4.8%	0.32 [0.18, 0.58]	
Otsuji 1998	43	154	674	1344	6.3%	0.39 [0.27, 0.56]	
Park 2008	116	251	11/1	2024	7.0%	0.63 [0.48, 0.81]	
Snim 2014	125	5005	900	2266	7.1%	0.75 [0.60, 0.95]	
Tang 2020	3211	5205	454	152	7.5%	1.08 [0.93, 1.27]	
Tokota 1998	39	93	305	1001	5.070 C 40/	0.67 [0.43, 1.05]	
Zhang 2010	167	210	900	1221	0.470	0.80 [0.01, 1.21]	-
Total (95% CI)		13602		37616	100.0%	0.78 [0.63. 0.96]	•
Total events	8119		23287				~
Heterogeneity: Tau ² = (0.14: Chi ²	= 172.50	df = 14	(P < 0.0	0001): I ² :	= 92%	
Test for overall effect: 2	Z = 2.38 (F	P = 0.02)					0.1 0.2 0.5 1 2 5 10
	Fundation						Favours SRC Favours NSRC
Saudu as Subasaus	Experim	Tetel	Evente	Total	Mainha	Udds Ratio	M H Bandom 95% Cl
Study of Subgroup	Events	70	Events	74	weight	M-H. Random. 95% C	M-H. Randolli, 55 % Cl
Alhara 2006	(76	11	/4	2.1%	0.58 [0.21, 1.59]	
Chen J 2018	3	28	16	84	1.6%	0.51 [0.14, 1.90]	-
Chen JN 2020	23	203	95	904	3.5%	1.09[0.67, 1.76]	
Chiu 2011	16	149	69	430	3.2%	0.63 [0.35, 1.12]	· +
Gronnier 2013	25	104	59	317	3.3%	1.38 [0.81, 2.35]	
Guo GG 2015	26	198	124	522	3.5%	0.49[0.31, 0.77]	
Hub 2012	31	388	63	253	3.0%	0.32 [0.20, 0.49]	-
Hull 2013	32	340	150	1512	3.7%	0.57 [0.39, 0.85]	
Hyung 2002	15	263	107	670	3.2%	0.32 [0.18, 0.56]	
imamura 2016	10	190	51	556	2.9%	0.55[0.27, 1.11]	
Jiang 2011	9	54	39	4/4	2.6%	2.23 [1.02, 4.90]	
Jin 2015	19	221	85	8//	3.4%	0.85[0.51, 1.43]	
Kao 2019	19	185	85	634	3.3%	0.74 [0.44, 1.25]	-
Kim BS 2014	31	345	217	1705	3.7%	0.68 [0.46, 1.01]	
Kim DY 2004	2	94	56	467	1.4%	0.16[0.04, 0.67]	
Kim HM 2011	24	419	41	288	3.3%	0.37 [0.22, 0.62]	
Kim JP 1994	14	185	219	581	3.2%	0.14[0.08, 0.24]	
Kim YH 2016	14	185	76	581	3.1%	0.54 [0.30, 0.99]	
Kunisaki 2004	11	120	48	393	2.9%	0.73 [0.36, 1.45]	
KW0N 2014	5	51	36	275	2.2%	0.72[0.27, 1.94]	
Lai 2016	47	745	270	2128	3.9%	0.46 [0.34, 0.64]	
Lee IS 2017	34	652	//	509	3.6%	0.31[0.20, 0.47]	
Lee SH 2015	4	114	69	582	2.1%	0.27 [0.10, 0.76]	
LIH 2016	3	20	4	75	1.0%	13.13 [2.16, 79.76]	
Maenara 1992	3	28	42	356	1.7%	0.90[0.26, 3.10]	
Nakamura 2019	6	209	2	105	1.2%	1.52[0.30, 7.67]	-
Nam 2010	23	720	34	1798	3.3%	1.71[1.00, 2.93]	
Otsuji 1998	5	94	39	4/4	2.2%	0.63 [0.24, 1.63]	
Wang IM 2010	15	102	63	320	3.1%	0.70[0.38, 1.30]	
wang JM 2010	9	38	9	65	2.1%	1.93 [0.69, 5.39]	
vvang 2 2015	9	115	39	219	2.7%	0.39[0.18, 0.84]	
1000 2016 7bas 2020	58	930	239	2128	3.9%	0.53[0.39, 0.71]	
Znao 2020 Zhu 2020	10	54	47	225	2.1%	0.86[0.40, 1.84]	-
Znu 2020	63	287	51	230	3.6%	0.99[0.65, 1.50]	<u></u>
200 2020	36	154	33	169	3.3%	1.20 [0.74, 2.14]	
Total (95% CI)		8252		20970	100 0%	0 64 [0 52 0 70]	
Total (95 % CI)	007	0203	0000	20919	100.0%	0.04 [0.02, 0.79]	•
Hotorogonoitu Toul - 4	0.26.04	- 120 04	2000	/D < 0 0	00041.12	- 76%	· · · · · · · · · · · · · · · · · · ·
Test for overall effects	7 = 4 40 /F	- 139.91	, ur = 34	(F < 0.0	0001); [*=	- / 0 /0	0.01 0.1 1 10 100
rest for overall enect: a	2 - 4.19 (F	< 0.000	,				Favours SRC Favours NSRC
	Experim	ental	Cont	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random. 95% C	M-H. Random. 95% Cl
Chen J 2018	32	34	76	95	5.0%	4.00 [0.88, 18.19]	
Chiu 2011	255	356	1089	1504	11.5%	0.96 [0.74, 1.24]	+
Jiang 2011	101	157	1189	1889	11.1%	1.06 [0.76, 1.49]	+
Kao 2019	459	570	1174	1582	11.5%	1.44 [1.14, 1.82]	+
Kim JP 1994	214	265	1819	2368	11.2%	1.27 [0.92, 1.74]	h
Kunisaki 2004	31	54	349	546	10.0%	0.76 [0.43, 1.34]	
Kwon 2014	42	57	295	386	9.6%	0.86 [0.46, 1.63]	-+-
Li C 2007	501	662	1867	4097	11.7%	3.72 [3.08, 4.49]	· ·
100000 0000000	14	23	842	1093	8.3%	0.46 [0.20, 1.08]	
Maehara 1992		00	635	870	10.1%	0.64 [0.37, 1, 10]	
Maehara 1992 Otsuji 1998	38	60			/ •		
Maehara 1992 Otsuji 1998	38	60	000				
Maehara 1992 Otsuji 1998 Total (95% CI)	38	2238	000	14430	100.0%	1.15 [0.74, 1.80]	•
Maehara 1992 Otsuji 1998 Total (95% CI) Total events	38 1687	2238	9335	14430	100.0%	1.15 [0.74, 1.80]	+
Maehara 1992 Otsuji 1998 Total (95% CI) Total events Heterogeneity: Tau ² = (38 1687 0.44; Chi [*]	2238 = 131.96	9335 6, df = 9 (14430 P < 0.00	100.0% 001); I ² =	1.15 [0.74, 1.80] 93%	+
Maehara 1992 Otsuji 1998 Total (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2	38 1687 0.44; Chi ^r Z = 0.63 (F	2238 = 131.96 P = 0.53)	9335 6, df = 9 (14430 P < 0.00	100.0% 001); I ^z =	1.15 [0.74, 1.80] 93%	0.01 0.1 1 10 100 Execute SPC Execute NSPC

FIGURE 7 | Forest plot displaying the results of meta-analysis. (A) Odds ratio for lymph node metastasis of patients. (B) Odds ratio for lymph node metastasis at early stage. (C) Odds ratio for lymph node metastasis at advanced stage. (LNM, lymph node metastasis).

DISCUSSION

SRC is a highly malignant carcinoma mucocellulare. Abundant mucin in the cytoplasm of SRC drives the nuclei to one side of the cells, inducing a ring-like cell conformation (9). Approximately 1% of SRC occurs in organs including colon, urinary tract, gallbladder, pancreas, breast, and stomach. Previous studies have shown that SRC accounts for 8 to 30% of all gastric neoplasms (63). The global incidence of GC has

recently declined, while that of gastric SRC is continually increasing (64). Although the included studies in this metaanalysis have reported the clinicopathological features of gastric SRC, the results are unclear.

Here, we found that gastric SRC was relatively frequently diagnosed in females; however, the underlying explanation for such an association has not yet been determined. Several studies have demonstrated the potential role of over-expressed estrogen in SRC, which has been associated with frequent metastasis in the



uterus or ovary in SRC patients (65). Furthermore, Kim et al. found a substantially poorer overall survival in female SRC patients than in the male patients, especially those with advanced GC and aged ≤45 years (66). Here, the mean age of SRC patients was substantially younger than that of NSRC patients. The typical intracytoplasmic mucin, compressed nuclei in the corner, the tendency to be larger and sprawl superficially to mucosal and submucosal layers have ensured the early diagnosis of SRC at the early stage or younger age. Postlewait and Yokota claimed that the tumor size of NSRC was smaller than that of SRC. However, our study found no marked difference in the tumor size between the two groups (7, 9). Compared with NSRC, SRC was more commonly found in the middle location of the stomach; meanwhile, no marked difference between upper and lower locations was observed (data not shown). Thus, considering the macroscopic features of EGC, we suggested that SRC had more depressed type than NSRC. For AGC, Borrmann type IV was more commonly found in SRC than NSRC, which probably contributed to the poor outcome.

LNM is known to play a marked role in GC research. Our study implied that SRC was associated with less LNM than NSRC, especially for EGC, while no noticeable relationship was observed for AGC. Unlike other histological types, the correlation between the increased rate of LNM in SRC and the tumor size is not recognized (29). Due to the CDH1 mutation, early SRC was associated with a less aggressive state (67). SRC is thought to arise in the undifferentiated stem cell in lamina propria of gland neck. At the early stage, SRC was found to widely spread in the mucous layer and slowly to submucosal layer than NSRC. When SRC spread into the submucosa, it rapidly metastasized (68).Wang et al. reported that SRC was associated with less ulceration than NSRC, which was considered a major predictor for LNM (15).

The difference in prognosis between SRC and NSRC remains debatable. However, several studies have shown that SRC was associated with worse prognosis than NSRC (5, 23). However, Lee and Maehara reported the opposite results (10, 11). Our study indicated that the overall survival of SRC patients was insignificantly different from that of NSRC patients. The improved survival reported by several studies was probably related to the younger age of the SRC patients at presentation. Early stage SRC was associated with less LNM, and thus, it had better prognosis than NSRC. As a matter of fact, most of the included studies displayed that early stage SRC patients had a higher five-year survival rate. We extracted HR from the Kaplan-Meier curves, and the outcome was significant. Several studies have indicated that advanced-stage SRC was associated with poorer prognosis than NSRC (9, 50), while other studies could not find such an association (13, 34). The current study indicated that the poor prognosis of SRC was accompanied by the lower overall survival rate, as compared to NSRC. Consequently, early diagnosis and detection were crucial to improve the overall survival of gastric SRC. Furthermore, less invasive strategies, such as endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR), have been suggested for early stage GC to improve the quality of life of the patients. However, the Japanese GC treatment guidelines state that ESD was not feasible for the undifferentiated histology type of GC (69), which leads to controversial opinions on ESD for SRC treatment. Recent studies have reported dissimilar outcomes of ESD therapy for SRC (70). One study reported that ESD resulted in a higher rate of en bloc resection and complete resection on SRC than the poorly differentiated types of GC (35), which suggested that ESD might be preferred for EGC patients diagnosed with SRC. On the other hand, curative resection has been suggested for extended lymph node dissection for AGC. Furthermore, the effect of chemotherapy, either neoadjuvant of adjuvant, on SRC is still controversial (71, 72). Turgeon demonstrated that surgery resulted in a higher five-year overall survival rate than perioperative, neoadjuvant, and adjuvant therapy for stage I SRC patients (73). The chemosensitivity of SRC is related to the CLDN18-ARHGAP26/6 fusion (74). Compared with NSRC, SRC is speculated to be more chemoresistant to conventional drugs, such as 5-FU and platinum (13, 23, 75). However, Pernot suggested that SRC possesses high sensitivity to taxane-based chemotherapeutic drugs or antiangiogenics (64). To improve the treatment strategy and prognosis is the important point of SRC.

This study has several limitations. First, most of the included studies were conducted in China, Korea, or Japan. The discrepancy in diet, heredity, and environment between Asia and other continents could have influenced the outcome. Second, no RCTs were included in this meta-analysis, and all the studies were retrospective analyses, which may result in a risk of bias.





Third, since the HR was calculated from the data or extrapolated from the Kaplan–Meier curves, it was associated with reduced reliability. Finally, heterogeneity was high in the statistics process, which could lead to unavoidable biases. Therefore,



additional data are essential to increase the quality and reliability of this meta-analysis.

CONCLUSION

Gastric SRC is associated with more female patients, younger patients, more occurrence at middle location of the stomach, more depressed type (EGC), higher incidence of Borrmann type IV (AGC), and less LNM (EGC) than NSRC. The prognosis of early stage SRC is better than that of other GC types, while the prognosis of SRC at the advanced stage was poor. Thus, SRC exhibits specific biological features and differential prognosis compared with NSRC, which may facilitate the development of tailored therapeutic strategy and individualized treatment.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

SZ and C-GJ designed this study. SZ, LL, and KZ performed search and collected data. J-CZ and C-GJ re-checked the data. SZ and YT performed analysis. LL and SZ wrote the manuscript. C-GJ reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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