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Evaluations of Biomarkers CDX1 and CDX2 in Gastric Cancer Prognosis: A Meta-analysis

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ABSTRACT

CDX1 and CDX2 are homeobox-type transcription factors that are potential biomarkers and are associated with prognostic significance in intestinal-type gastric cancer early disease before lymph node metastasis is associated with better prognosis. In addition, the genes IDH 1 and IDH 2 previously known to be involved in brain cancer are implicated in cancer-related molecular signatures as a result new targeted personalized therapies may be possible. Our retrospective study determined the correlation between CDX markers and clinicopathologic data including survival in patients with gastric cancer. This study included studies from 1997 to December 2022 a meta-analysis to provide odds ratios (ORs) and relative risks (RRs). We discussed in detail the impact of IDH 1/2 on the prognosis of gastric cancer outcomes and potential therapeutic strategies. Our meta-analysis included 20 studies identifying 11,163 patients with gastric cancer. We found that CDX 1 overexpression was associated with better overall survival (pooled HR: 1.28) and CDX 2 expression and better 3-year survival (pooled HR: 1.64) and 5-year survival was the pooled HR was correlated 1 94 with both showing statistical correlation. Evidence suggests that IDH 1/2 mutations and CDX 1/2 overexpression are closely associated with metabolic abnormalities epigenetic changes and mutations evidence suggests the potential for novel targeted therapies in gastric cancer. CDX 1/2 overexpression is associated with a favorable prognosis in gastric cancer cases. Further studies are needed to explore the clinical significance of IDH 1/2 mutations and CDX 1/2 expression.

Keywords: Gastric cancer, CDX2, CDX1, IDH1, IDH2 prognosis, biomarker, stomach cancer

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Introduction

About 10,880 died of gastric cancer (6,490 men and 4,390 women) according to the American Cancer Society's 2024 for stomach cancer in the United States. 1.5% of all new cancers diagnosed annually in the United States are gastric cancer. 26,890 new cases of gastric cancer (16,160 in men and 10,730 in women) were estimated (1). Based on data from 2017–2019, about 0.8 percent of men and women will be newly diagnosed with stomach cancer in their lifespan (2). The need for early diagnosis and informed therapy is critical, with a focus on innovative biomarkers. For instance, patients without distant nodal metastasis generally have a favorable prognosis (3), highlighting the early diagnosis importance. The caudal-related homeobox gene family's CDX1 and CDX2 are important players in the initiation and spread of stomach cancer (4,5). These elements might be employed as biomarkers since they are required for developing intestinal epithelial cells and because there is evidence connecting their expression to stomach cancer. While CDX2 expression is associated with better differentiation and reduced lymph node metastases (6,7,8), conflicting findings exist regarding its correlation with cancer spread to lymph nodes (5). IDH1, previously identified in brain cancer, is now highlighted in stomach cancer research (8). It plays a key role in the metabolic composition of the disease, suggesting potential targeted therapy options. While direct IDH1 mutations are rare in stomach neoplasms, their malfunction can significantly impact cancer behavior and patient survival (9). IDH2's role supports the importance of these enzymes in cancer development (10). This meta-analysis investigates the relation between CDX expression and gastric cancer's clinicopathological aspects, as well as 3-year and 5-year survival rates. It also assesses the predictive validity of CDX1 and CDX2 in gastric cancer and reviews treatment strategies based on CDX signatures and IDH1 as a prognostic biomarker and new targeted therapy. Our project is one of the biggest meta-analyses revealing a correlation between the expressions of CDX1/2 and IDH 1/2 signatures with the prognosis of stomach cancer.

Materials and methods

Aim and literature Search strategy

The main objective of this study is to compare the correlation of the expression of CDX (caudal-type homeobox) signature and the clinicopathological features of gastric cancer, as well as 3-year and 5-year overall survival rates, adhering to the PRISMA guidelines (11) and the MOOSE checklist (12) while performing the systematic review and meta-analysis of observational studies that evaluate the association of prognostic factors with the overall survival of Gastric Cancer. An advanced literature search was conducted using PubMed, MEDLINE, Cochrane, and EMBASE from the earliest possible date to May 1st, 2023. Included in the search phrases were ((("CDX2"(All Fields) AND ("stomach neoplasms"(MeSH Terms) OR ("stomach"(All Fields) AND "neoplasms"(All Fields)) OR "stomach neoplasms"(All Fields) OR ("gastric" (All Fields) AND "cancer"(All Fields)) OR "gastric cancer"(All Fields))) OR ("stomach neoplasms"(MeSH Terms) OR ("stomach"(All Fields) AND "neoplasms"(All Fields)) OR "stomach neoplasms"(All Fields) OR ("stomach"(All Fields) AND "cancer"(All Fields)) OR "stomach cancer"(All Fields)) OR ("adenocarcinoma" (MeSH Terms) OR "adenocarcinoma"(All Fields) OR "adenocarcinomas"(All Fields) OR "adenocarcinoma s"(All Fields))) AND ("prognosis"(MeSH Terms) OR "prognosis"(All Fields) OR "prognoses"(All Fields)) AND (("intestinalization"(All Fields) OR "intestinalized"(All Fields) OR

"intestinally"(All Fields) OR "intestinals"(All Fields) OR "intestine s"(All Fields) OR "intestines"(MeSH Terms) OR "intestines"(All Fields) OR "intestinal"(All Fields) OR "intestine"(All Fields)) AND "type"(All Fields)) AND ("biomarker s"(All Fields) OR "biomarkers"(MeSH Terms) OR "biomarkers"(All Fields) OR "biomarker"(All Fields)). A flow diagram of the search and study selection process is described in Figure 1.

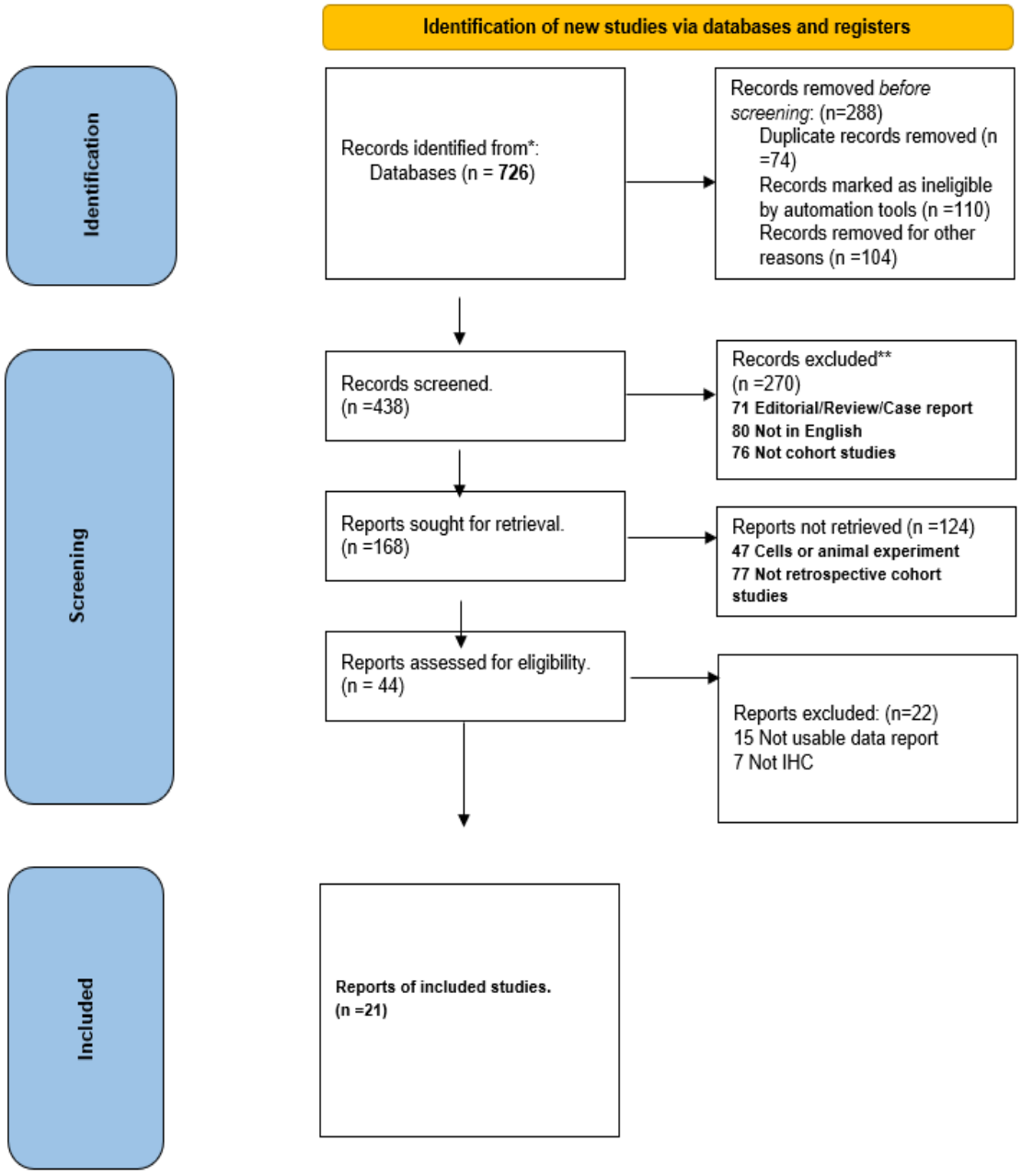

Fig. 1. PRISMA Flow diagram for our meta-analysis.

Inclusion and Exclusion Criteria

The selection criteria were in line with the inclusion and exclusion criteria used in selecting studies. In our meta-analysis, studies were included if they assessed the relationship between CDX 1/2 overexpression and the clinicopathological characteristics of gastric cancer or 3-year and 5-year overall survival rates. Exclusion criteria included papers that were abstracted only and studies of non-human subjects, and duplicate priority was given to research involving the largest sample sizes.

Data Acquisition and Quality Assessment

We started our search with a list of titles; subsequently, reviewers Khayyat A., Esmaeil Pour M.A., Zohouri S.A., and Pourcina O. The first author's surname, sample size, clinical pathological criteria, and results of the study reviewed the data for each publication in a different way. We critically evaluated each study according to strict publication methodology and controls to ensure the robustness of our meta-analysis. There was disagreement between Khayyat A and Zohouri S A regarding study selection or data extraction. Final decisions were made by two independent reviewers, Esmaeil Pour M.A. and Poursina O, based on their research, expertise, and judgment, ensuring the accuracy and reliability of the meta-analysis process.

Statistical analysis

The review data was analyzed by the Review Manager software v5.4.1. The statistical significance was derived from the pooled Hazard Ratio, RR, or OR at $P<0.05$ with a 95% Confidence Interval. Levels of heterogeneity were classified as low for I2 at 25%, medium at 50%, and high at 75%. To detect publication bias, a funnel plot was performed, and it considered the outlier studies as likely to impact heterogeneity.

Model Choice

The statistical models for our meta-analysis were tailored to the study objectives and the characteristics of the included publications. Model selection involved assessing factors such as heterogeneity levels, sample size, and study design to ensure accurate statistical inference.

Results

Eligible studies

According to the PRISMA diagram (Figure 1), our initial search yielded 762 studies. Using the inclusion and exclusion criteria, 21 studies [13-34] involving 11,163 patients with gastric cancer were included in this analysis. (Table 1a and 1b) Of these, six studies revealed the connection between CDX2 expression and 5-year survival rates, while seven studies did so for 3-year survival rates. Additionally, two studies demonstrated the link between CDX1 positivity and 3-year survival.

CDX1 & CDX2 positivity and 3-year survival

Our results for the linkage of CDX2 overexpression and 3- and 5-year survival rates were generated by combined studies using fixed and random effect models and hazard ratio (HR). From 21 studies, we utilized 2 studies showing a relationship between CDX1 overexpression and 3-year survival, but no positive link between CDX1 overexpression and overall survival of gastric cancer cases (pooled HR: 1.28; 95% Confidence Interval (CI): 0.41-4.05; p=0.67) with no heterogeneity (I2=0%, p = 0.83) was found (Figure 2). Furthermore, we analyzed the association between CDX2 overexpression and 3-year survival by adding 7 out of the 21 papers in our analysis. We found a positive association between CDX2

overexpression and poor survival (pooled HR: 1.64; 95% CI: 1.06-2.55; p=0.03), with no heterogeneity (I2=0%, p = 1.00) (Figure 3).

Table 1a. Information of included studies with/ without CDX1 or CDX2 expression.

Author/ Year	Case no. (CDX1 or 2 +/-)	Age means (y) or % (Age range)	CDX2+(M/F) */ CDX2- (M/F) *	CDX1 expression (mean)Recurrence/ Control	M/F *
Bai [13]	127 (36/91)	-	-		-
Bai [14]	228 (129/99)	60.72	-		170/58
Camilo [15]	201 (88/113)	63.2	49/39 / 75/38		124/77
Jian-ze [16]	67 (30/37)	61	23/7 / 26/11		49/18
Fan [17]	109 (40/69)	59	33/7 / 42/27		75/34
Ge [18]	166 (116/50)	-	-	-	-
Halder [19]	51 (27/24)	52.1	-	-	19/31
Kim [20]	259 (150/109)	57.8	114/36 / 61/48	-	175/84
Mizoshita [21]	177 (89/88)	63.2	-	-	105/72
Qin [22]	85(41/44)	61.7	30/11 / 30/14	-	60/25
Roessler [23]	190 (109/81)	61.1	57/52 / 33/48	-	90/100
Sardar [24]	80 (34/46)	80.0% (>50 YO$^{\$}$)	19/15 / 25/21	-	44/36
Schildberg [25]	79 (27/52)	-	-	-	-
Seno [26]	40(18/22)	61	-	-	26/14
Zhang [27]	109 (57/52)	62.4	-	-	63/46 (42.20)
Zhou [28]	130 (49/81)	52	40/9/49/32	-	89/41
Chen [29]	619 (406/213)	56.2% (<60 YO$^{\$}$)	252/154/169/44	-	421/198
Total Number	2587				

Table 1b. Information of included studies with/ without CDX1 or CDX2 expression cancer with EBV-negative and MMR-p groups.

Author/year	Total case no. CDX1/ CDX2	*Case no. (CDX1 +/- or CDX2 +/-)	Mean age (CDX1+/- ///CDX2+/-)	Male/Female (CDX1///CDX2)	Mean CDX1 expression with extra gastric recurrence/ control	Disease-free survival, mo. (CDX1(+/-) /// CDX2(+/-)) Or overall survival
Kim [30]	938/1027	CDX1:404/ 752 CDX2: 523/752	CDX1+/-: 57.3/57.1/// CDX2+/-: 56.6/56.9	618/320 /// 672/355	-	77.1±58.8/68.6±57.4///73.9 ±57.9/69.9±58.7
Nakayama [31]	**CDX1: 29/201 **CDX2: 55 / 175	***CDX1:295/581 ***CDX2:422/454	-	-	-	Higher overall survival in CDX1+/- CDX2 positive gastric cancers CDX1: p=0.218, CDX2: P=0.118
Samadani [32]	29/37	-	-	23/7	-	CDX1: 70% of samples showing decreased expression (P= 0.005) CDX2: 70% of samples showing increased expression (P = 0.004)
Min Kim [33]	1854	CDX1:16/32	60.2 ± 11.8	1227 /627	−2.4 ± 1.8/ −2.6 ± 2.0	-
Cases	4345	4231				
Total no.	8576					

** By using TCGA

*** By using the Kaplan-Meier plotter

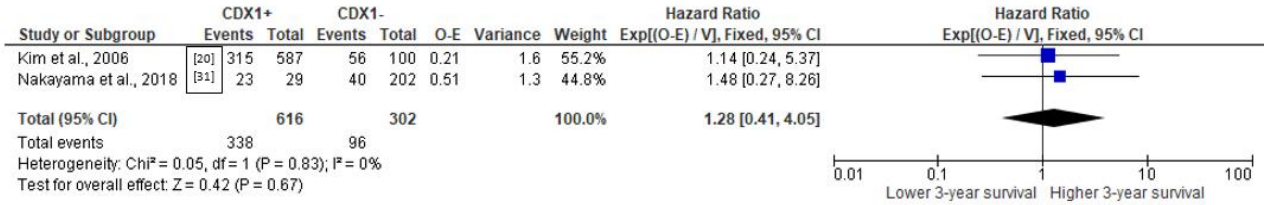

Fig. 2. 3-year survival of gastric tumors and *CDX1* expression.

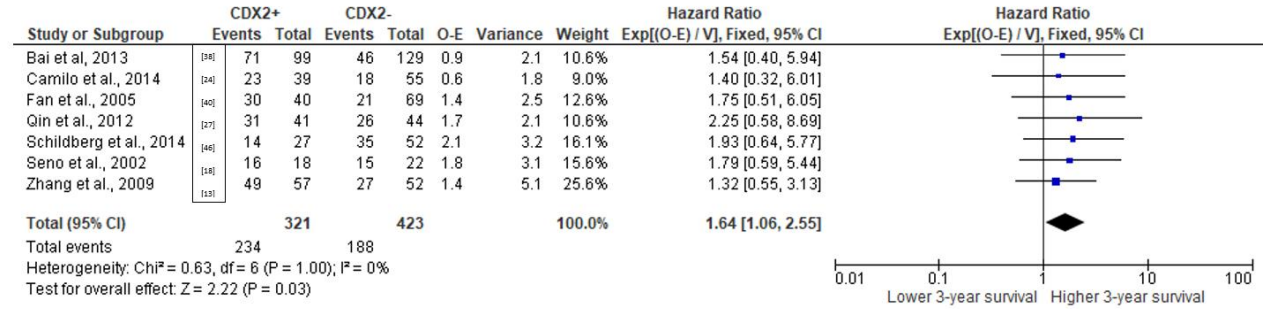

Fig. 3. 3-year survival of gastric tumors and *CDX2* expression.

5-year survival and CDX2 positivity

Nine of 21 studies analyzed the association between CDX2 overexpression and 5-year survival. Results showed a significant association between CDX2 overexpression and poor survival (pooled HR: 1.94; 95% CI: 1.35-2.80; p = 0.0004), with no heterogeneity detected (I2=0%, 0004) p = 1.00) (Figure 4).

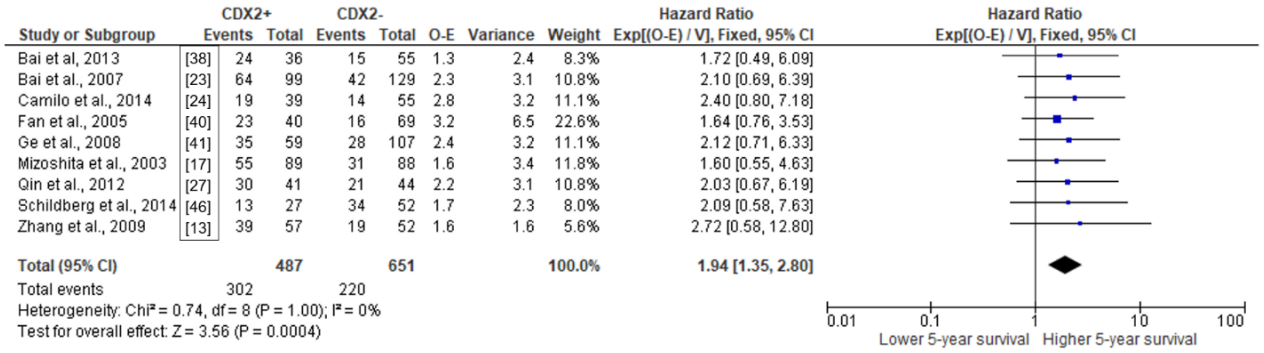

Fig. 4. 5-year survival of gastric carcinoma and *CDX2* expression.

CDX2 positivity and Lymph node metastasis of gastric carcinoma

Of the 21 studies, 6 studied (17, 20, 22, 23, 27, 34) the association between CDX2 overexpression in gastric cancer and lymph node metastasis. The findings showed a significant association between CDX2 overexpression in gastric cancer and lymph node metastasis, associated with adverse survival outcomes (RR: 1.52; 95% CI: 1.29-1.79; p = 0. 30, I2= 18%) (Figure 5).

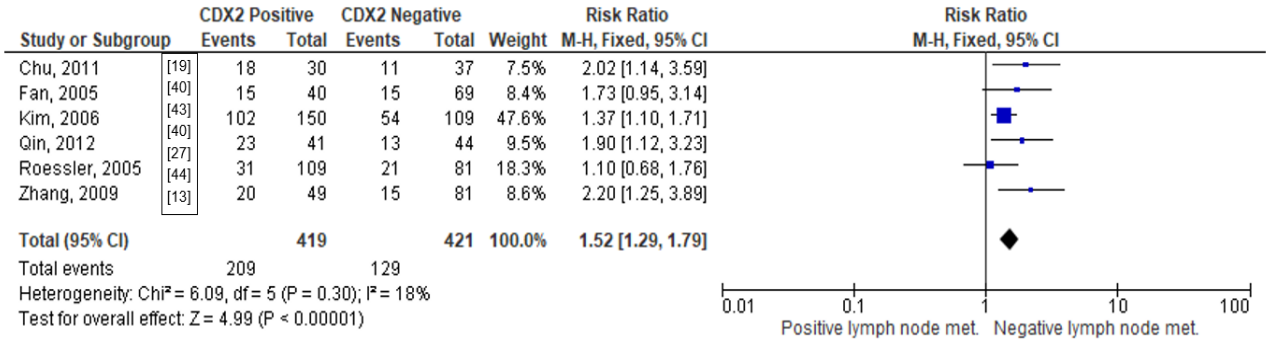

Fig. 5. Lymph node metastasis of gastric carcinoma and *CDX2* expression.

CDX2 positivity and differentiation of gastric carcinoma

Of the 21 studies, 4 investigated (17, 22, 27, 34) the association between CDX2 overexpression and gastric cancer differentiation. The findings showed that the difference between CDX2 overexpression and gastric cancer was associated with CDX2 overexpression (RR: 1.52; 95% CI: 1.22-1.87; p=0.0001), with a difference observed it is 46% (I2=46%, p = 0.14) (Figure 6).

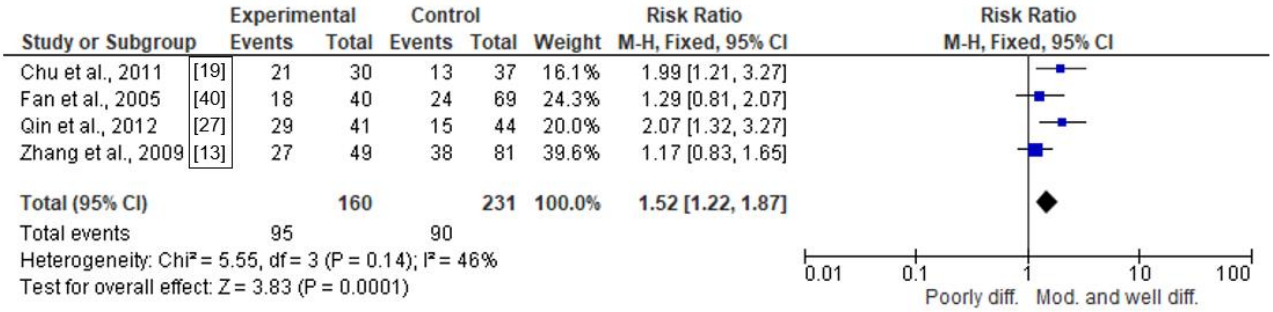

Fig. 6. Differentiation of gastric carcinoma and *CDX2* expression.

In the sensitivity analysis, after removing the outlier analysis by Zhang *et al*, we found RR: 1.74; 95%CI: 1.32–2.28; p <0.0001), with 0% detected abnormalities (I2=16%, p =0.30) (Figure 7).

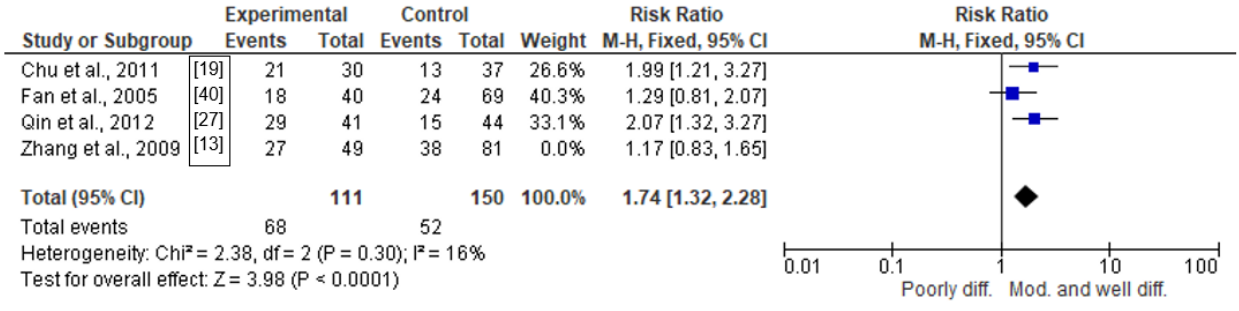

Fig. 7. Differentiation of gastric carcinoma and *CDX2* expression after removing outlier studies (sensitivity analysis).

CDX2 positivity and the size of gastric carcinoma:

Of the 21 studies, 3 (17, 20, 27) investigated the association between CDX2 overexpression and gastric cancer size. Analysis showed that CDX2 overexpression and large gastric cancer were not statistically significantly associated with CDX2 overexpression (RR: 1.02; 95% CI: 0.83-1.27; p=0.84), with 12% detected; heterogeneity (I2=12%, p = 0.32) (Figure 8).

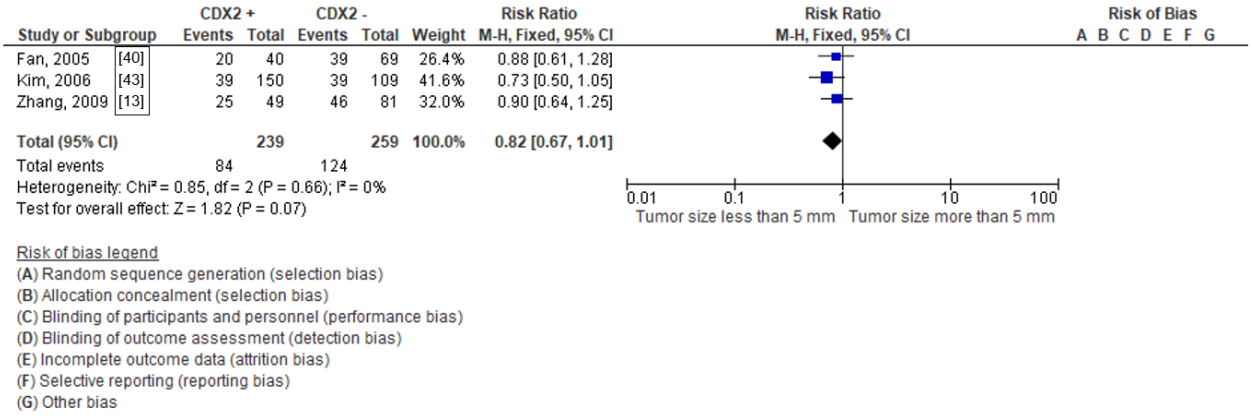

Fig. 8. The size of gastric carcinoma and *CDX2* expression.

CDX2 overexpression and gender (male/female) association:

Twelve out of the 21 studies (14-18, 20, 22-24, 27-29, 34) examined the association between CDX2 overexpression and sex (male/female). The analysis showed that CDX2 overexpression and sex (male/female) were not statistically associated with tumor CDX2 overexpression (OR: 0.96; 95% CI: 0.81-1.15; p=0.69), with 86 findings % heterogeneity (I2=86%, p < 0.00001) (Figure 9).

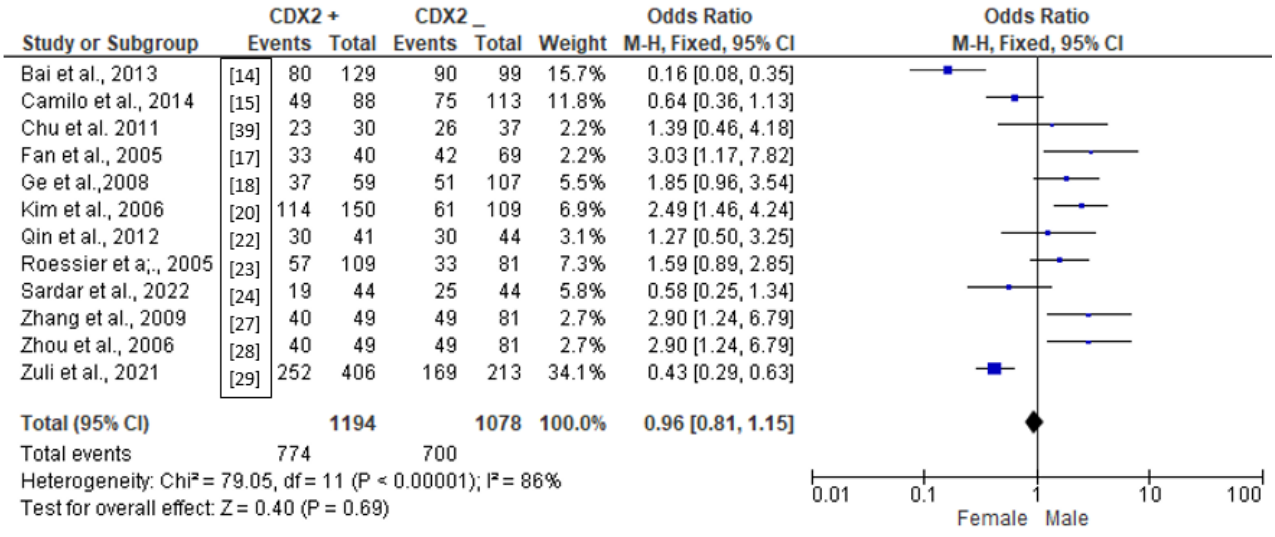

Fig. 9. Gender (male/female) and CDX2 overexpression in gastric carcinoma.

In the sensitivity analysis, after removing six external studies (13-18). A pool HR: 1.84; 95%CI: 1.36-2.49; p <0.0001), with 0% detected abnormalities (I2=0%, p =0.68) (Figure 10).

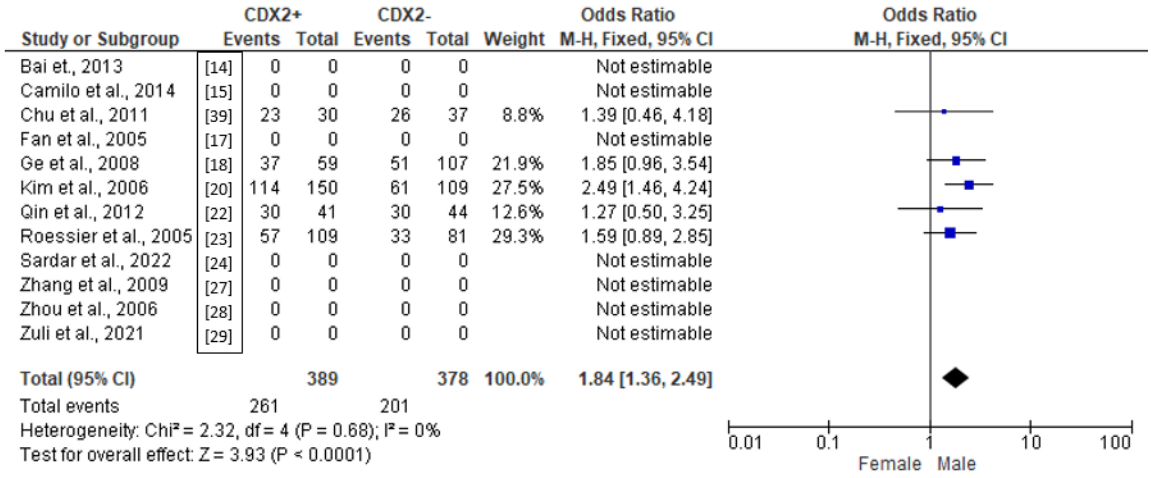

Fig. 10. Gender (male/female) and *CDX2* overexpression in gastric carcinoma after removing outlier studies (sensitivity analysis).

Correlation of CDX1 overexpression with clinicopathological parameters, survival, and recurrence

We assessed the data and the result of retrospective literature (30, 31, 34) with 4345 cases. Our finding and analysis revealed that CDX1 overexpression is not significantly linked to survival (pooled Hazard Ratio (HR): 1.28; 95% Confidence Interval (CI): 0.41-4.05; p=0.67), and there was no heterogeneity observed (I2=0%, p = 0.83). Our findings indicate that CDX1 positivity does not significantly impact survival with no observed heterogeneity. Notably, a large observational study by Kim et al. involving 1158 gastric cancer patients revealed higher CDX1 expression in males compared to females (618/320), with no substantial difference in mean age between CDX1-positive and CDX1-negative patients (57.3 vs. 57.1 years, respectively). Additionally, Nakayama et al., using the cBIOPORTAL database, reported higher overall survival in gastric cancer cases expressing CDX1 (p=0.0013). Furthermore, Samadani *et al*. observed that 70% of tumoral tissues exhibited decreased CDX1 expression compared to non-tumoral tissues (p= 0.005). Finally, Kim *et al*. found that the mean expression of CDX1 in extra-gastric recurrence of gastric tumors was significantly lower than in the control group with no recurrence (-4.6 ± 2.0 vs. -2.4 ± 1.8, respectively; p = 0.025) in a retrospective observational study.

Correlation of CDX2 with clinicopathological parameters

CDX2 expression was inversely associated with lymph node metastasis (high CDX2 expression was associated with decreased lymph node metastasis (RR=1.52, 95% CI: 1.29-1.79, P<0.00001) (Figure 5) however, CDX2 expression was significantly higher in poorly differentiated gastric cancers (RR=1.52, 1.52; and significantly higher in well-differentiated and latent gastric cancers marginal significance compared with 95% CI: 1.22-1.87, P<0.00001) (Figure 6) was observed (RR =0.82, 95%).CI =0.67-1.01, P=0.07) (Figure 8). However, CDX2 expression in gastric cancer does not show a statistically significant relationship with sex (gender)) (OR= 0.96, 95% CI: 0.81- 1.15, P=0.69) (Fig Seven external studies were removed for sex and CDX2 with 9 gastric cancers and male sex without heterogeneity (I2=0%) (OR= 1.84, 95% CI: 1.36-2.49, P<0.0001) (Figure 10).

Impact of CDX2 on the survival rate of patients with gastric cancer

It was possible to achieve quantitative aggregation of survival outcomes from previous research data on CDX2 and its role in 5-year survival rates. Using the above methodology, the risk ratio from nine studies involving 1,059 participants was calculated. The CDX2-overexpression status was associated significantly with a higher 5-year survival rate (RR = 1.95; 95% CI: 1.70-2.23; P < 0.00001) and showed no heterogeneity (Figure 10). We investigated the possibility of publication bias using the inverted funnel plot method described for meta-analyses. We constructed funnel plots for all comparisons and visually estimated their asymmetry. The shapes of the funnel plots showed a low chance of publication bias. A few outlier studies increased heterogeneity (I2); removing these outliers decreased the heterogeneity.

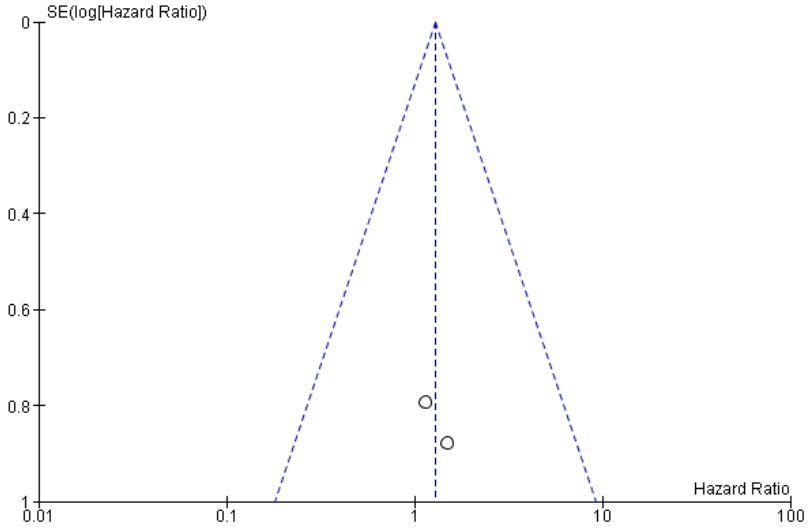

Fig. 11-1. The 3-year survival of gastric tumors and CDX1 expression funnel plot.

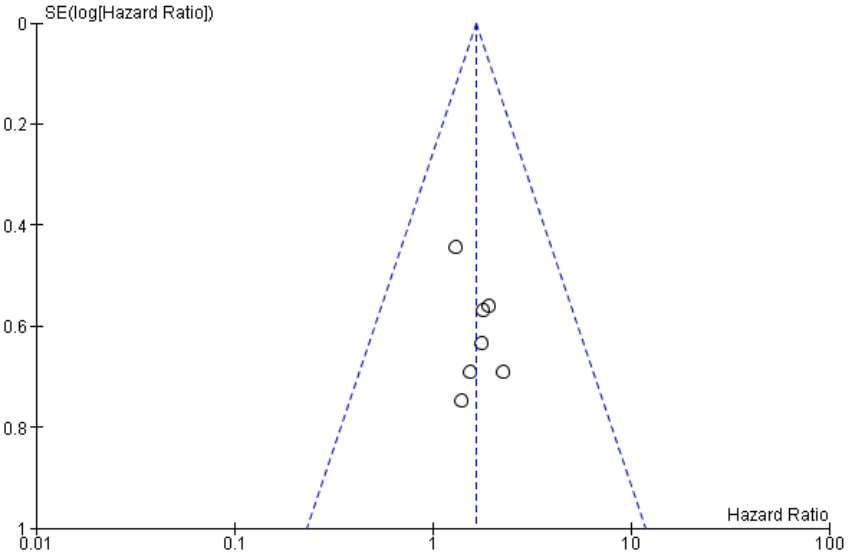

Fig. 11-2. The 3-year survival of gastric tumors and CDX2 expression funnel plot.

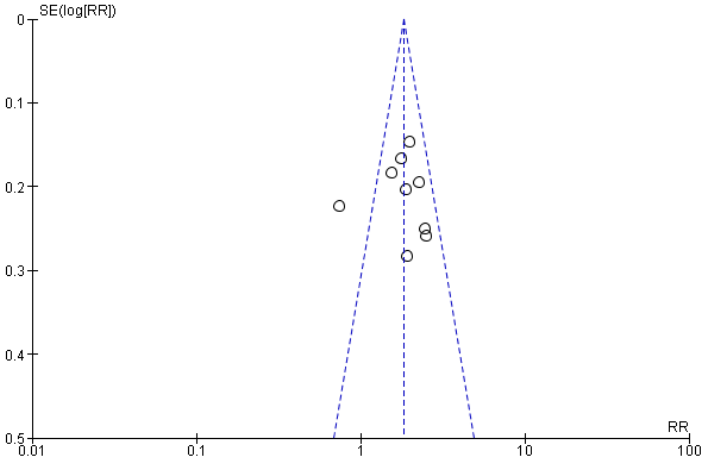

Fig. 11-3. The 5-year survival of gastric carcinoma and CDX2 expression funnel plot.

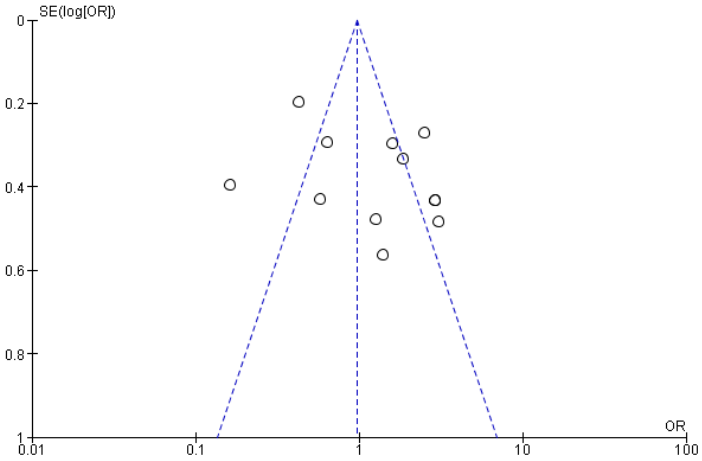

Fig. 11-4. Male-to-female and CDX2 expression in gastric carcinoma funnel plot.

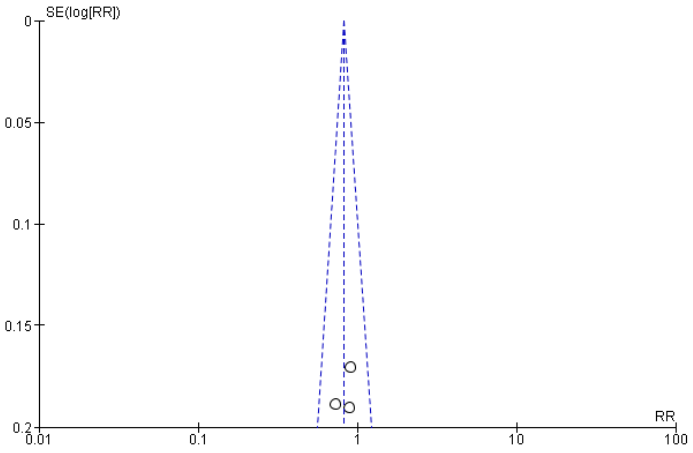

Fig. 11-5. Tumor size and CDX2 expression in gastric cancer funnel plot.

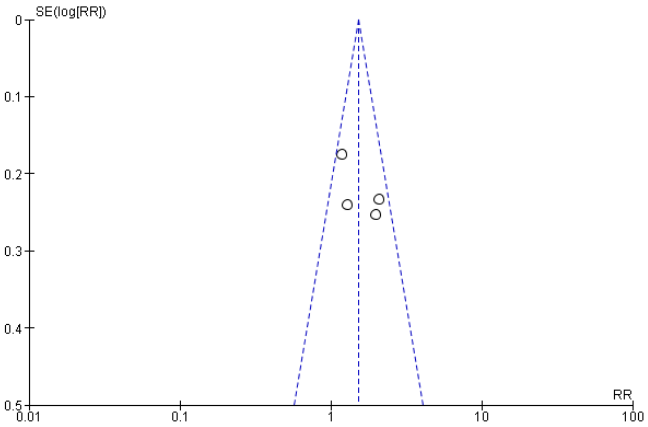

Fig. 11-6. Differentiation of gastric cancer and CDX2 expression funnel plot.

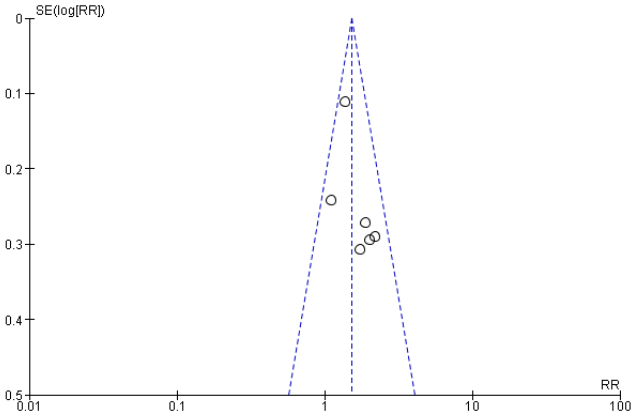

Fig 11-7. Lymph node metastasis of gastric cancer and CDX2 expression funnel plot.

Discussion

Gastric cancer forms a significant proportion of malignant causes of death worldwide and calls for continuous research in diagnostics and therapeutics. Biomarkers are vital in the early detection and management of gastric cancer, opening avenues for individualized treatment approaches. Among biomarkers, CDX1 and CDX2 are important, based on their role in the development and progression of gastric tumors. Evaluating CDX1 and CDX2 in gastric cancer has provided essential prognostic insights. These biomarkers, caudal-related homologues discovered in Drosophila, are known for regulating cell growth and differentiation in the intestinal lining, have been implicated in the development of intestinal metaplasia, and are considered risk factors for stomach cancer (1, 27, 35)

Even among patients with the same stage, the stomach cancer prognosis is not equal, it shows the importance of discovering reliable biomarkers like CDX1 and CDX2 (21, 26-28,35,36). Our study aimed to explore the association between CDX1 and CDX2 overexpression and various clinicopathological parameters in gastric carcinoma patients. We compared our results with those of several pertinent references to offer a comprehensive analysis of the topic.

Our meta-analysis analyzed 21 studies of 11,293 patients focused on Results showed that high CDX2 expression is associated with poor 3-year survival, as shown in the estimates on HR: 1.64; CI: 1.06-2.55; p=0.03 and 5-year survival, as shown in the estimates for HR: 1.94; CI: 1.35-2.80; p=0.0004. These results were in line with the findings of Xie *et al*. (4)

On the other hand, CDX1 was not related to the survival rates with a statistically insignificant value for HR: 1.28; CI: 0.41-4.05; p=0.67. This result is in agreement with a previous study by Kim *et al*., which found that variable expression relates to patient demographics and characteristics of the tumor without finding a statistically significant association, but what they concluded was that variable expression relates to a context dependency variable and could vary according to other molecular or environmental factors. Cho *et al*. highlighted the potential prognostic value of CDX1 mainly in subtypes of gastric cancer, stressing that the context dependency of CDX1 expression is a contextual variable, which might be variable according to other factors (20). Our analysis of overall survival aligned with the nationwide study by Nakayama *et al*., indicating a higher overall survival in gastric cancer cases expressing CDX1 (31).

Highlighting the strong role of these biomarkers in gastric cancer prognosis, these changes suggest that multiple factors, including sex and tumor stage, should be considered in these markers in the sense of translation.

Our finding concerned the association between CDX2 and lymph node metastasis. CDX2 overexpression showed a significant association with lymph node metastasis and tumor differentiation status in our study, which is in line with the results of Okayama et al. and Seno *et al*. (5,26). However, our findings differ from those of Samadani *et al*., who reported decreased CDX1 expression in tumoral tissues (32). These findings highlight the prognostic utility of CDX2 in distinguishing between differentiated and undifferentiated tumors, as noted by Hirasawa *et al*. (37).

Despite no significant correlation we found between CDX2 expression and tumor size or gender, studies like those by Bai *et al*. and Camilo *et al*. have suggested a broader association with clinicopathological features including tumor recurrence and gender differences (27, 28).

It is noted that the expression of CDX1 and CDX2 is also closely tied to the intestinal phenotype of gastric tumors, with significant implications for gastric cancer outcomes (27, 38). The clinical significance of CDX2 in gastric carcinoma has been explored by Zhou *et al*. (2006) and Qin *et al*. (2012), reinforcing its potential as a marker for tumor differentiation and progression (22, 28). Cho (2011) also emphasized the prognostic value of these biomarkers in tumor biology, aiding the development of more efficient therapies (39).

The predictive potential of CDX1 for gastric tumor recurrence has necessitated targeted therapeutic approaches, including those that use CDX1 inhibitors. This is based on the fact that the disruption of CDX1-related pathways may impede metastasis, and thus prove beneficial in increasing life chances for patients (30). In addition, the occurrence of conventional chemotherapy resistance, a common feature of gastric cancer, has initiated studies on alternative approaches based on chemotherapy resistance in subpopulations and gastric cancer stem cells (40, 41). In that regard, the inclusion of CDX1 inhibitors in the treatment schemes may have a very effective impact on patients with high CDX1 expression or who have developed resistance to conventional treatments.

Additionally, the potential of CDX2 as a tumor suppressor underscores its role in tumor differentiation and survival (4). A study also highlighted the predictive value of these biomarkers in tumor biology, which aids the development of more effective therapies (39). However, the variability in study findings necessitates cautious interpretation, as emphasized by some research (34, 42). The meta-analysis's statistical significance is notable, providing a solid foundation for considering these biomarkers as therapeutic targets for future gastric cancer treatments (43).

Given the significant impact of stomach cancer, a comprehensive review of management may prove useful, including cases with recurrence and resistance to drugs. Therapeutic efficacy could be enhanced by combining CDX1 inhibitors with current chemotherapy regimens, particularly for cases exhibiting high CDX1 expression. While CDX1 inhibitors show promising utility, numerous challenges remain. Further research is essential to confirm the efficacy and specificity of these inhibitors. It is also crucial to explore how CDX1 expression interacts with other molecular pathways in gastric cancer, such as the Hedgehog pathway (29). To be able to evaluate the efficacy as well as the side effects of CDX1 inhibitors for the management of gastric cancer, future research needs to examine comprehensive molecular analysis and experiments (40). The accumulation of findings from multiple studies suggests that targeting CDX1 could be a valuable therapeutic strategy, especially in scenarios where resistance to chemotherapy and recurrence are likely. Integrating this approach into existing treatment protocols could significantly improve patient outcomes. To fully comprehend and use CDX1 inhibitors in gastric cancer therapy, however, more investigation and research are warranted.

The assessment of publication bias using inverted funnel plots indicated a low possibility of bias in our meta-analysis, consistent with previous studies (11). Sensitivity analysis, where outlier studies were removed, led to more consistent results and reduced heterogeneity, as observed in previous meta-analyses (7, 13, 36).

IDH1/2 as two biomarkers of gastric cancer

IDH1 and IDH2 mutations have emerged as significant biomarkers in gastric cancer, shedding light on the molecular landscape of this disease. As we advance the literature search, the potential of IDH1-based therapeutic medications also emerges, further improving our arsenal in this challenging disease. Recent reports have significantly extended our learning of the roles of IDH1 (Isocitrate Dehydrogenase 1) and IDH2 in gastric cancer, revealing their role as new therapies (9). Schulten *et al*. provided a pan-cancer review that highlights gastric cancer, emphasizing the prevalence of IDH1/2 mutations in multiple cancer types, which is crucial for future novel therapies. Another data showed how curcumin inhibits cancer cell growth by affecting IDH1 activity, specifically in cancer of stomach MGC-803 cells (44). Research conducted in 2022 conducted a meta-analysis of whole-genome gene expression datasets, examining the molecular changes due to IDH1/2 mutations and laying the framework for targeted medications (45). Xu *et al*. identified wild-type IDH1 as a critical metabolic node, with the HNF4α pathway playing a main role in gastric cancers (8). This discovery underscores the central role of novel targets in gastric cancer treatment, including concerning metabolic dysregulations facilitated by IDH1. These data collectively reveal the intricate link between IDH1 and IDH2 mutations, metabolic changes, and epigenetic mechanisms in gastric tumors, paving the path for

further study to clarify their role in managing this cancer. This information could help with more personalized targeted therapies in the future.

In a comprehensive pan-cancer analysis, the prevalence of IDH1/2 mutations was explored among Chinese patients with various solid tumors (9). The study revealed a notable occurrence of these mutations across different cancer types, underscoring their potential as universal biomarkers. In gastric cancer specifically, a researcher elucidated the role of IDH2 dysfunction in contributing to the depletion of 5-hydroxymethylcytosine (5hmC), a key epigenetic modification (10). This dysregulation highlights the involvement of IDH2 in the pathogenesis of gastric cancer, implicating its potential as a diagnostic or prognostic marker in this malignancy.

Moreover, the dysregulation of IDH1 and IDH2 underscores their significance not only as diagnostic biomarkers but also as potential therapeutic targets in gastric cancer. Understanding the mechanistic implications of these mutations, particularly in the context of epigenetic alterations, offers novel insights into the development and progression of gastric cancer. Targeting IDH1/2 mutations may hold promise for precision medicine approaches, offering tailored therapeutic strategies for patients with gastric cancer. Further research into the molecular mechanisms underlying the role of IDH1/2 in gastric carcinogenesis is warranted to fully elucidate their potential as both diagnostic and therapeutic targets in clinical practice.

SDF-4, MSI-H, and PDL 1 as new markers of gastric cancer

Recent literature confirmed early diagnosis and initiation of targeted agents such as stromal cell-derived factor 4 (SDF-4) protein, microsatellite instability-high (MSI-H), and programmed death ligand 1 (PD-L1) plays a crucial role in the outcome of patients with gastric cancer diagnosis. Research in 2023 studied the prognostic significance role of SDF-4 which is secreted by stromal cells and affects angiogenesis, and immune adjustment, and is associated with tumor progression and metastasis relationship. SDF-4 is a promising target for therapeutic intervention and monitoring of disease progression (46).

However, microsatellite instability-high (MSI-H) is a distinct gastric molecular subcategory. This study underlined the crucial role of DNA methylation patterns in the initiation and progression of stomach cancer. MSI-H not only plays an important role as a diagnostic marker but also immune checkpoint inhibitor (ICI) and provides a standard guideline for management strategies for gastric cancer (47).

In addition, aberrant expression of death ligand 1 (PD-L1) is a crucial character of immunity in gastric cancer patients. PD-L1 as a transmembrane protein expressed on tumor cells and immune cells binds to T cells and suppresses the antitumor immune response. A study by Sato *et al*. (2023) revealed a dynamic between PD-L1 expression and tumor microenvironment. This underscores the importance of this molecule as a prognostic biomarker for immunotherapy response (46).

In conclusion, the expression of CDX1 and CDX2 seems to be intricately associated with gastric cancer survival, lymph node positivity, and tumor differentiation. Their role as prognostic indicators offers a promising future for stratifying patients for different therapeutic approaches, potentially allowing for better survival. Future trials should explore the integration of these biomarkers into the management of the patients, acknowledging the variability and potential biases that could impact their prognostic values. The collective insights from this literature highlight the significance of IDH1-based therapeutic medications in cancer of the stomach. The IDH1 gene can be a powerful biomarker for detecting high-risk patients and adjusting their

treatment plans. They underscore the gene's role in cancer advancement, provide evidence for the efficacy of targeted treatments, and offer a comprehensive view of the molecular changes associated with IDH1/2 mutations. These findings show the path for the development of personalized treatment strategies and, ultimately better patient outcomes in gastric cancer. The integration of other biomarkers into the management of the patients holds great significance for gastric cancer management and outcome improvement. Utilizing the diagnostic and prognostic value of SDF-4, MSI-H, and PD-1 will allow physicians to approach treatment appropriately by selecting therapies tailored to individual tumor molecular characteristics variety to allow for improved, and ultimately, patient outcomes in gastric cancer.

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