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Undifferentiated-predominant mixed-type early gastric cancer is more aggressive than pure undifferentiated type: a systematic review and meta-analysis

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ABSTRACT

Background Studies have shown that differentiated-predominant mixed-type early gastric cancer (EGC) is more aggressive than pure differentiated-type EGC. However, the biological behaviour of undifferentiated-predominant mixed-type (MU) EGC and pure undifferentiated-type (PU) EGC are controversial. This study was conducted to compare the biological behaviour of MU EGC and PU EGC.

Methods A systematic review and meta-analysis of observational studies was conducted using literature published through PubMed and Embase from inception to 9 November 2021. Inclusion criteria were: (1) a direct or indirect comparison of MU and PU; (2) patients with EGC; (3) a specified outcome of lymph node metastasis (LNM), lymphovascular invasion, submucosal invasion and/or ulcer findings; and (4) the primary lesion was obtained. The literature search, data extraction and quality assessment were performed by two independent reviewers. The meta-analysis was conducted with a random-effect model using the Mantel-Haenszel method.

Results Twelve publications with 5644 patients were included. Patients with MU EGC had significantly higher risk of LNM (OR 2.28; 95% CI 1.72 to 3.03) and submucosal invasion (OR 2.19; 95% CI 1.90 to 2.52) compared with patients with PU EGC. No difference was found between patients with MU and PU EGC with respect to lymphovascular invasion risk (OR 1.81; 95% CI 0.84 to 3.87). After stratifying the data according to depth of tumour invasion, a significantly higher risk for LNM was associated with intramucosal MU EGC (OR 2.56; 95% CI 1.66 to 3.95) and submucosal MU EGC (OR 2.63; 95% CI 2.06 to 3.06). Submucosal MU EGC also had a significantly higher risk of lymphovascular invasion (OR 2.40; 95% CI 1.79 to 3.21) compared with submucosal PU EGC.

Discussion Patients with MU EGC had an increased risk of submucosal invasion and LNM compared with patients with PU EGC . MU patients with submucosal EGC also had an increased lymphovascular invasion risk compared with PU patients. Therefore, attention should be focused on the clinical management of patients with MU EGC.

Strengths and limitations of this study

► This is the first meta-analysis to compare the biological behaviour between undifferentiated-predominant mixed-type and pure differentiated-type early gastric cancer.

► All included studies were carried out in Asia.

► There might be some selection bias that cannot be completely excluded as all studies were retrospective.

► The number of studies included in this meta-analysis was limited and the total number of patients included was relatively small.

BACKGROUND

Gastric cancer (GC) has become the fifth most common type of cancer and the third leading cause of death due to cancer in the world, and there were more than one million new cases of GC diagnosed in 2018.[1] The stage of GC at the time of diagnosis dictates patient prognosis; the 5-year overall survival rate of early gastric cancer (EGC) is 92.0%–97.2%,[2] whereas for advanced GC, the 5-year overall survival rate is only 23%–36%.[3] Therefore, early detection, diagnosis and treatment of GC are essential to optimise patient survival. EGC is defined as cancer tissue limited to the mucosa and submucosa, regardless of lymph node metastasis (LNM).[4] Endoscopic resection including endoscopic mucosal resection and endoscopic submucosal dissection (ESD), as well as surgery are treatment options for EGC, whereas a gastrectomy with adequate lymphadenectomy and chemotherapy is the only therapeutic option for advanced GC.[5] Histological types can be divided into the following four groups according to the proportions of differentiated and undifferentiated components:

pure differentiated-type (PD, differentiated components only), pure undifferentiated-type (PU, undifferentiated components only), differentiated-predominant mixed-type (MD, major differentiated and minor undifferentiated components), and undifferentiated-predominant mixed-type (MU, major undifferentiated and minor differentiated components). Previous studies have shown that MD EGC has a significantly higher risk of LNM and a higher rate of non-curative resection when compared with PD EGC.[6–8] However, the biological behaviour of MU EGC and PU EGC is controversial. Certain reports have claimed that MU EGC has a significantly higher risk of LNM than PU EGC.[9] However, Chen *et al* reported that MU EGC did not show an increase in the incidence of LNM compared with PU EGC.[10] Additionally, according to the treatment guidelines of the Japanese Gastric Cancer Association,[11] MU and PU EGC are collectively treated as undifferentiated-type EGC. Differences in the biological behaviour between PU and MU have not been given much consideration, and it remains unknown whether they should be treated using the same ESD indication criteria. It is necessary to combine data from the studies available to maximise the power of this research in a relatively rare circumstance to address this issue. The above-mentioned considerations prompted the generation of this meta-analysis to reveal the biological behaviours in MU and PU EGC and determine if there are important differences that can improve the clinical approach to treatment.

METHODS

This meta-analysis was completed according to the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[12]

Literature search

Studies from inception to 9 November 2021 were searched using the PubMed and Embase databases. Due to language limitations, only studies published in English were selected. Two independent evaluators (Peng Yang and Xiang-dong Zheng) used common key words associated with "early gastric cancer" and "mixed type" to search the databases. Details of the search strategy are shown in the online supplemental material. The titles and abstracts of each article were reviewed to exclude irrelevant publications, and full texts were read to determine whether the remaining studies meet the inclusion criteria. References of the included articles were carefully checked to ensure no literature was unintentionally omitted. Disagreements between the two evaluators were resolved by a third evaluator (Xiao-yong Wang). The detailed retrieval strategy is presented in figure 1.

Eligibility criteria

Sufficient information was required from the studies to construct a 2×2 contingency table for further analysis, and available information was either extracted directly or calculated from the data contained by the studies. This meta-analysis included studies with the following criteria: (1) direct and indirect comparison of the relationship between MU and PU; (2) patients with EGC; (3) a specified outcome of LNM, lymphovascular invasion, submucosal invasion and/or ulcer findings; and (4) the primary lesion was obtained by open surgery or laparoscopic surgery. For articles with overlapping data of the same source population, only the largest report was included.

Data extraction

Pertinent information was extracted from each study independently by two reviewers (Peng Yang and Xiang-dong Zheng) who followed the same criteria. Results were compared, and disparities were settled by a third evaluator (Xiao-yong Wang). The essential study information included: name of the first author(s); date of publication; region from which the study population was derived. The necessary clinicopathological factors included: LNM (yes or no); depth of tumour invasion (mucosal or submucosal
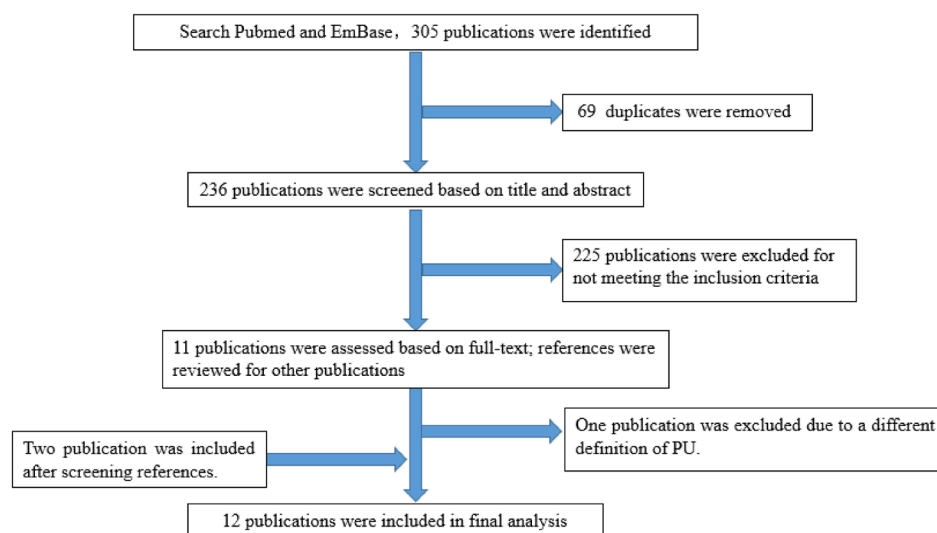

Figure 1 Flow chart summarising the steps of identification for relevant studies.

invasion); lymphovascular invasion (yes or no); and ulcer findings (yes or no).

Quality assessment

The quality of the included studies was assessed by two initial evaluators (Peng Yang and Xiang-dong Zheng) using the Newcastle-Ottawa Scale. There major aspects including selection, comparability and exposure/outcome were used to evaluate each paper. The final score ranged from 0 to 9, where 1 point was given for meeting one required item, and at most 2 points were given for comparability. Articles with a score ≥6 were considered high quality. Discrepancies were resolved by a third evaluator (Xiao-yong Wang).

Statistical analysis

Stata software, V.15.1 (StataCorp LLC 4905 Lakeway Drive, College Station, Texas 77845 USA) was used to perform all statistical analyses.

The pooled rates were calculated for LNM, submucosal invasion, lymphovascular invasion, and unclear findings between undifferentiated-predominant mixed-type and pure undifferentiated-type EGC groups, which were expressed as ORs with 95% CIs. In addition to the overall comparisons, mucosal/submucosal invasion-based and region-based (only articles from China and Japan which have enough data can be used for region-based subgroup analysis) subgroup analyses were also implemented.

A random-effect model using the Mantel-Haenszel method was performed for the meta-analysis [Stata code: metan tdeath tnodeath cdeath cnodeath, or random label (namevar=id, yearvar=year) counts]. Publication bias was tested using both Begg's and Egger's tests [Stata code: gen logor=log(_ES); gen selogor=_selogES; metabias6 logor selogor, graph(begg)]. In addition, a sensitivity analysis was performed to assess the stability and reliability of the results [Stata code: metaninf tdeath tnodeath cdeath cnodeath, label (namevar=id, yearvar=year) random or].

Table 1 Clinical characteristics of patients from each of the included studies

Author year	Country	Men/women; age (years)	MU/PU	LNM+	Depth (SM)	LVI+	Ulcerative findings	Score (NOS)
Hanaoka et al, 2009[13]	Japan	271/105; 229<60/147≥60	63/80	23/12	All SM	36/31		7
Ito et al, 2011[17]	Japan	204/123; 163<65/164≥65	36/122	11/13	M+SM			8
Nakata et al, 2012[18]	Japan	194/86; 126≤60/154≥61	20/98	2/4	M+SM			5
Huh et al, 2013[19]	Korea	301/187 59.1±10.6 51.7±12.0 51.2±11.7	24/464	2/73	17/271 M+SM	0/52		6
Takizawa et al, 2013[20]	Japan	240/170 61 (29–87)	42/184	8/11	All M	2/4	21/81	7
Miyamae et al, 2016[14]	Japan	169/70 69 (35–91)	45/38	14/3	All SM			7
Sekiguchi et al, 2016[21]	Japan	2006/1125 62 (23–88)	469/1202	96/103	252/437 M+SM	120/118		6
			252/437	80/72	All SM	119/115		
			217/765	16/31	All M	1/3		
Zhong et al, 2018[16]	China	206/92; 59.5±12.1 (18–86)	17/69		9/20 M+SM			6
Chen et al, 2020[10]	China	1069/527; 62 (17–88)	144/572	39/110	99/272 M+SM		23/61	7
Horiuchi et al, 2020[9]	Japan	711/714; 60 (19–91)	525/900	104/66	332/386 M+SM			7
			193/514	15/13	All M	0/9	143/364	
			332/386	99/53	All SM			
Liu et al, 2021[22]	China	571/241; 60.9±10.5	141/136	50/33	M+SM			8
Jin et al, 2021[23]	China	347/231; 411<65/194≥65	129/124	29/24	M+SM			6

LNM, lymph node metastasis; LVI, lymphovascular invasion; M, mucosal; MU, undifferentiated-predominant mixed-type; NOS, Newcastle-Ottawa Scale; PU, pure undifferentiated-type; SM, submucosal.

Patient and public involvement

There was no direct patient or public involvement in the design or conduct of this review.

RESULTS

Literature identification

As shown in figure 1, a total of 305 publications were retrieved through the initial literature search. Among these search results, 69 duplicates were removed, which left 236 for screening based on title and abstract. Two hundred and twenty-five were excluded for not meeting the inclusion criteria as stated in the methods section. Eleven publications were assessed based on the full text, and two additional publications were included after reading the references of these eleven publications in detail.[13 14] One publication was excluded due to a different definition of PU (only undifferentiated components vs more than 90% undifferentiated components).[15] After the thorough screening, 12 publications[9 10 13 14 16–23] with 5644 patients were included for this meta-analysis, and the basic summarising information from these articles is shown in table 1.

Meta-analysis

The risk of LNM and subgroup analysis

As shown in figures 2, 11 studies were used to compare PU and MU EGC regarding LNM risk. MU EGC was found to have an increased risk of LNM (OR 2.28; 95% CI 1.72 to 3.03) compared with PU EGC. When stratified according to region, a significantly increased risk for LNM associated with MU EGC was found in studies with

patients from Japan (OR 3.03; 95% CI 2.48 to 3.71) and China (OR 1.52; 95% CI 1.14 to 2.02).

A subgroup analysis was performed to evaluate the LNM risk according to the depth of tumour invasion. This subgroup analysis revealed that mucosal MU EGC had a significantly higher LNM risk compared with mucosal PU EGC (OR 2.56; 95% CI 1.66 to 3.95), and submucosal MU EGC also had a significantly higher LNM risk compared with submucosal PU EGC (OR 2.63; 95% CI 2.06 to 3.06; figure 3).

The risk of submucosal invasion and subgroup analysis

Five studies were used to compare PU and MU EGC regarding submucosal invasion risk. MU EGC was found to be associated with an increased risk of submucosal invasion (OR 2.19; 95% CI 1.90 to 2.52; figure 4). When stratified according to region, a significantly higher submucosal invasion risk associated with MU EGC was found in both Japanese (OR 2.16; 95% CI 1.85 to 2.52) and Chinese (OR 2.46; 95% CI 1.71 to 3.55) population-based studies (figure 4).

The risk of lymphovascular invasion and subgroup analysis

As indicated in figure 5, five studies were used to compare PU and MU EGC with respect to lymphovascular invasion risk, and no significant difference was found (OR 1.81; 95% CI 0.84 to 3.87). When stratified by region, a significantly higher lymphovascular invasion risk associated with MU EGC was found in the Japanese-based studies (OR 2.33; 95% CI 1.27 to 4.28).

As shown in figure 6, when stratified by the depth of tumour invasion, the subgroup analysis revealed that
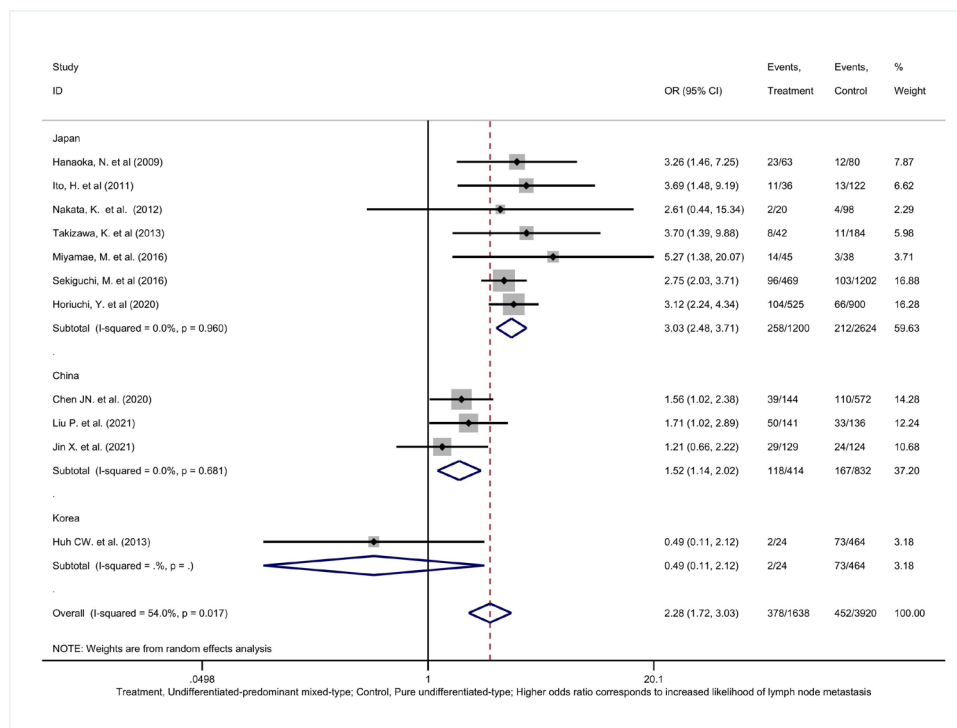

Figure 2 Forest plots showing ORs with 95% CIs comparing undifferentiated-predominant mixed-type with pure undifferentiated-type early gastric cancer for the risk of lymph node metastasis. Subgroup analysis was based on region.
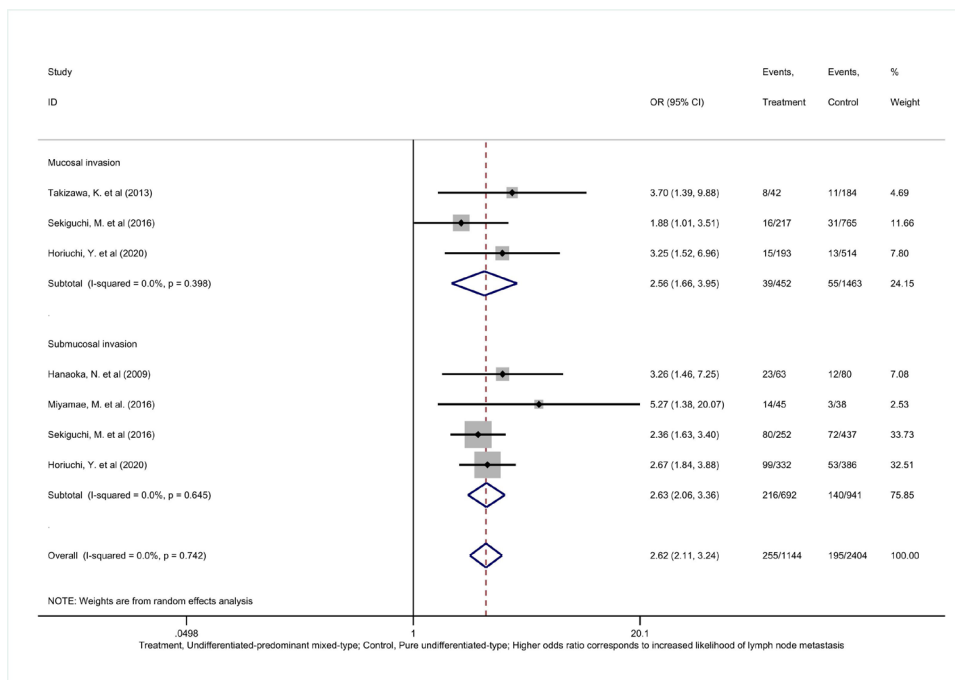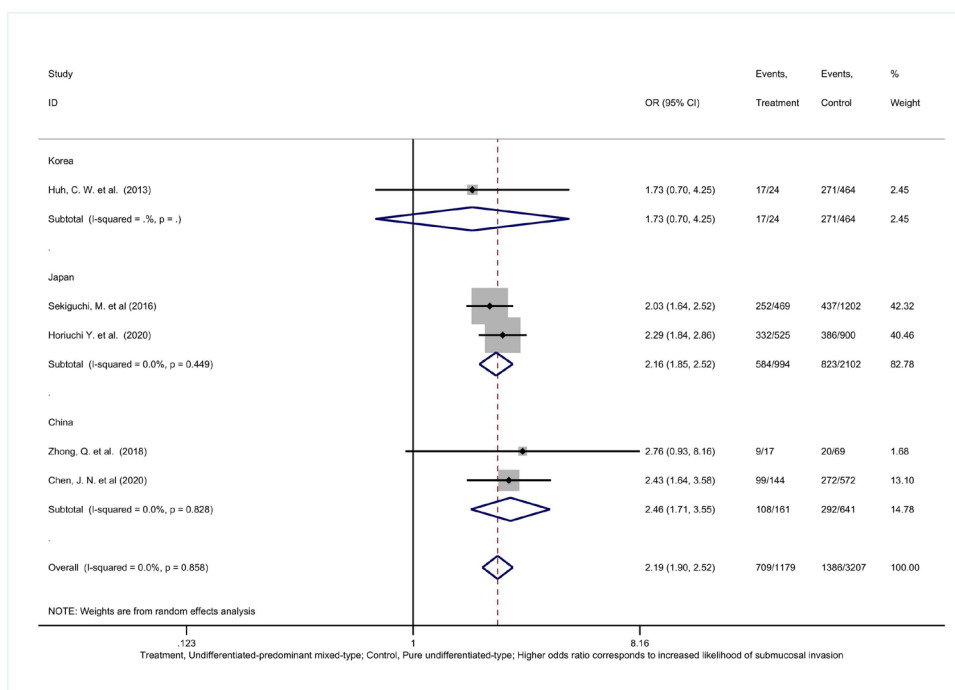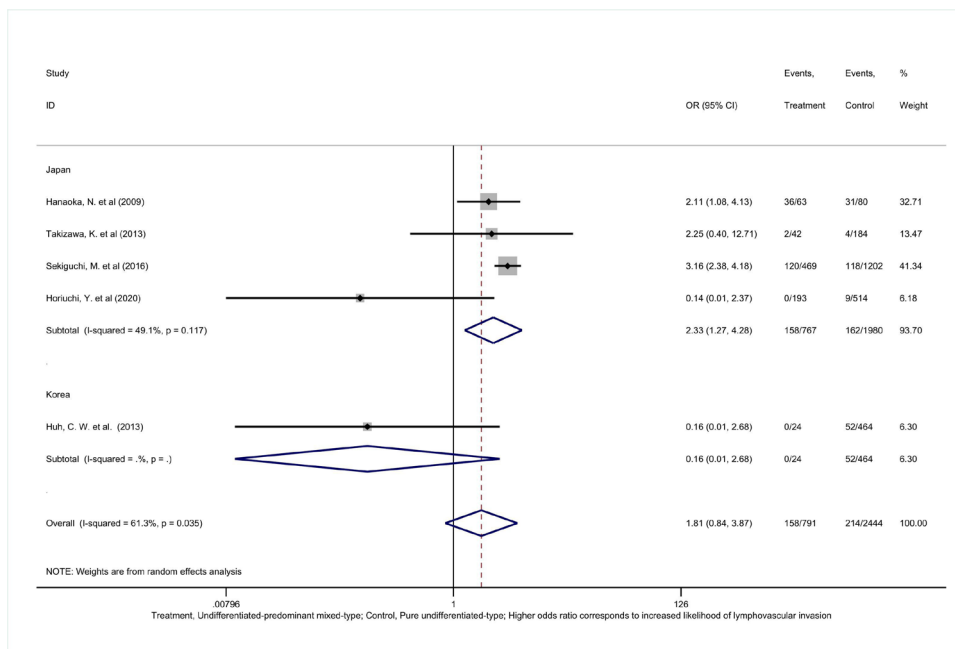
Figure 3 Forest plots showing ORs with 95% CIs comparing undifferentiated-predominant mixed-type with pure undifferentiated-type early gastric cancer for the risk of lymph node metastasis. Subgroup analysis was based on mucosal/submucosal invasion.

submucosal MU EGC had a significantly higher lymphovascular invasion risk compared with submucosal PU EGC (OR 2.40; 95% CI 1.79 to 3.21), whereas intramucosal PU and intramucosal MU EGC were comparable (OR 0.94; 95% CI 0.18 to 4.81).

The risk of ulcer finding

Data regarding ulcer findings were also extracted to compare MU and PU EGC from three studies, but no statistically significant difference was found (OR 1.30; 95% CI 0.99 to 1.71; figure 7).

Figure 4 Forest plots showing ORs with 95% CIs comparing undifferentiated-predominant mixed-type with pure undifferentiated-type early gastric cancer for the risk of submucosal invasion. Subgroup analysis was based on region.
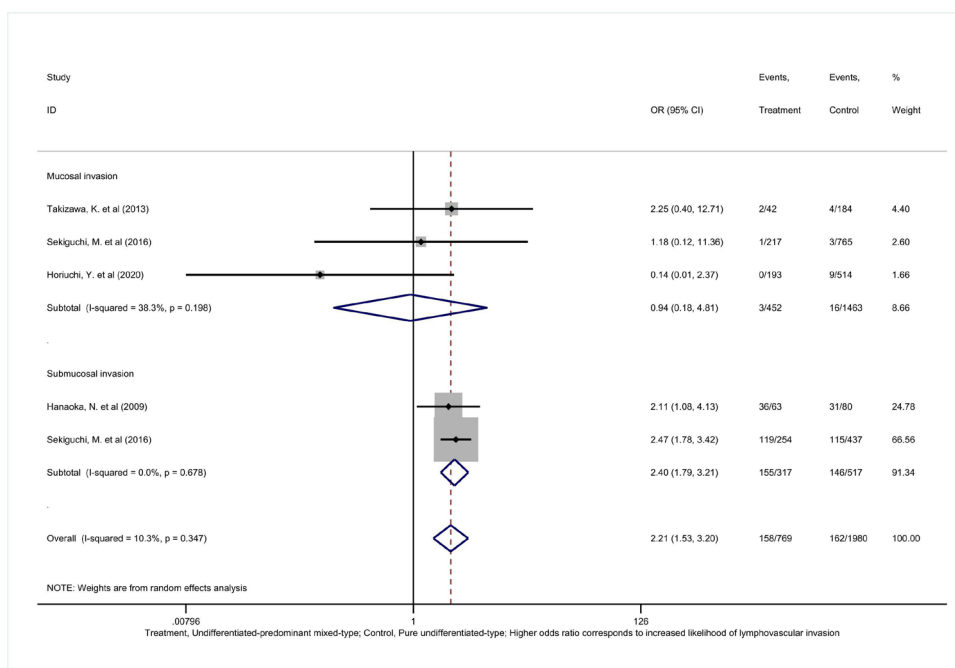
Figure 5 Forest plots showing ORs with 95% CIs comparing undifferentiated-predominant mixed-type with pure undifferentiated-type early gastric cancer for the risk of lymphovascular invasion. Subgroup analysis was based on region.

Sensitivity analysis and publication bias

To assess publication bias of the included studies, Begg's and Egger's tests were performed. There was no evidence of publication bias in our meta-analysis for risk of LNM (Begg's test: p=0.755; Egger's test: p=0.708; figure 8), or submucosal invasion (Begg's test: p=0.806; Egger's test: p=0.813). Therefore, it can be suggested that the publication bias for the included studies was relatively small. Furthermore, the

results of our meta-analysis may represent real differences in the biological behaviour between MU and PU EGC.

A sensitivity analysis was also performed by removing one study at one time. The results concerning LNM and submucosal invasion risk were not reversed with the sequential removal of each study. Therefore, it can be concluded that MU EGC is associated with a higher risk of LNM and submucosal invasion as compared with PU EGC.

Figure 6 Forest plots showing ORs with 95% CIs comparing undifferentiated-predominant mixed-type with pure undifferentiated-type early gastric cancer for the risk of lymphovascular invasion. Subgroup analysis was based on mucosal/submucosal invasion.
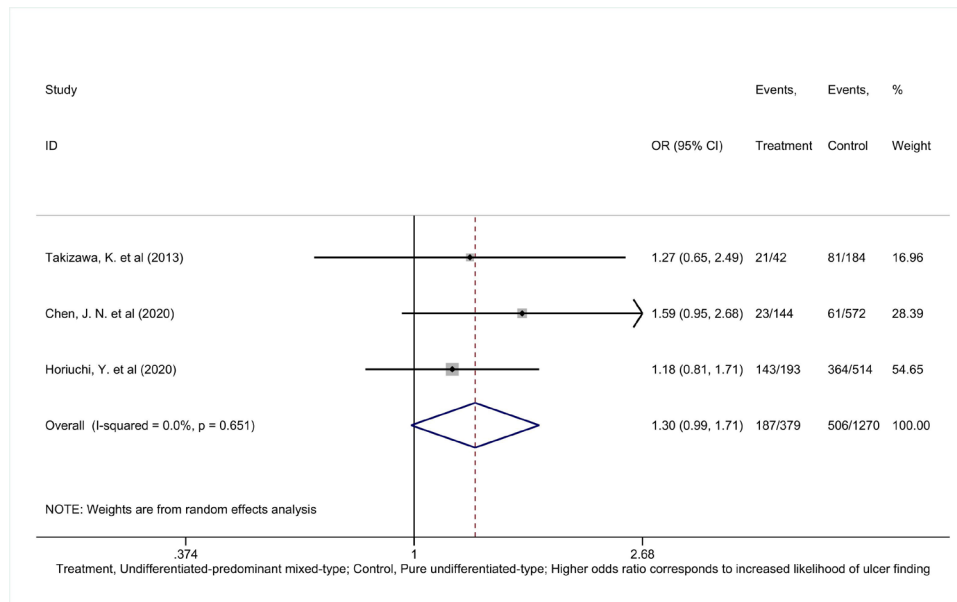
Figure 7 Forest plots showing ORs with 95% CIs comparing undifferentiated-predominant mixed-type with pure undifferentiated-type early gastric cancer for the risk of ulcer findings.

DISCUSSION

This meta-analysis confirmed that MU and PU EGC display different biological behaviours. Patients with MU EGC had a significantly higher risk of LNM and submucosal invasion compared with patients with PU EGC. Regarding lympho-vascular invasion, no statistically significant difference was found between patients with PU and MU EGC. However, MU EGC was found to have an increased risk when compared with PU EGC only in studies involving patients with submucosal invasion. Consequently, more attention should be given to patients with MU EGC for clinical management of the disease. Careful assessment is essential for patients with MU EGC before they undergo a treatment procedure.

The biological mechanism whereby MU is more aggressive than PU EGC is inconclusive, but previous studies can provide insight and propose areas of research to be investigated. From the viewpoint of molecular pathology, the genomic instability

Figure 8 Funnel plot comparing undifferentiated-predominant mixed-type with pure undifferentiated-type early gastric cancer for the risk of lymph node metastasis.

subtype of GC has been shown to be associated with different histological types: the chromosomal instability subtype of GC was significantly associated with increased histological numbers and mixed-type GC, whereas the genomic stability subtype of GC showed a significant relationship with pure-type GC.[24] From the viewpoint of epigenetics, it has been reported that the elevated methylation levels of CpG islands, which inhibit the expression of tumour suppressor genes, may promote the development of mixed-type GC over diffuse-type or intestinal-type GC.[25] Taken together, genomic instability, the expression level of related genes, and elevated methylation levels of CpG islands might contribute to the more aggressive behaviour of MU compared with PU-type EGC. Although the exact mechanisms remain unknown, additional articles exploring the mechanism of this aggressive biological behaviour of MU EGC would provide valuable insight in the future.

Previous studies have reported the biological behaviours and clinicopathological features that differ between PU and MU EGC, but controversies remain. This meta-analysis brings together all the available information to draw a more substantial conclusion. However, the present study has several limitations. First, all included studies were carried out in Asia. Consequently, extending these results beyond Asia may be inaccurate and require further study with data from different races and regions. Second, all studies were retrospective. Therefore, there might be some selection bias that cannot be completely excluded. Third, the number of studies included in this meta-analysis was limited, and the total number of patients included was relatively small. As a result, the statistical effectiveness of the meta-analysis is somewhat low. Nevertheless, despite these limitations, this is the first meta-analysis to compare the biological behaviour between MU and PU EGC. Additional large-scale, multicenter studies are expected to validate these results.
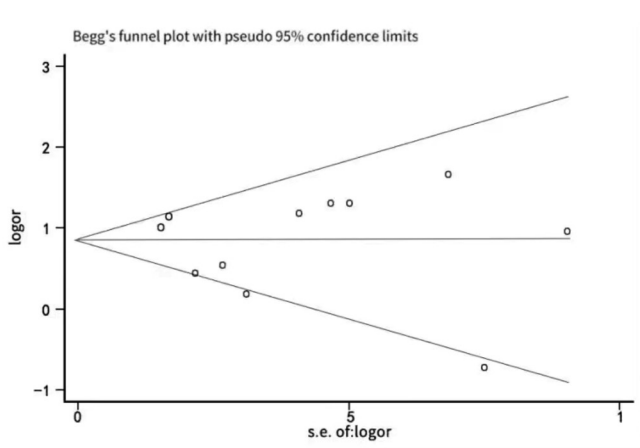
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CONCLUSIONS

In conclusion, this study identified that patients with MU EGC had an increased risk of LNM and submucosal invasion compared with patients with PU EGC. With respect to lymphovascular invasion, no difference was found between PU and MU EGC in the mucosal subgroup. However, MU EGC was found to have an increased risk when compared with PU EGC only in studies involving patients with submucosal invasion. Hence, we suggest that the lymph node dissection in patients with EGC with PU may be appropriately reduced and the lymphadenectomy in patients with EGC with MU may be appropriately raised. In future clinical practice, extra effort should be dedicated to further substantiate the outcomes of the present study. These results will help doctors to select the appropriate clinical management and therapy options for patients with MU EGC to improve their outcomes.

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