Original Article

Clinicopathological characteristics and survival outcomes of younger patients with gastric cancer: a systematic review and meta-analysis

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Background: Survival outcomes of gastric cancer in younger patients have been reported in several studies with controversial results. This systematic review and meta-analysis investigated the clinicopathological characteristics, postoperative complications, and survival outcomes between younger and older patients.

Methods: We systematically reviewed clinical researches from PubMed, The Cochrane Library, Embase, and Web of science published up to December 2019. The effect size for the included studies was estimated with the odds ratio (OR). Heterogeneity was investigated using the χ^2 test and I^2 test, while sensitivity analyses were performed to identify the source of substantial heterogeneity.

Results: A total of 25 clinical studies involving 81,188 gastric cancer patients were included in this meta-analysis, of which one was a prospective study. Younger patients were more likely to be females, pTNM stage IV and peritoneal metastasis. The incidence of postoperative complications, lymph node metastasis, as well as hepatic metastasis of younger patients was significantly lower than that of the older. There was no statistical difference in overall survival (OS) between the younger and older patients with gastric cancer. After stratification for patients with gastrectomy, however, younger patients were associated with a better 5-year OS relative to older patients.

Conclusions: In conclusion, younger patients with gastric cancer were more often diagnosed as poorly differentiation and later pTNM tumor stage. However, younger cancer patients following gastrectomy had a better OS rate than patients in older group. Future large-scale analyses are expected to confirm our findings.

Keywords: Gastric cancer; younger adult; clinicopathological characteristics; survival outcomes; meta-analysis

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Introduction

Gastric cancer is an aggressive malignancy and remains the third leading cause of cancer-related death worldwide (1,2). Although the overall incidence of gastric cancer showed a decline worldwide, younger cancer patients had increased obviously during the last decades (3). The growing incidence, as well as its aggressive biological behavior as reported (4,5), has renewed interest in the surgery-based management of younger gastric cancer patients with a focus on therapeutic strategies.

To date, the survival outcomes of younger patients were still controversial. Previous data reported that younger patients had worse survival rates than older (6-9), whereas several studies showed a similar prognosis (10-20). Some studies even expressed that younger patients were associated with improved survival outcomes (21-30). A significant reason for these inconsistent findings from published studies was the different age cutoffs on defining younger patients (6,7,29,30). A published meta-analysis has reported improved 5-year survival in the younger group. However, it was primarily limited to the small sample size and significant heterogeneity (31). Besides, there was currently no randomized clinical trial that targeted the issue.

As such, our study aimed to compare the clinicopathological characteristics, postoperative complications, as well as survival outcomes between younger and older patients with gastric cancer through systematic review and meta-analysis, thus providing evidence for the development of guiding strategies for younger gastric cancer patients. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-2024).

Methods

Search strategy

Clinical studies were systematically searched from PubMed, Web of Science, Embase, and The Cochrane Library. The following fields were used for the search: "gastric" or "stomach," "cancer" or "carcinoma" or "neoplasm" or "tumor," "young adult" or "younger" or "youth." These searches were limited to clinical articles published up to December 2019.

Inclusion and exclusion criteria

Studies met the following criteria were included: (I) researches compared gastric cancer in the younger group (≤40 years of age) and older group (>40 years of age); (II) analyses contained quantitative clinicopathological information; (III) researches involved at least one of the mentioned survival outcomes.

Studies were excluded from the analysis as follow: (I) publications were position papers, editorials, case reports, comments, or review articles; (II) literature duplication based on an author or center; (III) research data was inappropriate or cannot be extracted; (IV) studies lacked control group for meta-analysis.

Data extraction

Two independent reviewers extracted predesigned data from the included studies. The extracted information was as follows: Basic characteristics of the study, including authors, country, patient inclusion criteria, sample size, design as well as quality assessment; Clinicopathological characteristics of patients, including gender, tumor location, differentiation, Lauren type, Borrmann classification, pTNM stage, and therapeutic regimens (involving chemotherapy, total/subtotal gastrectomy, curative resection, and lymphadenectomy); Survival outcomes, including metastasis, recurrence, and the short or long-term survival rates on different clinical tumor stage. The stage of gastric cancer was based on the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) staging system. Lymphadenectomy was divided into D1 to D4, depending on the primary tumor location and removal of each lymph node station (32). Gastrectomy was defined as patients received surgery with or without D2 lymphadenectomy, while curative gastrectomy was defined as resection with D2 lymphadenectomy and a negative margin. The disagreement was resolved through discussion among the reviewers.

Quality assessment

The quality of the included studies was evaluated using The Newcastle-Ottawa Quality Assessment Scale (NOS) (33). The NOS checklist consisted of three major categories (selection, comparability, and outcome) with a maximum of nine stars. Each included study achieving six or more number of stars was graded high quality. Any disagreement was discussed to reach a consensus.

Statistical analysis

We conducted the review and meta-analysis using Revman software, version 5.3 (Cochrane Collaboration, Oxford, United Kingdom). Categorical variables were analyzed by the odds ratio (OR), while the corresponding 95% confidence interval (CI) was recorded. The Z test was conducted to determine the OR, with $P<0.05$ considered statistical significance. Heterogeneity was investigated using the χ^2 test and the I^2 test. If significant heterogeneity existed, we employed the random effect model; otherwise, the fixed

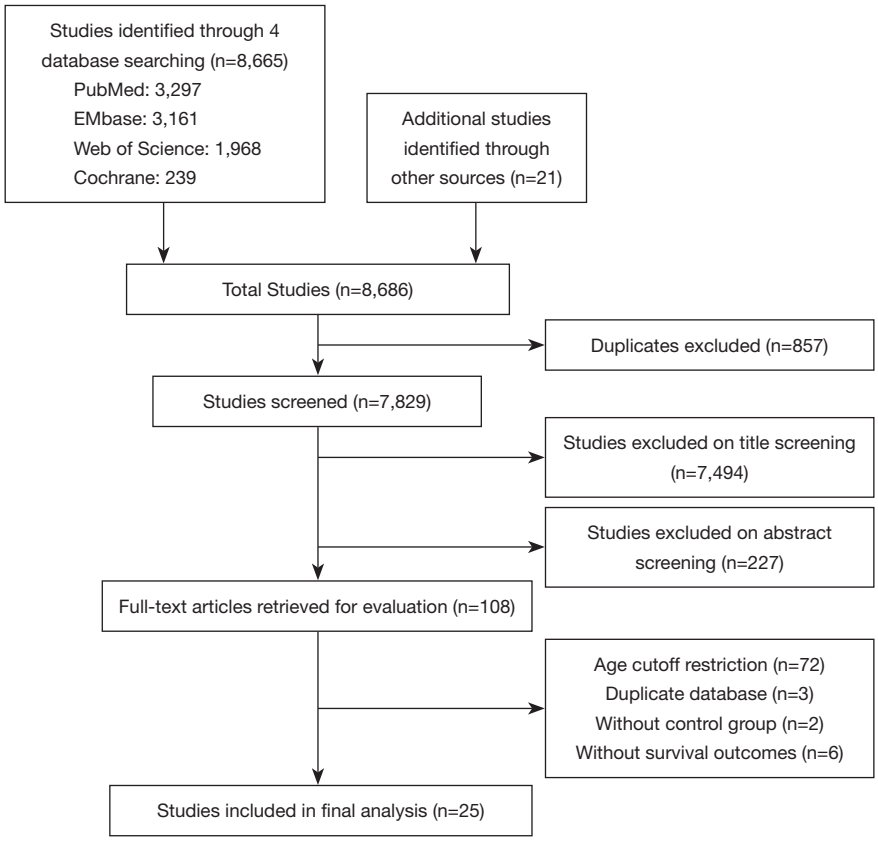

Figure 1 The flow chart of the research process until December 2019.

effects model was adopted (34,35). Sensitivity analyses were undertaken to investigate sources of substantial heterogeneity.

Results

Studies selection

Our initial search strategy generated a total of 8,686 relevant clinical studies. After a screening of titles and abstracts, 108 articles were scrutinized by a full-text review. Eighty-three studies were eventually excluded by following the exclusion criteria and inclusion criteria. In total, the eligible 25 clinical studies (4,5,8-30) involving 81,188 gastric cancer patients were entered into the review and meta-analysis, of which one was a prospective study (17), three were multicenter studies (16,19,21), and the rest were all retrospective studies. *Figure 1* showed the flow chart of the search process. The NOS scores and essential characteristics of the eligible studies were shown in *Table 1*.

Clinicopathological characteristics

The clinicopathologic characteristics of the gastric cancer patients were presented in *Tables 2* and *S1*. Compared with the older group, younger patients with gastric cancer were more often female from pooled 25 studies (OR =2.09, 95% CI: 1.81–2.41, P<0.001, I^2=76%) (*Figure S1*). Younger patients were more likely to be a diffuse type (OR =4.29, 95% CI: 3.15–5.85, P<0.001, I^2=82%), pTNM stage IV (OR =1.21, 95% CI: 1.08–1.35, P<0.001, I^2=0), poorly differentiation (OR =3.59, 95% CI: 2.89–4.47, P<0.001, I^2=82%), and a signet ring cell carcinoma (OR =4.81, 95% CI: 4.33–5.33, P<0.001, I^2=0) (*Figure S2*).

Concerning to therapeutic regimen, six studies showed that younger group had a higher chemotherapy rate when compared to older group (OR =1.79, 95% CI: 1.49–2.16, P<0.001, I^2=43%). In addition, the proportions of younger patients underwent subtotal gastrectomy or D1 resection were significantly lower than those of the older (OR =0.88, 95% CI: 0.79–0.99, P=0.03, I^2=39%; OR =0.59, 95% CI: 0.48–0.73, P<0.001, I^2=25%, respectively). However, there

Table 1 Basic characteristics of the included 25 studies

Authors	Country	Patient criteria	Document type	NOS	Group	No.	Age	Gender		Tumor location			pTNM stage			
								Male	Female	Upper	Middle	Lower	I	II	III	IV
Song *et al.* (4)	China	GC underwent surgery (2007–2011)	Retrospective Study	7	YG ≤40	112	–	59	53	12	21	64	5	30	59	18
					OG ≥70	358	–	274	84	61	64	208	25	89	206	38
Cormedi *et al.* (5)	Brazil	GC (2011–2013)	Retrospective Study	8	YG ≤40	71	37	34	37	–	–	–	4	5	23	36
					OG >40	223	63.74	135	88	–	–	–	35	29	52	89
Tavares *et al.* (8)	Portugal	GC with surgery (2000–2005)	Retrospective Study	7	YG ≤40	23	–	12	11	–	–	–	6	6	4	6
					OG >40	360	–	207	153	–	–	–	76	43	105	97
Guan *et al.* (9)	the United States	GC (1973–2014)	Retrospective Study	8	YG <35	1,369	–	728	641	338	133	275	51	59	119	385
					OG ≥65	46,521	–	28,104	18,417	11,839	3,617	12,243	3,838	3,407	3,604	4,358
Isobe *et al.* (10)	Japan	GAC (1977–2006)	Retrospective Study	8	YG ≤40	169	34.5±4.8	79	90	34	70	40	68	30	23	48
					OG >40	3,649	64.5±10.0	2,518	1,131	790	1,047	1,341	1,765	471	628	782
Kim *et al.* (11)	Korea	GC (1986–2000)	Retrospective Study	8	YG ≤35	137	30.6±5.1	63	74	23	50	56	41	21	36	39
					OG >70	194	73.3±3.1	131	63	16	41	130	60	41	55	38
Kunisaki *et al.* (12)	Japan	GC underwent curative surgery (1985–1999)	Retrospective Study	8	YG ≤40	131	35.2±5.0	64	67	44	65	19	79	16	24	12
					OG ≥55	918	60.2±3.2	658	260	340	386	168	510	123	174	111
Liu *et al.* (13)	China	GC underwent surgery; no chemotherapy; no metastasis. (2008–2014)	Retrospective Study	7	YG ≤40	198	–	115	83	–	–	–	–	–	–	–
					OG ≥55	1,096	–	895	201	–	–	–	–	–	–	–
Okamoto *et al.* (14)	Japan	GC underwent laparotomy (1960–1984)	Retrospective Study	6	YG <30	34	24.9	10	24	3	13	7	–	–	–	–
					OG ≥75	132	77.9	97	35	12	37	66	39	7	31	55
Takatsu *et al.* (15)	Japan	GC underwent surgical resection (2000–2010)	Retrospective Study	8	YG ≤40	136	36 [16–39]	72	64	25	70	35	65	21	28	22
					OG ≥60	1,435	65 [60–69]	1,024	411	385	581	416	786	206	253	190
Tekesin *et al.* (16)	Turkey	GC (1990–2014)	Retrospective Cohort Study	7	YG ≤40	92	36 [22–40]	53	39	17	–	–	5	4	17	52
					OG >40	774	60 [41–75]	553	221	141	–	—	25	46	195	372
Wang *et al.* (17)	China	GC underwent gastrectomy (1998–2006)	Prospective Study	7	YG ≤40	21	34.9±1.1	9	12	1	7	13	–	–	–	–
					OG >55	36	67.1±0.8	22	14	4	7	25	11	9	15	1

Table 1 (*continued*)

Table 1 (*continued*)

Authors	Country	Patient criteria	Document type	NOS	Group	No.	Age	Gender		Tumor location			pTNM stage			
								Male	Female	Upper	Middle	Lower	I	II	III	IV
Hsieh *et al.* (18)	Japan	GAC underwent curative gastrectomy (1981–1992)	Retrospective Study	7	YG ≤40	115	–	46	69	14	27	68	23	22	56	14
					OG >60	1,009	–	626	373	194	160	626	293	160	467	89
Ma *et al.* (19)	China	GC underwent curative surgery (2009–2011)	Retrospective Study	7	YG ≤40	125	–	76	49	–	–	–	30	24	71	–
					OG >40	1,752	–	1,341	411	–	–	–	403	400	946	–
Mitsudomi *et al.* (20)	Japan	GC (1970–1984)	Retrospective Study	7	YG <40	128	–	66	62	13	58	31	–	–	–	–
					OG ≥50	1,275	–	863	412	131	379	550	–	–	–	–
Kulig *et al.* (21)	Poland	GC (1977–1998)	Retrospective Study	6	YG ≤40	214	35.0	119	95	24	56	56	24	14	25	63
					OG >40	3,217	61.0	2,277	940	387	733	677	315	251	380	770
Bani-Hani *et al.* (22)	Jordan	GAC (1991–2001)	Retrospective Study	7	YG ≤40	17	36.3±0.9	7	10	5	3	3	4	2	4	7
					OG >40	159	63.8±0.7	104	55	26	39	83	11	39	55	46
Kim *et al.* (23)	Korea	GC underwent surgery (1993–2000)	Retrospective Study	7	YG ≤40	175	34.58±4.26	100	75	19	67	83	79	20	49	37
					OG >40	1,124	59.25±9.17	765	359	120	364	624	439	145	304	236
Lai *et al.* (24)	Korea	GC underwent curative surgery (1987–2004)	Retrospective Study	8	YG ≤40	883	35	476	407	125	–	–	444	135	213	91
					OG >40	6,071	58.7	4,195	1,876	720	–	–	2,850	1,057	1,567	597
Maehara *et al.* (25)	Japan	GC underwent surgery (1965–1991)	Retrospective Study	6	YG <40	174	38.8±4.9	89	85	31	58	63	–	–	–	–
					OG >70	356	74.8±3.9	247	109	90	86	152	–	–	–	–
Silva *et al.* (26)	Brazil	GAC (1988–2005)	Retrospective Study	7	YG ≤40	62	–	38	24	9	–	50	21	–	35	–
					OG >40	453	–	288	165	68	–	385	127	–	280	–
Zhou *et al.* (27)	China	GC resections (2004–2014)	Retrospective Study	7	YG ≤40	152	33.7±5.54	53	99	8	57	75	39	32	66	15
					OG >40	250	62.9±10.4	178	72	75	53	115	141	35	52	22
Adachi *et al.* (28)	Japan	GC underwent surgery (1981–1990)	Retrospective Study	7	YG <40	36	–	20	16	–	–	6	16	5	8	7
					OG >60	68	–	43	25	–	–	27	25	13	16	14
Bautista *et al.* (29)	the United States	Non-cardia GAC (2000–2010)	Retrospective Cohort Study	8	YG <40	46	34.1±4.1	24	22	1	10	14	–	–	–	–
					OG ≥50	1,208	71.5±3.8	714	494	65	379	426	–	–	–	–
Wang *et al.* (30)	China	GC underwent curative gastrectomy (2005–2010)	Retrospective Study	8	YG ≤40	342	34.1±5.2	198	144	53	79	177	82	97	137	26
					OG >40	3,588	61.4±10.1	2,448	1,140	841	741	1,783	876	927	1,522	263

No., number of patients; pTNM, pathological (p), primary tumor (T), lymph nodes (N) and distant metastases (M); GC, gastric cancer; GAC, gastric adenocarcinoma.

Table 2 Subgroup meta-analysis of clinicopathological characteristics and survival outcomes between the younger group and older group

Subgroup	Included studies	Included patients	I^2 (%)	Effect model	OR/WMD	95% CI	P
Female	25	81,188	76	Random	2.09	1.81–2.41	<0.001
Diffuse type	10	56,335	82	Random	4.29	3.15–5.85	<0.001
pTNM stage IV	16	26,202	0	Fixed	1.21	1.08–1.35	<0.001
Poorly differentiation	19	75,349	82	Random	3.59	2.89–4.47	<0.001
SRCC	5	52,262	0	Fixed	4.81	4.33– 5.33	<0.001
Therapeutic regimen							
Subtotal gastrectomy	9	14,427	39	Fixed	0.88	0.79–0.99	0.03
Curative gastrectomy	14	18,159	10	Fixed	0.93	0.82–1.06	0.30
D1 lymphadenectomy	4	7,387	25	Fixed	0.59	0.48–0.73	<0.001
≥ D2 lymphadenectomy	4	7,387	27	Fixed	1.77	1.44–2.18	<0.001
Chemotherapy	6	8,750	43	Fixed	1.79	1.49–2.16	<0.001
Postoperative complications	5	6,309	73	Random	0.44	0.24–0.79	0.006
Recurrence/metastasis							
Peritoneal recurrence	4	1,965	11	Fixed	1.93	1.31–2.84	0.001
Lymph node metastasis	8	3,901	0	Fixed	0.83	0.69–0.98	0.03
Hepatic metastasis	9	11,126	0	Fixed	0.68	0.47–0.98	0.04
Peritoneal metastasis	9	11,695	63	Random	1.63	1.16–2.27	0.004
5-year OS	9	59,647	60	Random	1.01	0.79–1.30	0.92
5-year OS underwent surgery	18	26,770	56	Random	1.35	1.16–1.57	<0.001
Stage I-OS	8	6,536	11	Fixed	2.38	1.56–3.61	<0.001
Stage II-OS	8	3,347	46	Fixed	1.28	0.98–1.66	0.07
Stage III-OS	7	5,702	27	Fixed	1.36	1.14–1.63	<0.001
Stage IV-OS	7	1,483	0	Fixed	1.93	1.30–2.85	0.001
5-year OS underwent curative surgery	12	19,012	60	Random	1.39	1.12–1.72	0.002
Stage I-OS	4	5,261	51	Random	1.73	0.86–3.49	0.13
Stage II-OS	4	2,771	51	Random	0.95	0.60–1.51	0.83
Stage III-OS	4	4,639	0	Fixed	1.29	1.05–1.58	0.01
Stage IV-OS	3	1,016	0	Fixed	1.86	1.20–2.89	0.006

pTNM, pathological (p), primary tumor (T), lymph nodes (N) and distant metastases (M); SRCC, signet ring cell carcinoma; OS, overall survival.

were no statistical differences in curative resection rate between the two groups (OR =0.93; 95% CI: 0.82–1.06, P=0.30, I^2=10%) (*Figure S3*).

Postoperative complications

A total of 6,309 patients from five studies were enrolled in postoperative complications. The result revealed that the proportion of complications in younger patients was significantly lower compared to the older (OR =0.44, 95% CI: 0.24–0.79, P=0.006), and the heterogeneity between the younger and older group was significant (I^2=73%) (*Figure S4*).

Survival outcomes

Figure 2 presented the meta-analysis of the 5-year overall survival (OS) with total patients, gastrectomy group, and only curative gastrectomy group, respectively. There was no significant difference for total patients based on the nine included studies (OR =1.01, 95% CI: 0.79–1.30, P=0.92, I^2=60%). However, the pooled 18 and 12 studies respectively showed that younger adults in gastrectomy group and only curative gastrectomy group were associated with better survival relative to that of the older (OR =1.35, 95% CI: 1.16–1.57, P<0.001, I^2=56%; OR =1.39, 95% CI: 1.12–1.72, P=0.002, I^2=60%).

Moreover, further survival analyses between younger and older patients were done under the different pTNM tumor stage. Four of the studies provided survival rates for gastrectomy group, and the meta-analysis showed that younger patients at pTNM stage I, stage III, and stage IV were associated with better 5-year OS than older (OR =2.38, 95% CI: 1.56–3.61, P<0.001, I^2=11%; OR =1.36, 95% CI: 1.14–1.63, P<0.001, I^2=27%; OR =1.93, 95% CI: 1.30–2.85, P=0.001, I^2=0%, respectively) (*Figure 3*). For the only curative gastrectomy group, three of the included studies revealed that younger patients at pTNM stage III and stage IV also had improved survival (OR =1.29, 95% CI: 1.05–1.58, P=0.01, I^2=0%; OR =1.86, 95% CI: 1.20–2.89, P=0.006, I^2=0%, respectively), but there was no statistical difference in gastric cancer at stage I (OR =1.73, 95% CI: 0.86–3.49, P=0.13, I^2=51%) (*Figure 4*). The short-term (including the 1-, 2-, 3-year) survival rates were presented in *Table S2*.

Concerning to the metastasis status of gastric cancer, nine of the 25 studies showed that younger group was predominant in peritoneal metastasis (OR =1.63, 95% CI: 1.16–2.27, P=0.004, I^2=63%). Some included studies reported the lymph node metastasis and hepatic metastasis of gastric cancer, and our result showed that both lymph node metastasis and hepatic metastasis ratio was lower in younger group compared with those of the older (OR =0.83, 95% CI: 0.69–0.98, P=0.03, I^2=0%; OR =0.68, 95% CI: 0.47–0.98, P=0.04, I^2=0%). In addition, 4 related studies indicated that the incidence of peritoneal recurrence was significantly higher in younger group (OR =1.93, 95% CI: 1.31–2.84, P=0.001, I^2=11%) (*Figure S5* and *Table S3*).

Discussion

The review and meta-analysis involved 24 retrospective comparative trails and one prospective study with 81,188 patients with gastric cancer. Our findings demonstrated that the younger group after gastrectomy or only curative gastrectomy was correlated with a better OS, but there was no significant difference for total patients between the two groups. To our best knowledge, this analysis was the most extensive evaluation to compare the clinicopathological feature and prognosis between the younger and older group.

Several findings regarding the clinicopathological characteristics in the meta-analysis were in agreement with previous researches, including a higher proportion of female, poorly differentiation, signet ring cell carcinoma, diffuse histology, and pTNM tumor stage IV in younger adults (8-21). Our survey revealed that younger patients had a higher proportion of females, while male predominance was mostly seen in the older group. Although the reasons for female predominance in younger patients were not clear, some potential explanations had been identified. Several studies considered hormonal factors, such as estrogens and higher percentages of estrogen receptor-positive cells might be associated with the predominance of younger females (36,37). Compared to older patients, younger patients with gastric cancer had been believed to be related to genetic changes rather than environmental factors (38). Thereby more frequent exposure to environmental carcinogens, such as cigarettes, might lead to the dominance among older male patients (39). Concerning to histological type, our analysis revealed that poorly differentiation, diffuse-type, and signet ring cell carcinoma were predominant in the younger group. In comparison, more patients in the older group were diagnosed as intestinal type and mucous adenocarcinoma. The primary reason may be germline mutations, specifically in the *CDH1* gene, as reported in

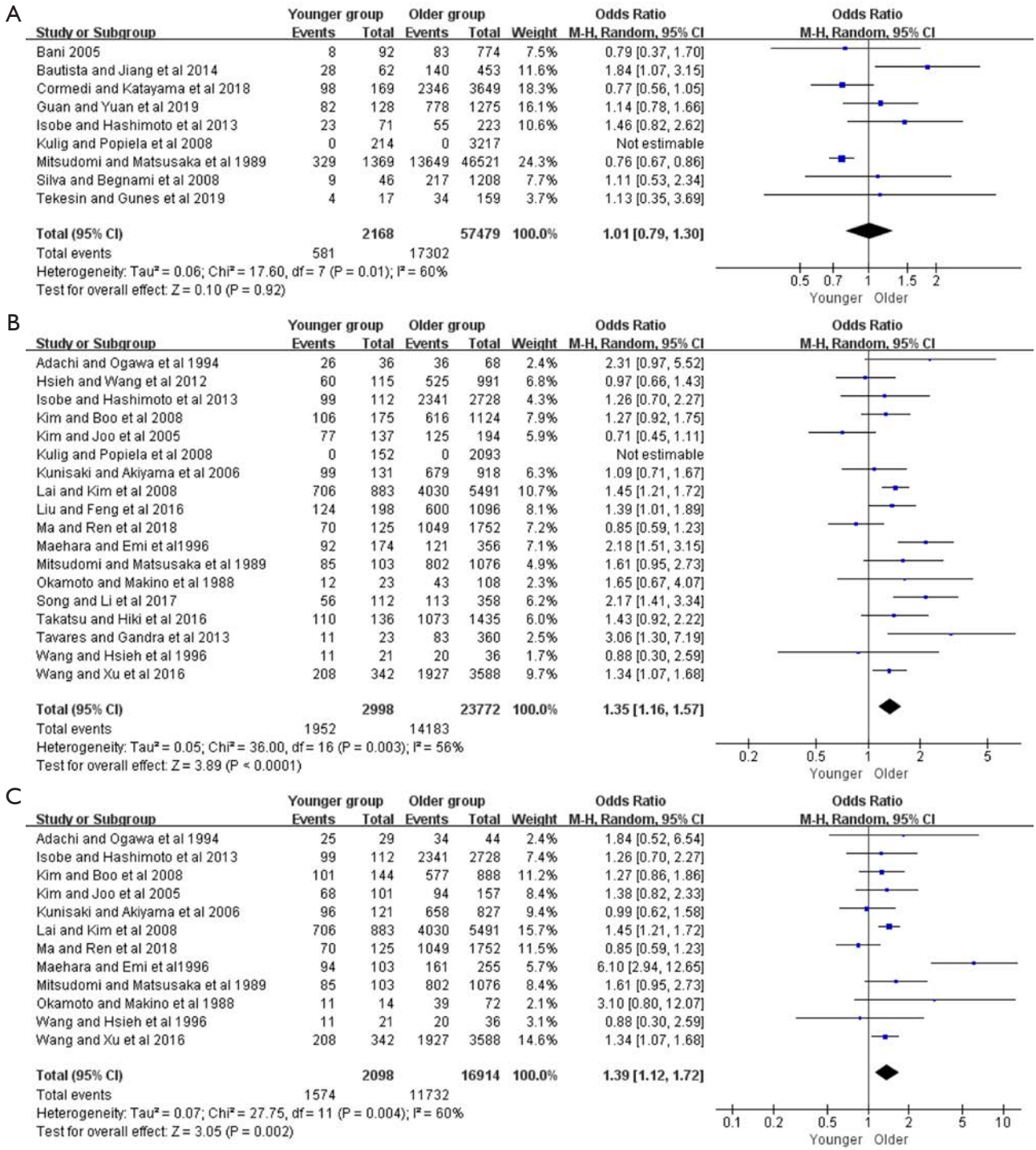

Figure 2 The 5-year overall survival for gastric cancer between younger and older group. (A) The 5-year overall survival of total patients; (B) the 5-year overall survival of patients underwent gastrectomy; (C) the 5-year overall survival of patients underwent curative gastrectomy.

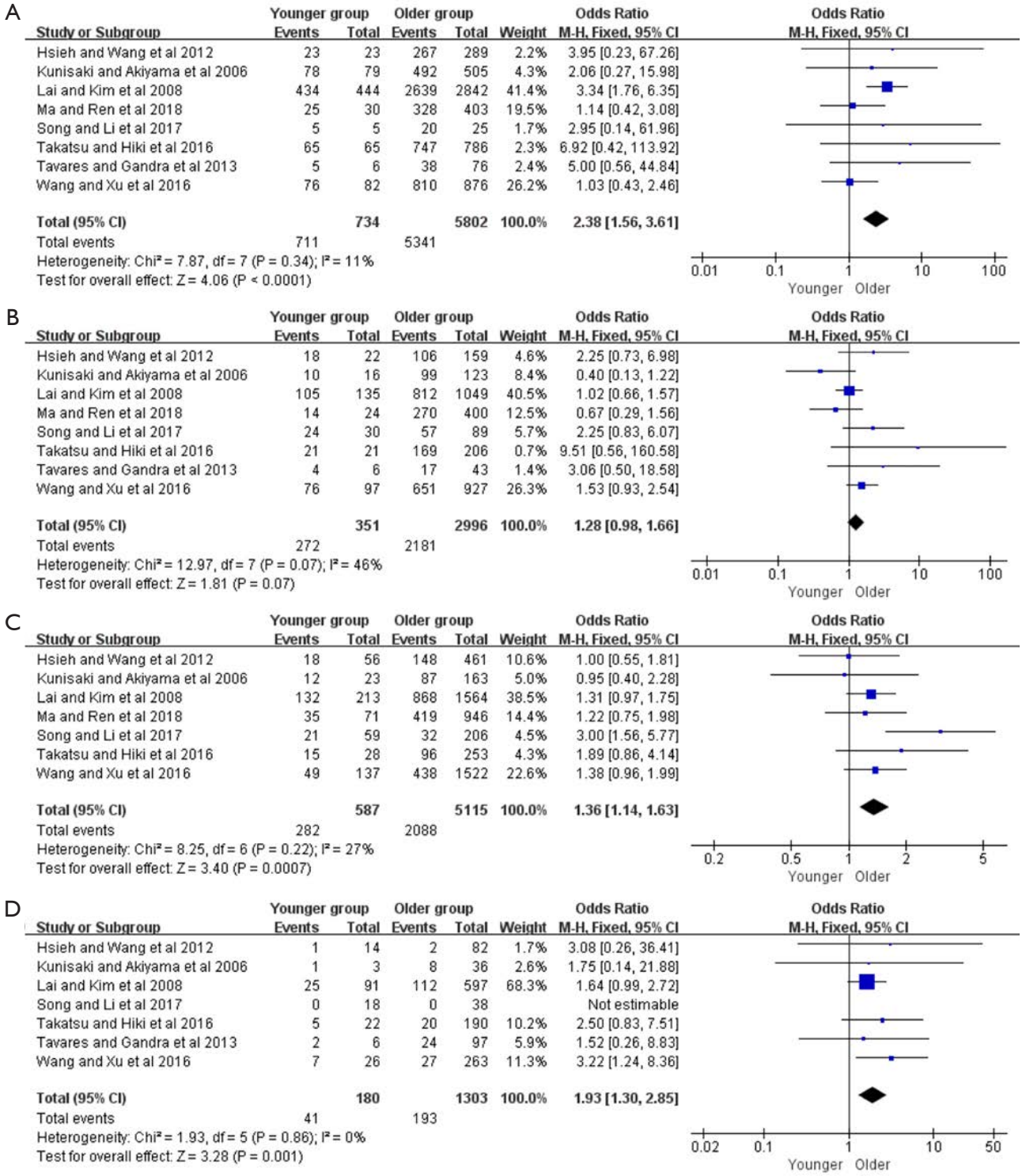

Figure 3 The 5-year overall survival of gastric cancer underwent gastrectomy between younger and older group. (A) Meta-analysis of patients at pTNM stage I; (B) meta-analysis of patients at pTNM stage II; (C) meta-analysis of patients at pTNM stage III; (D) meta-analysis of patients at pTNM stage IV.

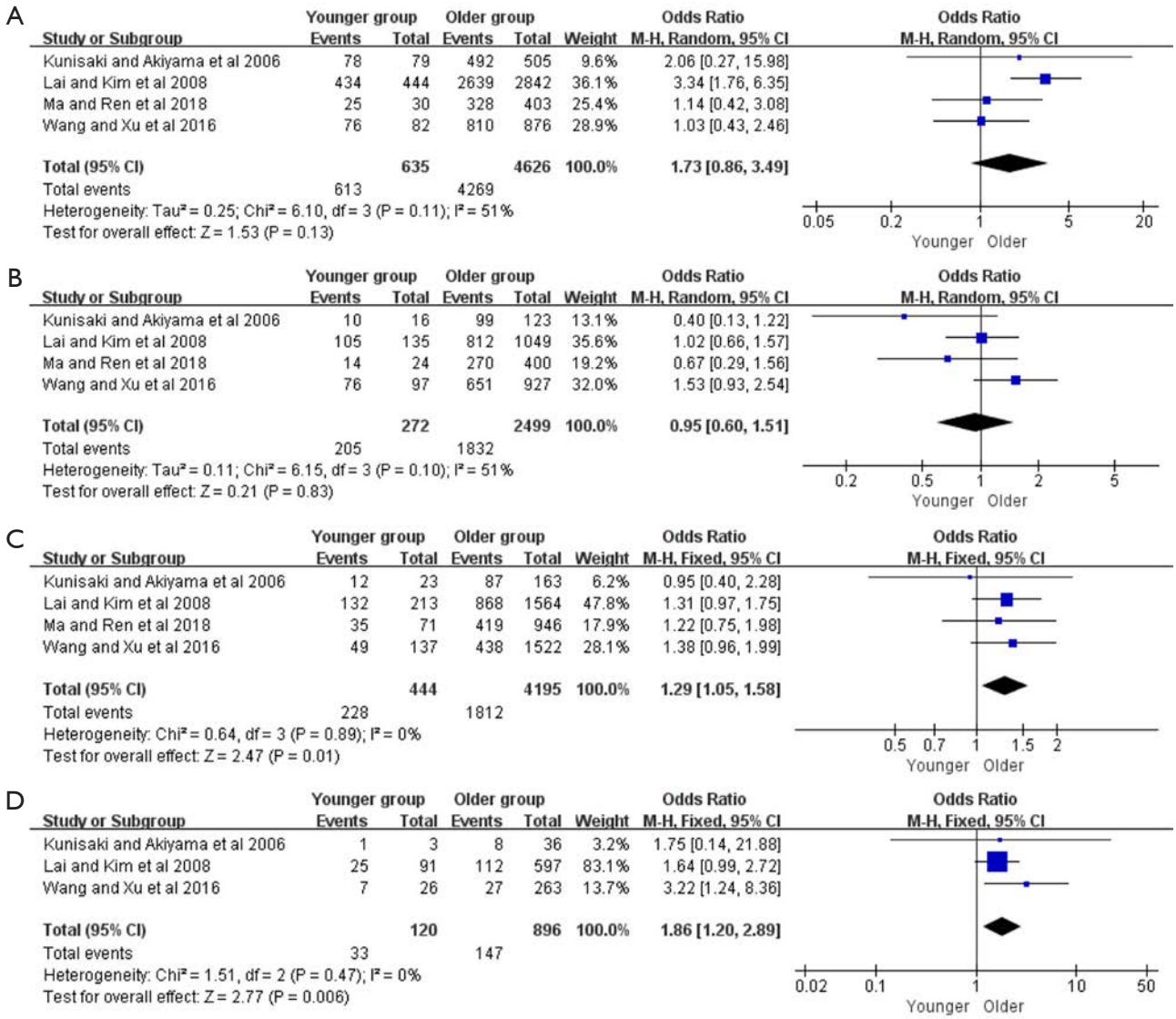

Figure 4 The 5-year overall survival of gastric cancer underwent curative gastrectomy between younger and older group. (A) Meta-analysis of patients at pTNM stage I. (B) meta-analysis of patients at pTNM stage II; (C) meta-analysis of patients at pTNM stage III; (D) meta-analysis of patients at pTNM stage IV.

some researches (26,40,41). While the included studies rarely capture the duration of symptoms before initial diagnosis, other researches have reported delayed diagnosis, and hereditary factors may be closely correlated with advanced gastric cancer (42,43).

Surgery, especially curative resection, was an important approach for patients with gastric cancer (44). There were higher proportions of chemotherapy and ≥ D2 lymphadenectomy in the younger group compared with the older. However, the percentages of total gastrectomy and curative resection revealed no statistical differences between younger and older groups, while subtotal gastrectomy was frequently performed in older patients. These results may be due to the significant comorbidities and impairment of functional status in older patients (45-47). Moreover, a previous study demonstrated that the ratio of older patients who had other synchronous or previous malignancies at initial diagnosis was up to 21% based on Munich Cancer Registry data (48). In our review, postoperative complications were more prevalent in the

older group, which also reflected a worse tolerance for surgery or chemotherapy. Several studies investigated that the incidence of postoperative complications was closely correlated with poor prognosis (49,50), thus providing a survival advantage for the younger group.

In this analysis, a tendency of peritoneal metastasis in the younger group may reflect the genetic susceptibility, such as CDH1 and RhoA, that could lead to more aggressive biological behaviors (40,51). Moreover, the infiltration of poorly differentiated gastric cancer was more pronounced in the vertical direction, thus conferring lymph node involvement and peritoneal dissemination. Metastasis was the leading cause of recurrence, and it had been thought that peritoneal metastasis was the most common form of repetition in gastric carcinoma (15). Our finding indicated a higher incidence of peritoneal recurrence in younger patients, which was similar to the other conclusion (12).

Younger gastric cancer patients as a group revealed similar long-term OS compared to older, and this finding was consistent with previous studies (5,10,11,20). In the subgroups of gastrectomy and only curative gastrectomy, both the short-term (including the 1-, 2-, 3-year) and long-term (including the 5-year) OS for older group was more miserable than those of the younger group, possibly due to a more significant percentage of comorbidities and complications. When the 5-year OS under different pTNM stages was evaluated, the results differed substantially between the younger and older group. A trend towards better long-term survival in the younger group may reflect a higher tolerance for the patients given a younger age and fewer comorbidities. Moreover, the shorter life expectancy of the older group compared to the younger may also be responsible.

There were several limitations in the analysis because of the characteristics of the included studies identified. Firstly, only one of the trials we identified was a prospective study. Secondly, most of the included studies were from Eastern Asia, which might not have a great representative and guiding value across the globe, especially in Western countries. Thereby, more related researches were expected to evaluate in gastric cancer patients at a younger age. Thirdly, there were inevitable heterogeneities, such as female ratio, diffuse type, as well as several survival variables in the analysis. The contribution of each included study to the pooled estimate was evaluated in the sensitivity analyses, and the result showed that sources of these heterogeneities were mainly from the selection bias. Furthermore, the lack of available patient data did not allow our analysis to assess disease-specific survival and disease-free survival. Despite these limitations, the study to our knowledge was the most extensive analysis evaluating the clinicopathological characteristics and survival outcomes in the younger and older patients, which may overcome the limitation of small sample size and single-institution targeted the field. Besides, all of the clinical studies involved in the meta-analysis had a high quality and met our inclusion criteria, thus might provide more valuable resources for the clinicians in patients' management and decision-making.

Conclusions

In conclusion, younger patients with gastric cancer were more often diagnosed as poorly differentiation and later pTNM tumor stage. However, younger cancer patients following gastrectomy had a better OS rate than patients in older group. Future large-scale analyses are expected to confirm our findings.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Clinicopathological characteristics of the included 25 studies

Authors	Group	No.	Tumor size ± SD (cm)	Pain	Bleeding	Cardiopulmonary disease	Differentiation		SRCC	Mucinous	Lauren type			Borrmann classification			
							Well	Poor			Intestinal	Diffuse	Mixed	I	II	III	IV
Song *et al.* (4)	YG	112	≤6 n=70; >6 n=42	–	–	–	6	106	–	–	–	–	–	–	–	–	–
	OG	358	≤6 n=239; >6 n=119	–	–	–	83	275	–	–	–	–	–	–	–	–	–
Cormedi *et al.* (5)	YG	71	–	–	–	–	–	–	–	–	3	57	3	–	–	–	–
	OG	223	–	–	–	–	–	–	–	–	78	74	14	–	–	–	–
Tavares *et al.* (8)	YG	23	–	12	3	–	4	12	–	–	8	15	0	–	–	–	–
	OG	360	–	160	100	–	56	89	–	–	255	105	0	–	–	–	–
Guan *et al.* (9)	YG	1,369	5.00±3.00	–	–	–	31	916	558	25	668	652	–	–	–	–	–
	OG	46,521	4.00±1.47	–	–	–	2493	22,616	5756	990	37,799	7,021	–	–	–	–	–
Isobe *et al.* (10)	YG	169	–	–	–	–	–	66	75	4	–	–	–	–	–	–	–
	OG	3,649	–	–	–	–	–	943	600	82	–	–	–	–	–	–	–
Kim *et al.* (11)	YG	137	5.07±3.23	–	–	–	–	–	25	4	–	–	–	5	13	93	26
	OG	194	5.16±3.45	–	–	–	–	–	6	10	–	–	–	10	43	128	13
Kunisaki *et al.* (12)	YG	131	<5 n=76; ≥5 n=55	–	–	–	30	101	–	–	–	–	–	–	–	–	–
	OG	918	<5 n=536; ≥5 n=382	–	–	–	479	439	–	–	–	–	–	–	–	–	–
Liu *et al.* (13)	YG	198	–	–	–	0	7	164	–	–	–	–	–	–	–	–	–
	OG	1,096	–	–	–	29	123	587	–	–	–	–	–	–	–	–	–
Okamoto *et al.* (14)	YG	34	–	–	–	–	–	22	2	0	–	–	–	0/20	0	12	4
	OG	132	–	–	–	–	–	51	1	5	–	–	–	3/85	25	34	14
Takatsu *et al.* (15)	YG	136	–	–	–	–	13	123	–	–	–	–	–	–	–	–	–
	OG	1,435	–	–	–	–	662	773	–	–	–	–	–	–	–	–	–
Tekesin *et al.* (16)	YG	92	–	22	6	–	–	–	–	–	39	45	7	–	–	–	–
	OG	774	–	191	52	–	–	–	–	–	526	220	21	–	–	–	–
Wang *et al.* (17)	YG	21	<5 n=13; ≥5 n=8	–	–	–	4	10	4	1	–	–	–	1	6	12	2
	OG	36	<5 n=23; ≥5 n=13	–	–	–	10	4	2	5	–	–	–	2	13	19	1
Hsieh *et al.* (18)	YG	115	4.80±3.50	–	–	–	17	98	–	–	17	64	13	–	–	–	–
	OG	1,009	4.50±3.00	–	–	–	453	556	–	–	491	279	103	–	–	–	–
Ma *et al.* (19)	YG	125	–	–	–	–	3	111	–	–	–	–	–	–	–	–	–
	OG	1,752	–	–	–	–	93	1,228	–	–	–	–	–	–	–	–	–
Mitsudomi *et al.* (20)	YG	128	–	48	6	3	5	94	–	–	–	–	–	2	11	28	20
	OG	1,275	–	20	3	14	600	449	–	–	–	–	–	20	175	347	106
Kulig *et al.* (21)	YG	214	–	90	12	2	–	–	–	–	42	80	18	–	–	–	–
	OG	3,217	–	1831	186	293	–	–	–	–	1,106	623	207	–	–	–	–
Bani-Hani *et al.* (22)	YG	17	–	12	2	–	–	8	–	–	6	11	–	–	–	–	–
	OG	159	–	109	23	–	–	41	–	–	121	18	–	–	–	–	–
Kim *et al.* (23)	YG	175	–	–	–	–	42	133	–	–	–	–	–	–	–	–	–
	OG	1,124	–	–	–	–	608	516	–	–	–	–	–	–	–	–	–
Lai *et al.* (24)	YG	883	≤4 n=586; >4 n=288	–	–	–	135	711	–	–	–	–	–	10	114	297	75
	OG	6,071	≤4 n=354; >4 n=2,488	–	–	–	2,661	3,232	–	–	–	–	–	665	812	2,039	405
Maehara *et al.* (25)	YG	174	7.10±4.20	–	–	–	39	135	–	–	–	–	–	–	–	–	–
	OG	356	6.30±3.80	–	–	–	225	129	–	–	–	–	–	–	–	–	–
Silva *et al.* (26)	YG	62	≤5 n=31; >5 n=27	–	–	–	–	–	–	–	15	36	11	–	–	–	–
	OG	453	≤5 n=179; >5 n=259	–	–	–	–	–	–	–	230	146	77	–	–	–	–
Zhou *et al.* (27)	YG	152	–	73	19	–	–	–	–	–	14	120	18	–	–	–	–
	OG	250	–	98	11	–	–	–	–	–	156	73	21	–	–	–	–
Adachi *et al.* (28)	YG	36	6	23	–	0	–	33	–	–	–	–	–	–	–	–	–
	OG	68	6.05	16	–	21	–	35	–	–	–	–	–	–	–	–	–
Bautista *et al.* (29)	YG	46	–	–	–	3	0	37	–	–	14	32	–	–	–	–	–
	OG	1,208	–	–	–	564	40	759	–	–	754	494	–	–	–	–	–
Wang *et al.* (30)	YG	342	–	–	–	–	16	258	86	16	64	166	112	18	114	156	54
	OG	3,588	–	–	–	–	172	2,244	534	233	790	2,049	1,027	272	1,252	1,756	308

No., number of patients; Pain, abdominal pain; SRCC, signet ring cell carcinoma; YG, younger group; OG, older group.

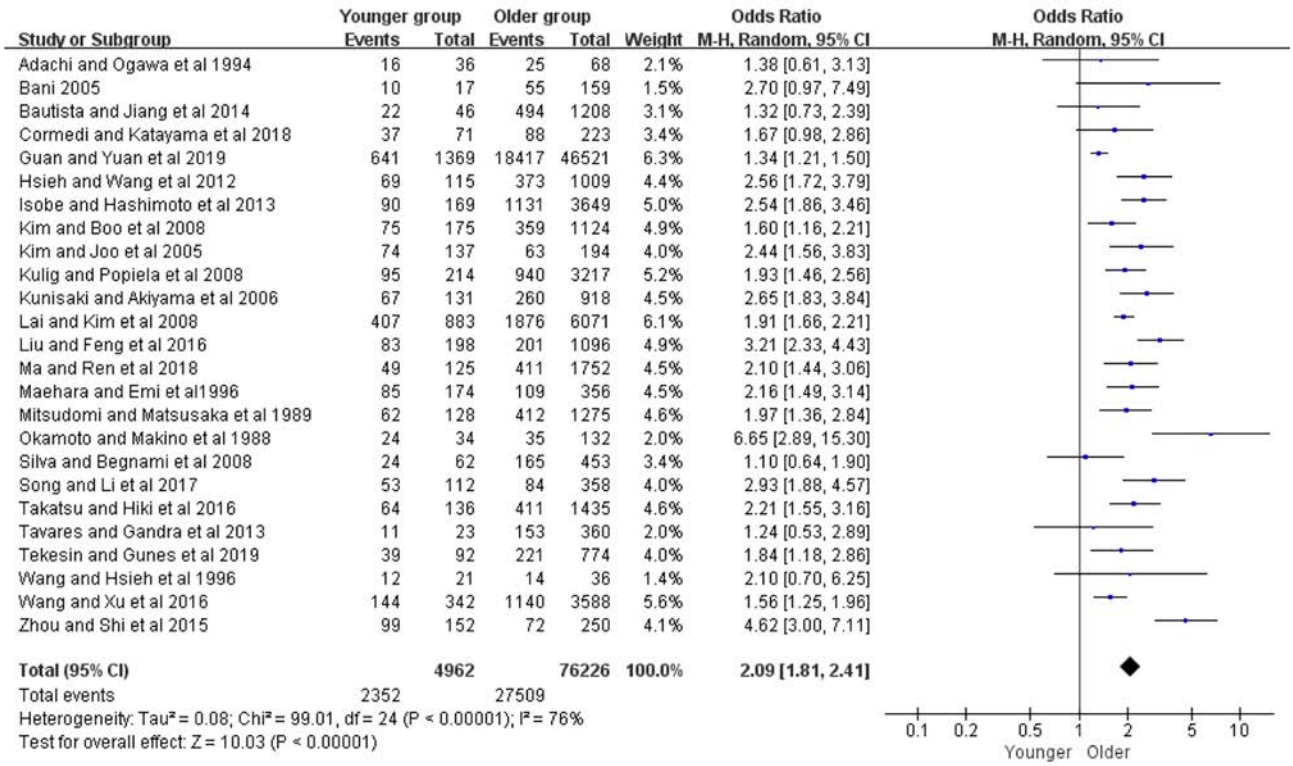

Figure S1 Meta-analysis of female ratio between younger and older group.

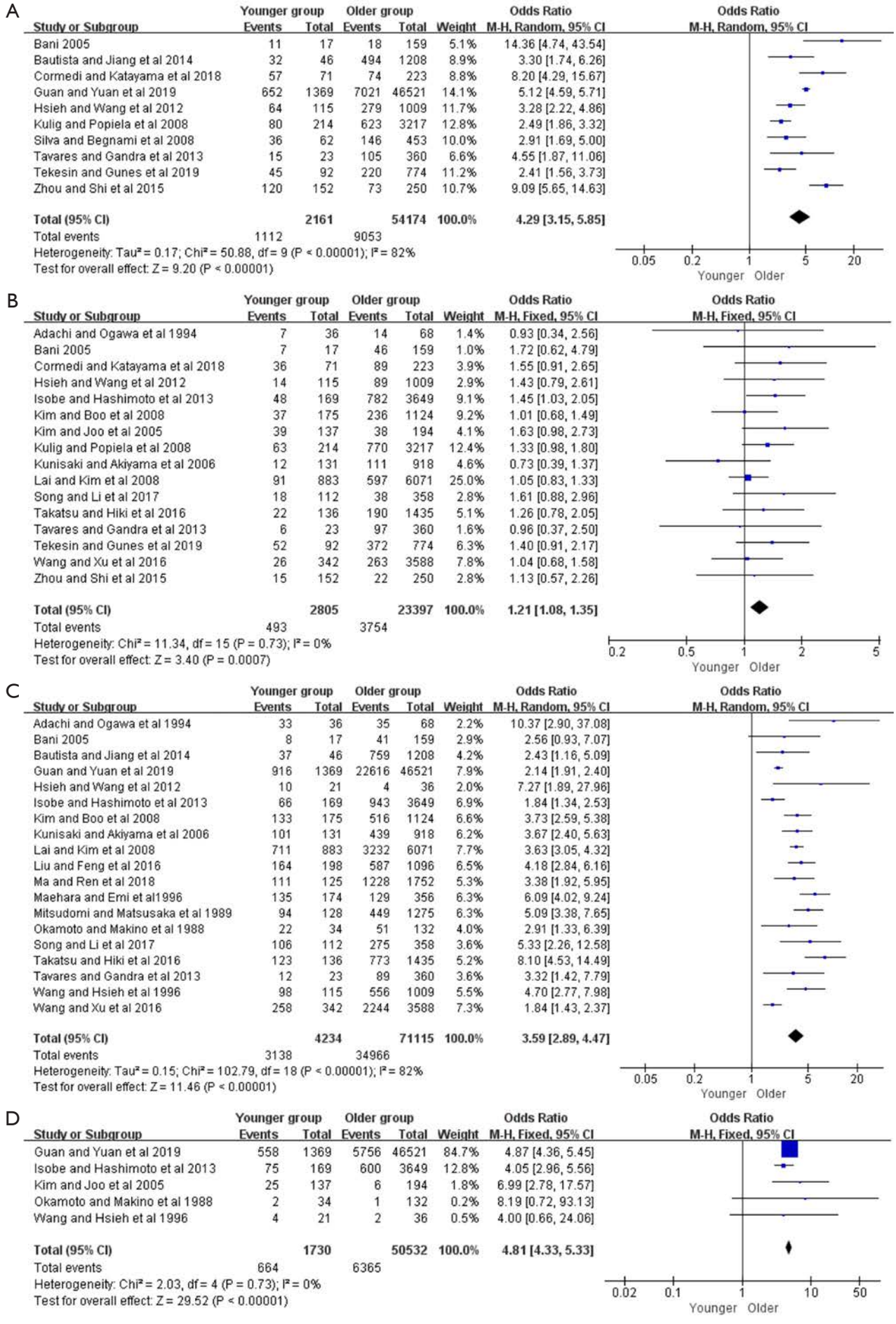

Figure S2 The proportion of clinicopathologic feature between younger and older group. (A) Meta-analysis of diffuse type; (B) meta-analysis of pTNM stage IV; (C) meta-analysis of poorly differentiation; (D) meta-analysis of signet ring cell carcinoma.

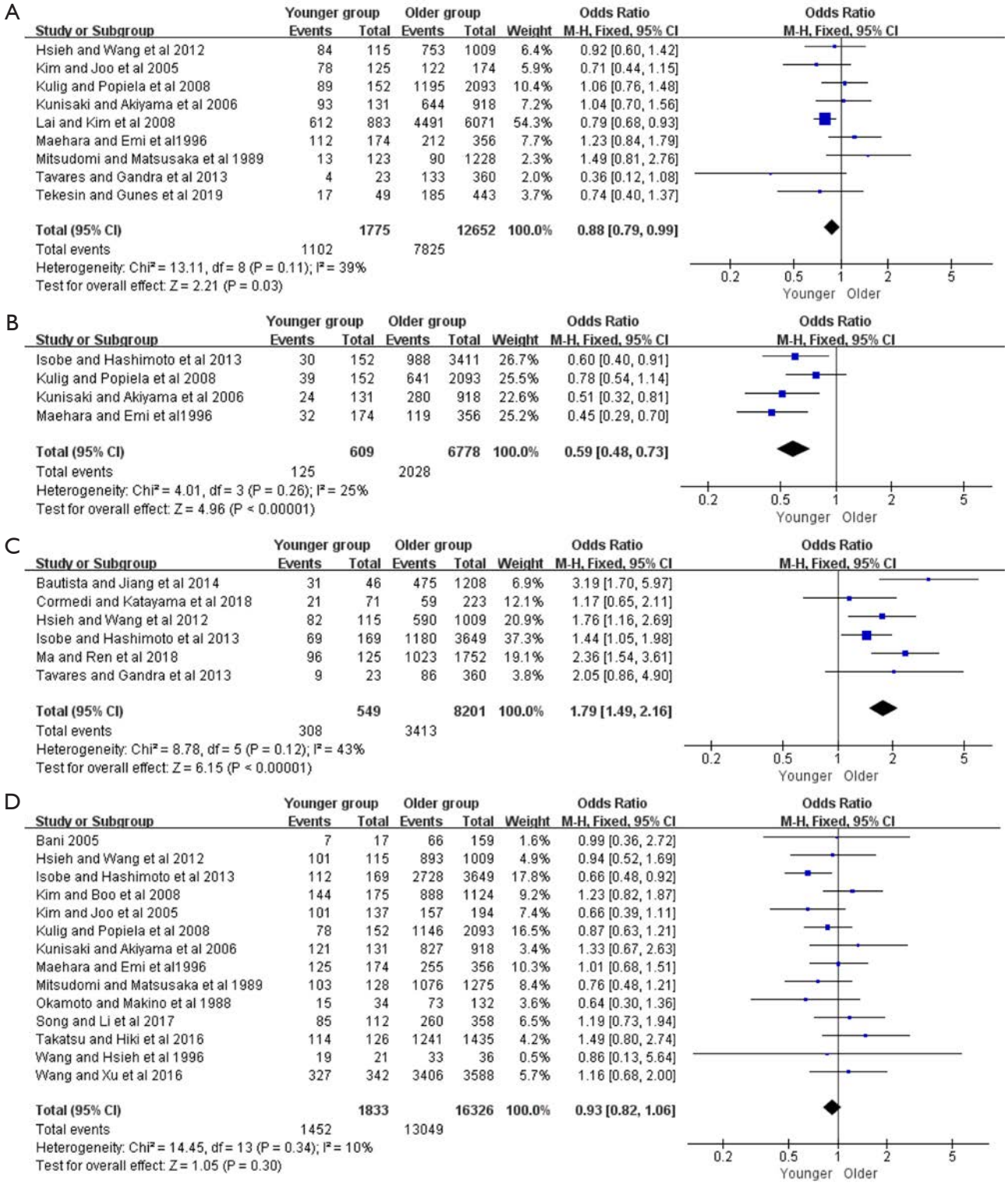

Figure S3 The proportion of therapeutic regimen between younger and older group. (A) Meta-analysis of subtotal gastrectomy; (B) meta-analysis of D1 lymphadenectomy; (C) meta-analysis of chemotherapy; (D) meta-analysis of curative resection.

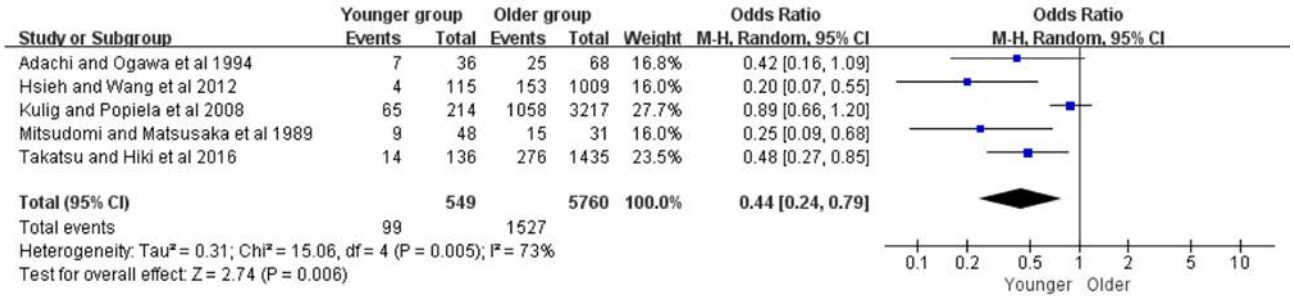

Figure S4 Meta-analysis of the proportion of postoperative complications between younger and older group.

Table S2 Subgroup meta-analysis of overall survival comparison between the younger group and older group

Subgroup	Included studies	Included patients	I^2 (%)	Effect model	OR/WMD	95% CI	P
OS							
1-year OS	8	59,132	81	Random	1.08	0.80–1.45	0.63
2-year OS	8	59,132	78	Random	1.04	0.79–1.36	0.79
3-year OS	8	59,132	74	Random	1.01	0.78–1.32	0.93
5-year OS	9	59,647	60	Random	1.01	0.79–1.30	0.92
OS underwent gastrectomy							
1-year OS	15	18,442	0	Fixed	1.20	1.04–1.39	0.01
2-year OS	15	18,442	56	Random	1.31	1.08–1.58	0.005
3-year OS	15	18,442	1	Fixed	1.33	1.19–1.48	<0.001
5-year OS	18	26,770	56	Random	1.35	1.16–1.57	<0.001
Stage I-OS underwent gastrectomy[1]							
1-year OS	5	5,437	0	Fixed	5.18	1.03–26.03	0.05
2-year OS	5	5,437	0	Fixed	2.29	1.11–4.71	0.02
3-year OS	5	5,437	0	Fixed	3.32	1.72–6.40	<0.001
5-year OS	8	6,536	11	Fixed	2.38	1.56–3.61	<0.001
Stage II-OS underwent gastrectomy							
1-year OS	5	2,735	0	Fixed	1.54	0.72–3.33	0.27
2-year OS	5	2,735	0	Fixed	1.25	0.80–1.94	0.33
3-year OS	5	2,735	45	Fixed	1.47	1.01–2.14	0.04
5-year OS	8	3,347	46	Fixed	1.28	0.98–1.66	0.07
Stage III-OS underwent gastrectomy							
1-year OS	5	4,499	61	Random	1.41	0.81–2.45	0.22
2-year OS	5	4,499	55	Random	1.53	1.07–2.20	0.02
3-year OS	5	4,499	60	Random	1.62	1.14–2.31	0.007
5-year OS	7	5,702	27	Fixed	1.36	1.14–1.63	<0.001
Stage IV-OS underwent gastrectomy							
1-year OS	5	1,341	74	Random	1.18	0.54–2.58	0.68
2-year OS	5	1,341	83	Random	3.46	1.26–9.56	0.02
3-year OS	5	1,341	41	Fixed	1.77	1.23–2.54	0.002
5-year OS	7	1,483	0	Fixed	1.93	1.30–2.85	0.001
OS underwent curative surgery							
1-year OS	11	12,660	0	Fixed	1.35	1.05–1.72	0.02
2-year OS	11	12,660	33	Fixed	1.22	1.03–1.45	0.02
3-year OS	11	12,660	0	Fixed	1.36	1.17–1.58	<0.001
5-year OS	12	19,012	60	Random	1.39	1.12–1.72	0.002
Stage I-OS underwent curative surgery							
5-year OS	4	5,261	51	Random	1.73	0.86–3.49	0.13
Stage II-OS underwent curative surgery							
5-year OS	4	2,771	51	Random	1.07	0.80–1.43	0.67
Stage III-OS underwent curative surgery							
5-year OS	4	4,639	0	Fixed	1.29	1.05–1.58	0.01
Stage IV-OS underwent curative surgery							
5-year OS	3	1,016	0	Fixed	1.86	1.20–2.89	0.006
OS underwent Non-curative surgery							
1-year OS	3	268	70	Random	1.31	0.40–4.29	0.66
2-year OS	3	268	38	Fixed	0.92	0.49–1.71	0.87
3-year OS	3	268	0	Fixed	1.37	0.72–2.61	0.34
5-year OS	3	268	0	Fixed	1.14	0.56–2.36	0.72

[1]stage, pTNM stage. OS, overall survival.

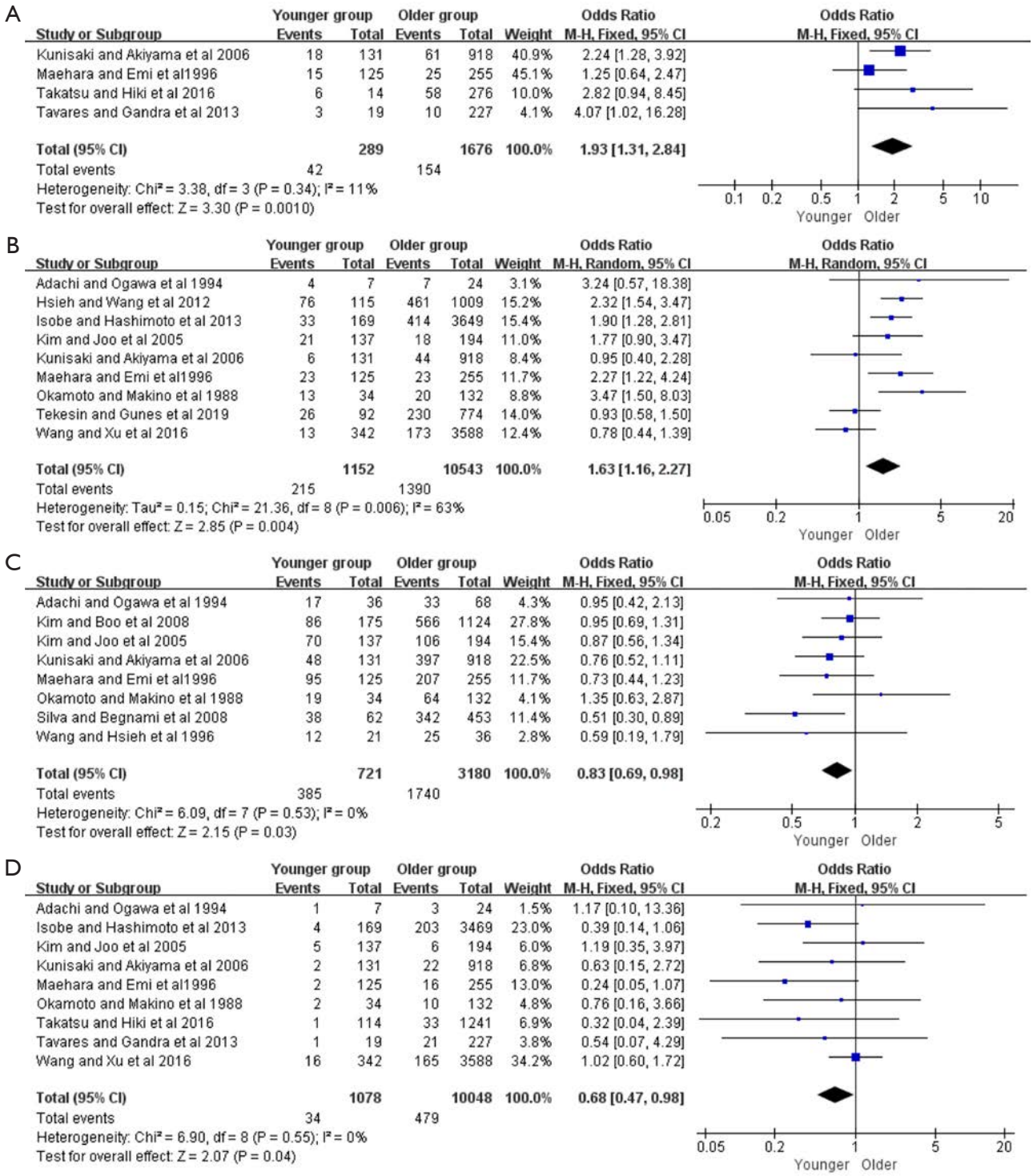

Figure S5 The proportion of metastasis and recurrence between younger and older group. (A) Meta-analysis of peritoneal recurrence; (B) meta-analysis of peritoneal metastasis; (C) meta-analysis of lymph node metastasis; (D) meta-analysis of hepatic metastasis.

Table S3 Therapeutic regimens and survival outcomes of the included studies

Authors	Group	No.	Type of gastrectomy		Resection margin		Lymphadenectomy			Chemotherapy	Complication	Peritoneal recurrence	Metastasis			
			Subtotal	Total	R0	R1/R2	D0	D1	≥D2				Lymph node	Vessel	Hepatic	Peritoneal
Song *et al.* (4)	YG	112	–	–	85	27	–	–	–	–	–	–	–	–	–	–
	OG	358	–	–	260	98	–	–	–	–	–	–	–	–	–	–
Cormedi *et al.* (5)	YG	71	–	–	–	–	–	–	–	21	–	–	–	–	–	–
	OG	223	–	–	–	–	–	–	–	59	–	–	–	–	–	–
Tavares *et al.* (8)	YG	23	4	19	–	–	–	–	–	9	–	3	–	–	1	–
	OG	360	133	227	–	–	–	–	–	86	–	10	–	–	21	–
Guan *et al.* (9)	YG	1,349	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	OG	46,521	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Isobe *et al.* (10)	YG	169	–	52	112	–	3	30	119	69	–	–	–	–	4	33
	OG	3,649	–	936	2,728	–	217	988	2,205	1,180	–	–	–	–	203	414
Kim *et al.* (11)	YG	137	78	47	101	–	–	–	–	–	–	–	70	–	5	21
	OG	194	122	52	157	–	–	–	–	–	–	–	106	–	6	18
Kunisaki *et al.* (12)	YG	131	93	25	121	–	–	24	107	–	–	18	48	34	2	6
	OG	918	644	274	827	–	–	280	638	–	–	61	397	332	22	44
Liu *et al.* (13)	YG	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	OG	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Okamoto *et al.* (14)	YG	34	–	–	15	–	10	–	–	–	–	–	19	–	2	13
	OG	132	–	–	73	–	23	–	–	–	–	–	64	–	10	20
Takatsu *et al.* (15)	YG	126	–	32	114	22	–	–	–	–	14	6	–	–	1/114	–
	OG	1,435	–	445	1,241	194	–	–	–	–	276	58	–	–	33/1,241	–
Tekesin *et al.* (16)	YG	92	17	32	–	–	–	–	–	–	–	–	–	29	–	26
	OG	774	185	260	–	–	–	–	–	–	–	–	–	254	–	230
Wang *et al.* (17)	YG	21	–	–	19	–	–	–	–	–	4	–	–	20	–	76
	OG	36	–	–	33	–	–	–	–	–	153	–	–	155	–	461
Hsieh *et al.* (18)	YG	115	84	31	101	14	–	–	–	82	–	–	12	–	–	–
	OG	1,009	753	256	893	116	–	–	–	590	–	–	25	–	–	–
Ma *et al.* (19)	YG	125	–	–	–	–	–	–	–	96	–	–	–	43	–	–
	OG	1,752	–	–	–	–	–	–	–	1,023	–	–	–	451	–	–
Mitsudomi *et al.* (20)	YG	128	13	29	103	–	–	–	–	–	9	–	–	–	–	–
	OG	1,275	90	236	1,076	–	–	–	–	–	15	–	–	–	–	–
Kulig *et al.* (21)	YG	214	89	63	78	74	–	39	113	–	65	–	–	–	–	–
	OG	3,217	1,195	898	1,146	947	–	641	1,452	–	1,058	–	–	–	–	–
Bani-Hani *et al.* (22)	YG	17	–	–	7	–	–	–	–	–	–	–	–	–	–	–
	OG	159	–	–	66	–	–	–	–	–	–	–	–	–	–	–
Kim *et al.* (23)	YG	175	–	–	144	31	–	–	–	–	–	–	86	–	–	–
	OG	1,124	–	–	888	236	–	–	–	–	–	–	566	–	–	–
Lai *et al.* (24)	YG	883	612	262	–	–	–	–	–	–	–	–	–	–	–	–
	OG	6,071	4,491	1,519	–	–	–	–	–	–	–	–	–	–	–	–
Maehara *et al.* (25)	YG	174	112	62	125	–	–	32	141	–	–	15	95	15	2	23
	OG	356	212	139	255	–	–	119	237	–	–	25	207	81	16	23
Silva *et al.* (26)	YG	–	–	–	–	–	–	–	–	–	–	–	38	–	–	–
	OG	–	–	–	–	–	–	–	–	–	–	–	342	–	–	–
Adachi *et al.* (28)	YG[2]	36	–	–	–	–	–	–	–	–	7	–	17	–	1/7	4/7
	OG[3]	68	–	–	–	–	–	–	–	–	25	–	33	–	3/24	7/24
Bautista *et al.* (29)	YG	46	–	–	–	–	–	–	–	31	–	–	–	–	–	–
	OG	1,208	–	–	–	–	–	–	–	475	–	–	–	–	–	–
Wang *et al.* (30)	YG	342	–	–	327	15	–	–	–	267	–	–	–	–	16	13
	OG	3,588	–	–	3,406	182	–	–	–	2,856	–	–	–	–	165	173

No., number of patients; YG, younger group; OG, older group; R, resection margin.