Ki67 for evaluating the prognosis of gastrointestinal stromal tumors: A systematic review and meta-analysis

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Abstract. Overexpression of Ki67 is observed in tumor cells, and it has been suggested to be a marker for cancer prognosis. However, the relationship between Ki67 expression and the risk of recurrence of gastrointestinal stromal tumors (GISTs) remains poorly defined. In the present study, a meta-analysis was used to examine the associations between Ki67 levels and GIST recurrence. Studies reporting GIST and Ki67 were found by searching Cochrane Library, PubMed and Embase until October 14, 2021. The Newcastle-Ottawa Scale (NOS) was used to verify the quality of the evidence. Totally, 1682 patient cases were included. The odds ratio (OR) estimates and 95% confidence interval (CI) for each publication were determined by a fixed-effects (Mantel-Haenszel) model. A total of 20 studies that fulfilled the inclusion criteria were finally included in the analysis. The average score of quality evaluation was 6.4 points according to NOS. It was found that Ki67 levels were significantly higher in the NIH L group compared with the NIH VL group (OR: 0.51; 95% CI: 0.26-0.99; P=0.04; P heterogeneity=0.44). There was also greater Ki67 overexpression in the NIH I group compared with the NIH L group (OR: 0.45, 95% CI: 0.31-0.65; P<0.0001; P heterogeneity=0.32), while Ki67 levels were greater in the NIH H group than in the NIH I group (OR: 0.20; 95% CI: 0.15-0.28; P<0.00001; P heterogeneity=0.56). In conclusion, Ki67 overexpression may be a useful marker of the risk of recurrent GIST transformation.

Introduction

Gastrointestinal stromal tumor (GIST) is an uncommon gastrointestinal cancer, accounting for less than 3% of overall gastrointestinal neoplasms but 80% of those of mesenchymal origin (1) and approximately half of the cases are malignant (2). Although tumors may develop in any part of the gastrointestinal tract, they occur most frequently in the stomach (60%) and small intestine (between 20 and 30%) (3-5). The worldwide annual incidence is 7-15 per million (6,7), with geographical variations. For instance, in Europe and North America, the incidence is 10-15 annual cases per million of population but is higher in Asia at 16-20 per million (6). To evaluate the prognosis of GIST, a consensus risk assessment of recurrence was developed by the National Institutes of Health (NIH) in 2008 (Table I), subsequently revised to the modified NIH risk scale (8). According to the scale, the principal evaluation indices are the tumor size and mitosis count, and are divided into four grades: i) very low, ii) low, iii) intermediate and iv) high risk. A relationship between GIST risk and prognosis has been well documented (9). However, there is considerable variation in both the clinical behavior and prognosis of GIST, particularly in high-risk populations. Thus, a comprehensive and objective assessment of GIST biology and malignant progression, particularly in terms of histological and clinical features, is important.

Ki67 is expressed in cell nuclei during proliferation (10), visible in the cortex of the nucleolus in interphase, and associated with chromosomes during mitotic condensation (11). The level of the protein rises between G1 and mitosis, after which it declines sharply and is found in the nucleus during the G1, S and G2 phases but is not expressed during G0 (12,13). Thus, the level of Ki67 can be used as an index of proliferation. Overexpression of Ki67 is observed in tumor cells, and it has been suggested to be a marker for cancer prognosis (14). To date, several studies have reported the use of Ki67 levels in the prediction of GIST prognostic risk, with higher levels indicating an elevated risk of tumor spread and recurrence after surgery and the need for increased observation and management (15-18). Another study has reported that the Ki67 index together with raised levels of RacGAP1 are effective in combination with risk stratification and clinical parameters in assessing the likely outcome of GIST (19). However, did no correlation between Ki67 overexpression and mitotic activity in tumors was identified by Demir *et al* (20). It is thus apparent that there is controversy surrounding the use of Ki67 in predicting risk in GIST, possibly due to the influence of small sample sizes. Although the relationship

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between Ki67 and GIST through meta-analysis was examined by Zhou *et al* (21) in 2017, only 9 studies were included at that time. In addition, the quality of the included studies was not evaluated in the aforementioned study, thus the quality of the studies was difficult to estimate. Thus far, more studies have discussed the relationship between Ki67 and prognosis of GIST. In the present study, a meta-analysis was re-used to examine the associations between Ki67 levels and GIST recurrence.

Materials and methods

Literature search and selection criteria. PubMed, Cochrane Library and EMBASE databases were searched for relevant articles using the terms 'GIST' and 'Ki67' by JL and ARW. Differences were resolved through discussion with a third researcher SQL. The search took place on October 14, 2021. In situations where patients were described in multiple publications, the most complete or recent articles were selected. As the analysis was based on published studies, neither ethical approval nor patient consent was required.

Inclusion criteria. The criteria for inclusion were as follows: i) Patients must be assessed for Ki67 expression by immunohistochemistry; ii) The prognostic risk of GIST was assessed by the NIH Risk System; iii) The full text or original data could be retrieved during October 2021.

Exclusion criteria. Articles that did not include information on Ki67 in relation to NIH risk assessment were excluded, as were case reports and articles describing studies in animals or cell lines.

Data extraction. The required information from the publications was independently recorded by JL and ARW. Specifically, this information included the first author, publication date, classification method, number of NIH risk categories, demographic parameters (such as age and sex), the sample size and Ki67 measurement. Any disagreements between the two researchers were resolved through discussion with the third researcher (SQL).

Statistical analysis. The Newcastle-Ottawa Scale (NOS) was used to verify the quality of the evidence. Data were analyzed with Review Manager Version 5.3 (Cochrane Collaboration), with P<0.05 representing statistical significance. Inter-study heterogeneity was evaluated using the I2 statistic and Cochran's Q test. When there was no significant heterogeneity (Q test: P≥0.1), the fixed-effects (Mantel-Haenszel) model was used to combine odds ratio (OR) values; otherwise, the random-effect (DerSimonian and Laird) model was used. The significance of combined ORs was evaluated using the z-test. Examination of the effects of changes in inclusion criteria on the final results was conducted by sensitivity analysis. The combined OR and 95% confidence interval (CI) of dichotomous variables were calculated. Funnel plots were used to assess possible publication bias, with bias indicated by plot asymmetry. Egger's test was applied to evaluate asymmetry in funnel plots, and unpaired t-tests were used to measure intercept significance (P<0.05).

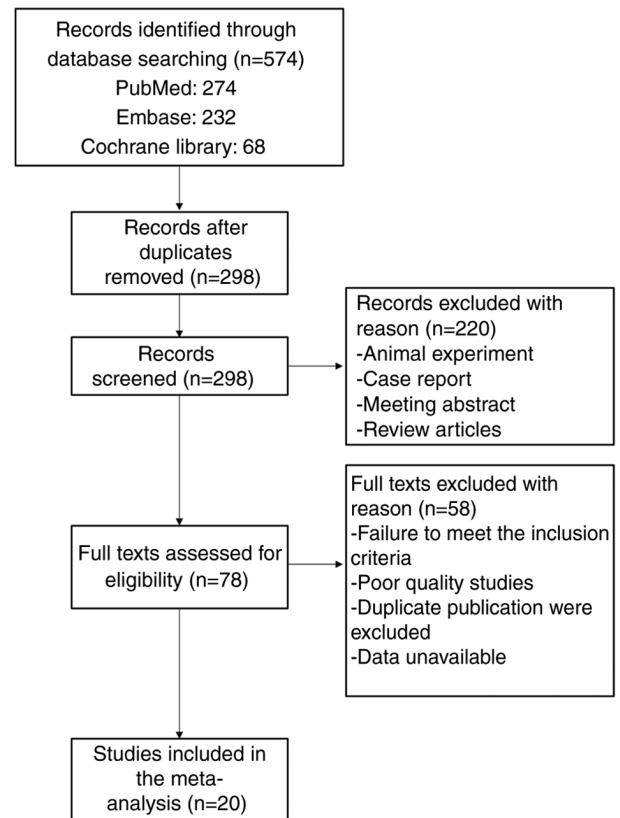Figure 1. Flow chart of screening strategy for included studies.

Results

Features of the included studies. The titles and abstracts of the publications were reviewed, resulting in the exclusion of a number of studies due to insufficient information for calculating the OR (Fig. 1). A total of 20 studies that fulfilled the inclusion criteria were finally included in the analysis (15,22-40). The NOS was used to verify the quality of the evidence. Table II summarizes the principal characteristics of these studies. In all, 1682 patient cases were included. A flow chart of the screening process is shown in Fig. 1.

Meta-analysis. It was found that Ki67 levels were significantly higher in the NIH L group compared with the NIH VL group (OR: 0.51, 95% CI: 0.26-0.99; P=0.04; P heterogeneity=0.44) (Fig. 2A). There was also greater Ki67 overexpression in the NIH I group compared with the NIH L group (OR: 0.45, 95% CI: 0.31-0.65; P<0.0001; P heterogeneity=0.32) (Fig. 2B), while Ki67 levels were greater in the NIH H group than in the NIH I group (OR: 0.20, 95% CI: 0.15-0.28; P<0.00001, P heterogeneity=0.56) (Fig. 2C). Due to the small heterogeneity, the fixed-effects (Mantel-Haenszel) model was used. Heterogeneity analysis of the 20 studies revealed no heterogeneity (P>0.05), and sensitivity analysis indicated that no individual study influenced the pooled OR (data not shown).

Publication bias. No asymmetry was visible in the funnel plots, indicating an absence of publication bias (Fig. 3A-C).

Table I. National Institutes of Health system of risk grading for GIST.

Risk class	Tumor size, cm	Mitotic count	Primary tumor location
Very low	<2	<5/50 HPF	Any location
Low	2-5	≤5/50 HPF	Any location
Intermediate	2-5	>5/50 HPF	Stomach
	≤5	>5/50 to ≤10/50 HPF	Any location
	>5 to ≤10	≤5/50 HPF	Stomach
High	Any size	Any mitotic rate	Tumor rupture
	>10	Any mitotic rate	Any location
	Any size	>10/50 HPF	Any location
	>5	>5/50 HPF	Any location
	2-5	>5/50 HPF	Not in the stomach
	>5 to ≤10	≤5/50 HPF	Not in the stomach

GIST, gastrointestinal stromal tumor; HPF, high-power field.

Table II. Main characteristics of all studies included in the meta-analysis.

First author (year)	Country	NIH (VL/L/I/H)	Age, years	Sex (male/female)	Total cases	NOS score	(Refs.)
Nakamura (2005)	Japan	0/22/25/33	-	39/41	80	6	(22)
Pleşea (2014)	Romania	0/1/2/12	62.4	10/5	15	6	(23)
Peker (2014)	Turkey	0/28/21/31	58.55±10.59	-	72	7	(24)
Tsumuraya (2010)	Japan	1/4/4/6	59.2±14.05	7/8	15	8	(25)
Jiang (2016)	China	6/12/10/12	58.5 (40-83)	22/18	40	5	(26)
Güler (2015)	Turkey	3/6/7/20	57.2 (23-74)	15/22	37	6	(27)
Li (2018)	China	10/61/29/48	61 (9-86)	69/82	151	5	(15)
Wang (2014)	China	5/26/17/36	61.5 (23-78)	46/38	84	8	(28)
Zhao (2014)	China	32/152/62/124	59	199/171	370	6	(29)
Nanding (2014)	China	3/12/4/22	52.52±13.21	20/21	41	6	(30)
Lu (2013)	China	5/15/16/75	57 (18-82)	59/52	111	6	(31)
Segales-Rojas (2018)	Mexico	0/6/11/26	55 (23-86)	21/22	43	8	(32)
Jiang (2012)	China	3/24/24/45	55 (26-82)	57/39	96	5	(33)
Liu (2013)	China	5/15/16/77	60	61/52	113	6	(34)
Alghamdi (2019)	Saudi Arabia	0/5/17/14	54 (17-28)	13/23	36	6	(35)
Ngo (2019)	Vietnam	6/42/40/67	55 (15-88)	72/83	155	6	(36)
Podda (2020)	Italy	16/10/3/10	58.6±17.3	25/14	39	8	(37)
Tepeoğlu (2018)	Turkey	24/17/7/17	-	31/34	65	7	(38)
Wei (2020)	China	16/25/27/33	-	49/52	101	6	(39)
Taniguchi (2021)	Japan	0/10/6/2	63.6±12	8/10	18	7	(40)

H, high risk; I, intermediate risk; L, low risk; NIH, National Institutes of Health; VL, very low risk; NOS, Newcastle-Ottawa Scale; all studies report clinicopathological outcomes.

Discussion

GIST develops from the gastrointestinal mesenchyme and is a relatively common sarcoma of soft tissue (41). The outcome usually depends on the size, site, and mitotic index of the tumor with tumors <5 cm in diameter originating in the stomach, with mitotic indices below 5/50 high-power field linked to more favorable prognoses (42,43). The NIH used these parameters to develop prediction tools for GIST progression and outcome, assessing the risk of poor outcome as very low, low, intermediate, or high as outcome prediction tools using these (8). In addition to this, numerous studies have been undertaken to investigate the possibility of basing prediction on molecular, as well as clinical, factors. A meta-analysis of Asian, European, and North American patients found that mutations in KIT exon 11 were associated with superior treatment responses and survival compared with exon 9 polymorphisms (44,45). A previous study showed that deletions in exon 11 (codons 557

A

Study or Subgroup	NIH VL group Events	Total	NIH L group Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Abiyasi Nanding et al, 2014	1	3	4	12	3.8%	1.00 [0.07, 14.64]
Beril Güler et al, 2015	0	3	1	6	3.4%	0.52 [0.02, 16.83]
CANRONG LU et al, 2013	2	5	4	15	4.3%	1.83 [0.22, 15.33]
Hao Wang et al, 2014	0	5	11	26	13.8%	0.12 [0.01, 2.45]
Huali Li et al, 2018	1	10	3	61	2.7%	2.15 [0.20, 22.97]
Jiang et al, 2012	0	3	4	24	3.9%	0.65 [0.03, 14.94]
Jiang et al, 2016	0	6	1	12	3.5%	0.59 [0.02, 16.68]
Li-Cheng Liu et al, 2013	2	5	2	15	2.2%	4.33 [0.42, 44.43]
Mauro Podda et al, 2020	2	16	3	10	11.6%	0.33 [0.04, 2.48]
Merih et al, 2018	1	24	7	17	28.3%	0.06 [0.01, 0.57]
Ngo et al, 2019	1	6	5	42	3.8%	1.48 [0.14, 15.38]
Sheng-cai Wei et al, 2020	0	16	1	25	4.1%	0.49 [0.02, 12.90]
TSUMURAYA et al, 2010	0	1	0	4		Not estimable
Wen-Yi Zhao et al, 2014	0	32	11	152	14.5%	0.19 [0.01, 3.30]
Total (95% CI)		135		421	100.0%	0.51 [0.26, 0.99]
Total events	10		57			

Heterogeneity: Chi² = 12.07, df = 12 (P = 0.44); I² = 1%
Test for overall effect: Z = 2.00 (P = 0.04)

B

Study or Subgroup	NIH L group Events	Total	NIH I group Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Abiyasi Nanding et al, 2014	4	12	2	4	2.4%	0.50 [0.05, 4.98]
Alghamdi et al, 2019	3	5	8	17	1.7%	1.69 [0.22, 12.81]
Beril Güler et al, 2015	1	6	1	7	0.9%	1.20 [0.06, 24.47]
CANRONG LU et al, 2013	4	15	3	16	2.6%	1.58 [0.29, 8.61]
Hao Wang et al, 2014	11	26	9	17	7.5%	0.65 [0.19, 2.23]
Huali Li et al, 2018	3	61	4	29	6.2%	0.32 [0.07, 1.55]
Jiang et al, 2012	4	24	11	24	11.0%	0.24 [0.06, 0.90]
Jiang et al, 2016	1	12	4	10	4.8%	0.14 [0.01, 1.51]
Kemal Peker et al, 2014	2	28	13	23	15.9%	0.06 [0.01, 0.31]
Li-Cheng Liu et al, 2013	2	15	2	16	2.0%	1.08 [0.13, 8.80]
Mauro Podda et al, 2020	3	10	2	3	2.6%	0.21 [0.01, 3.37]
Merih et al, 2018	7	17	1	7	1.0%	4.20 [0.41, 43.04]
Nakamura et al, 2005	2	22	9	25	9.2%	0.18 [0.03, 0.94]
Ngo et al, 2019	5	42	10	40	10.8%	0.41 [0.13, 1.31]
Patricia et al, 2018	2	6	3	11	1.7%	1.33 [0.15, 11.50]
Plesea et al, 2014	1	1	2	2		Not estimable
Sheng-cai Wei et al, 2020	1	25	2	27	2.2%	0.52 [0.04, 6.13]
TANIGUCHI et al, 2021	2	10	3	6	3.6%	0.25 [0.03, 2.32]
TSUMURAYA et al, 2010	0	4	2	4	2.7%	0.11 [0.00, 3.35]
Wen-Yi Zhao et al, 2014	11	152	7	62	11.1%	0.61 [0.23, 1.66]
Total (95% CI)		493		350	100.0%	0.45 [0.31, 0.65]
Total events	69		98			

Heterogeneity: Chi² = 20.23, df = 18 (P = 0.32); I² = 11%
Test for overall effect: Z = 4.25 (P < 0.0001)

C

Study or Subgroup	NIH I group Events	Total	NIH H group Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Abiyasi Nanding et al, 2014	2	4	22	22	2.1%	0.02 [0.00, 0.61]
Alghamdi et al, 2019	8	17	12	14	3.7%	0.15 [0.03, 0.87]
Beril Güler et al, 2015	1	7	12	20	2.8%	0.11 [0.01, 1.11]
CANRONG LU et al, 2013	3	16	44	75	6.7%	0.16 [0.04, 0.62]
Hao Wang et al, 2014	9	17	29	36	4.7%	0.27 [0.08, 0.96]
Huali Li et al, 2018	4	29	29	48	10.0%	0.10 [0.03, 0.35]
Jiang et al, 2012	11	24	30	45	6.0%	0.42 [0.15, 1.17]
Jiang et al, 2016	4	10	8	12	2.3%	0.33 [0.06, 1.91]
Kemal Peker et al, 2014	13	23	20	21	4.8%	0.07 [0.01, 0.57]
Li-Cheng Liu et al, 2013	2	16	33	77	5.3%	0.19 [0.04, 0.90]
Mauro Podda et al, 2020	2	3	9	10	0.7%	0.22 [0.01, 5.28]
Merih et al, 2018	1	7	13	17	3.5%	0.05 [0.00, 0.56]
Nakamura et al, 2005	9	25	18	33	5.3%	0.47 [0.16, 1.36]
Ngo et al, 2019	10	40	36	67	10.8%	0.29 [0.12, 0.68]
Patricia et al, 2018	3	11	19	26	4.4%	0.14 [0.03, 0.67]
Plesea et al, 2014	2	2	9	12	0.3%	1.84 [0.07, 48.68]
Sheng-cai Wei et al, 2020	2	27	16	33	7.1%	0.09 [0.02, 0.42]
TANIGUCHI et al, 2021	3	6	1	2	0.4%	1.00 [0.04, 24.55]
TSUMURAYA et al, 2010	2	4	3	6	0.6%	1.00 [0.08, 12.56]
Wen-Yi Zhao et al, 2014	7	62	58	124	18.3%	0.14 [0.06, 0.34]
Total (95% CI)		350		700	100.0%	0.20 [0.15, 0.28]
Total events	98		421			

Heterogeneity: Chi² = 17.39, df = 19 (P = 0.56); I² = 0%
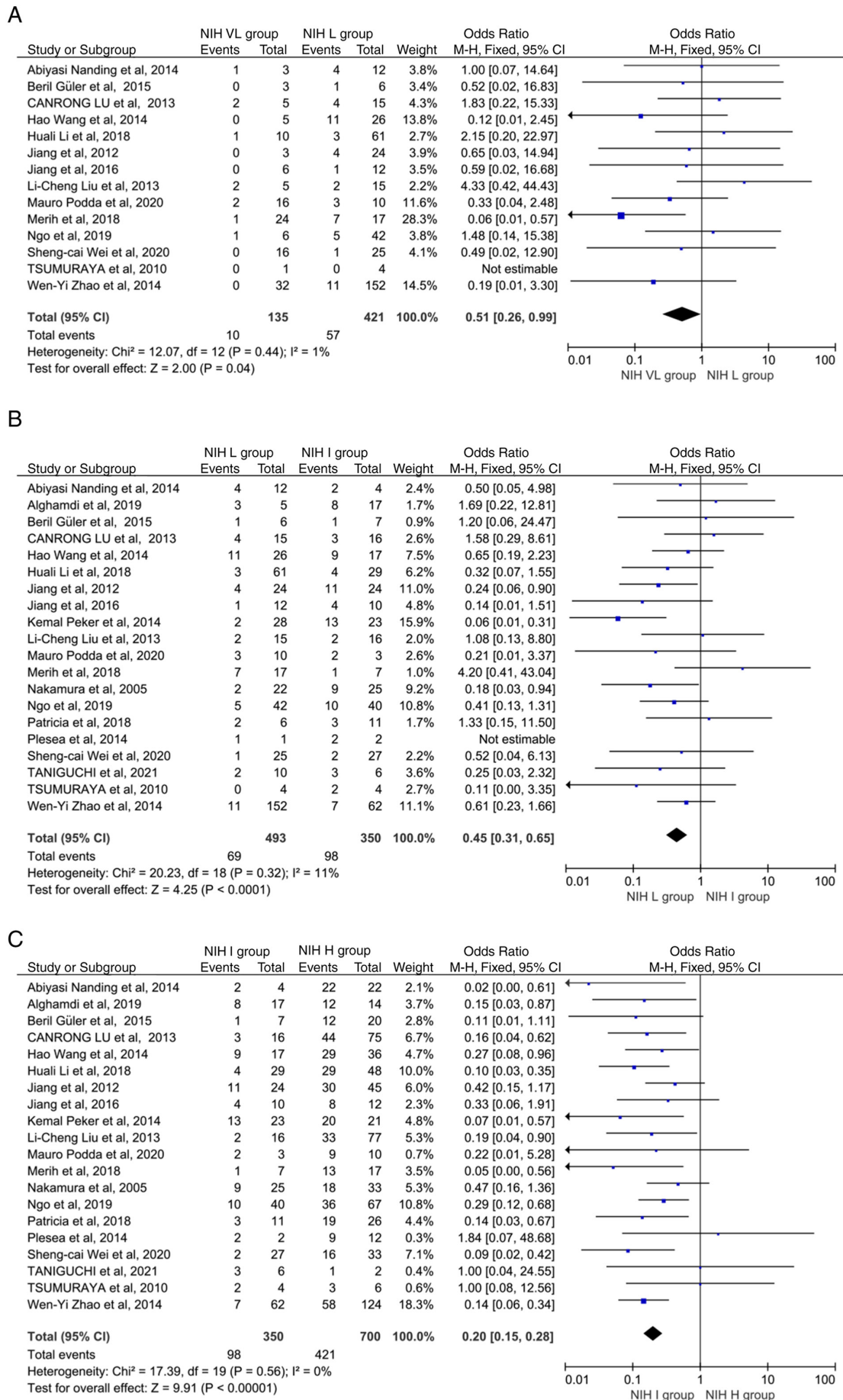Test for overall effect: Z = 9.91 (P < 0.00001)

Figure 2. Meta-analysis of incidence of Ki67 overexpression among NIH subgroups. (A) NIH VL group vs. NIH L group. (B) NIH L group vs. NIH I group. (C) NIH I group vs. NIH H group. H, high risk; I, intermediate risk; L, low risk; NIH, National Institutes of Health; VL, very low risk.

and/or 558) of KIT were linked to significantly lower rates of disease-free survival in European patients with GIST (46). Mutations in exon 18 of PDGFRA have also been associated with significantly reduced GIST progression and improved outcomes (47,48). In the present study, a meta-analysis was conducted at the molecular level to determine whether KI67 can determine the prognosis of GIST.

Ki67 was discovered by Gerdes *et al* (48) in 1983. Ki67 is a nucleoprotein marker for cell proliferation and is associated particularly with mitosis, although it is present throughout the cell cycle apart from G0. The mitosis index is related to tumor morphology and refers specifically to the m-phase of the cell cycle. Therefore, Ki67 is a more accurate reflection of the degree of tumor malignancy than the mitotic index (49). Ki67 expression can be induced by hypoxia (50). In breast, lung, prostate, cervical, and central nervous system cancers, Ki67 is recognized as a reliable marker of important prognostic significance (51). It is currently considered that the expression level of Ki67 is an independent factor affecting the prognosis of GIST (29). Nilsson *et al* (52) described both tumor size and Ki67 >5% as independent risk factors for poor prognosis of GIST. It is known that Ki67 defines cell proliferation in relation to the cell cycle, and is, therefore, a useful measure of GIST recurrence (53,54). However, Wong *et al* (55) considered that Ki67 was not as reliable as the mitotic count, despite its usefulness is measuring the proliferative rate of GIST cells. Furthermore, Segales-Rojas *et al* (32) reported that tumor recurrence was not related to Ki67 but only to tumor size and gender. Kramer *et al* (56) reached a similar conclusion, reporting that patients with GIST younger than 50 years old and female patients have an improved prognosis.

To clarify these conflicting reports, the relationship between Ki67 levels and GIST prognosis was investigated through meta-analysis. In this meta-analysis, Ki67 levels were found to be higher in the NIH L group than in the NIH VL group, while those in the NIH I group were significantly increased in comparison with the NIH L group. Ki67 was also overexpressed in the NIH H group compared with the NIH I group. In the present study, different results were obtained compared with Zhou *et al* (21). The results revealed that the higher the risk, the higher the overexpression rate of Ki67, suggesting that Ki67 expression may be a useful addition to the NIH assessment system for GIST risk prediction. Although the mitotic index has been considered to be only an indication of the M mitotic phase (57), Ki67 is expressed throughout the cell cycle apart from the G0 phase and is an important predictor of poor prognosis in GIST (P<0.0003). It was found that Ki67 had higher observer reliability than the mitotic count in the evaluation of mitotic activity (32), and the Ki67 index may thus be used as a replacement index for the mitotic count in the future.

Nevertheless, the present meta-analysis has several limitations. First, it is difficult to reach a precise conclusion due to the limited sample size, differences in antibody clones and possible heterogeneity. Second, the clinicopathological information of patients was derived from case reports, and differences in the practices and diagnostic criteria of different pathologists may also lead to bias. Therefore, since adjuvant imatinib is standard for high risk GIST, it is considered that a
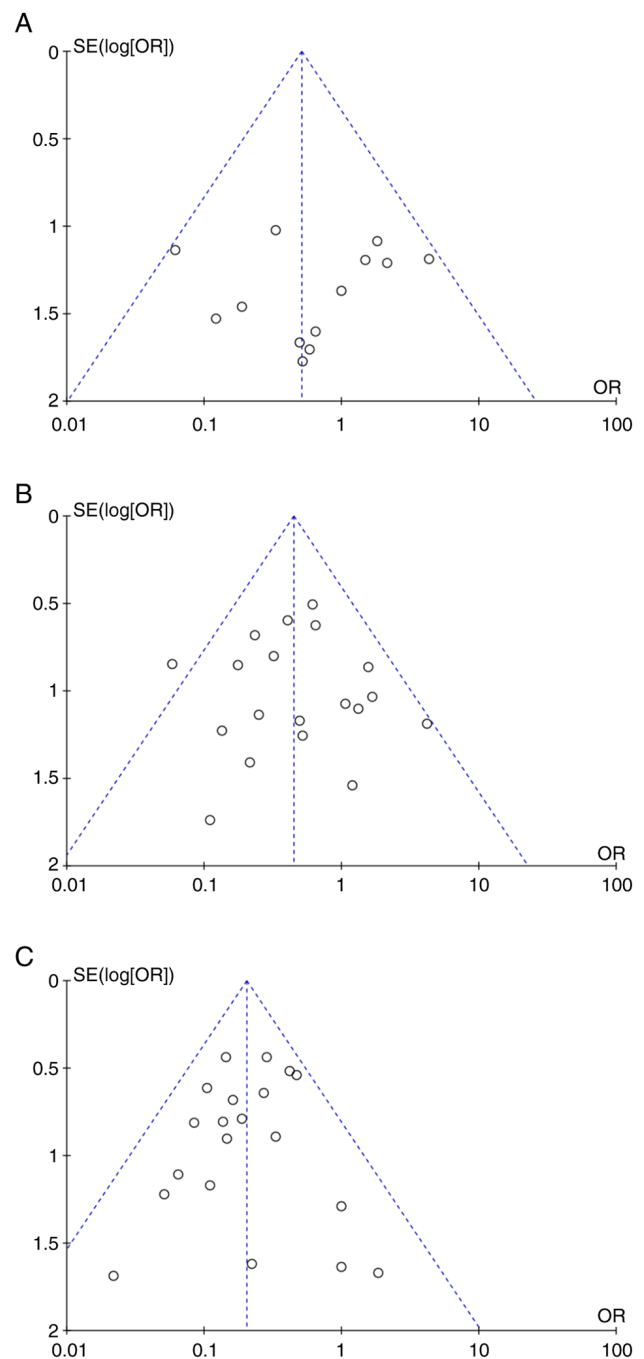

Figure 3. Begg funnel plot for publication bias test. (A) NIH VL group vs. NIH L group. (B) NIH L group vs. NIH I group. (C) NIH I group vs. NIH H group. H, high risk; I, intermediate risk; L, low risk; NIH, National Institutes of Health; VL, very low risk.

large-scale, multi-center prospective study is necessary in the future, taking the low-risk group not receiving imatinib as the control group, and the high-risk group receiving treatment as the experimental group, to compare the long-term survival of the results of the two groups, and use multivariate regression analysis to clarify whether the Ki67 index, gene mutation site, medication compliance and blood drug concentration were related to survival outcomes. Despite these limitations, the present findings contributed to the further discovery of new predictors of adverse outcomes and to the improvement of existing classification criteria.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

JL and SQL contributed to the conception, design and modification of the study. ARW, XDC and HP extracted the data and organized the database search. JL and ARW performed the statistical analysis. SQL, XDC and HP drafted the manuscript. JL and SQL confirm the authenticity of all the raw data. All authors contributed to manuscript revision, read, and approved the submitted version. All authors agreed to be 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. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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