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ORIGINAL RESEARCH

Prognostic value of the Glasgow prognostic score in colorectal cancer: a meta-analysis of 9,839 patients

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Purpose: The aim of this study was to perform a systematic review and meta-analysis to evaluate the value of the Glasgow prognostic score (GPS) or modified Glasgow prognostic score (mGPS) in patients with colorectal cancer (CRC).

Methods: A comprehensive medical literature search was performed using the online databases PubMed, Embase, Web of Science, and the Cochrane Library. After extracting basic characteristics and prognostic data from the included studies, overall survival (OS) and cancer-specific survival (CSS) were pooled as primary outcomes. Subgroup analyses were performed according to therapeutic strategies, models, cutoff values, regions, tumor, node, metastasis stages, sample size, and ages.

Results: Forty-three independent cohorts from 41 studies with 9,839 CRC patients were included in the present study. Correlation between GPS or mGPS and OS was analyzed in 32 cohorts of 7,714 patients, and 23 independent cohorts of 5,375 patients focused on the correlation between GPS or mGPS and CSS. The overall outcomes showed that patients with elevated GPS or mGPS were associated with poor OS (HR: 2.20, 95% CI: 1.88–2.57, P<0.001). Elevated GPS or mGPS also resulted in worse CSS (HR: 1.86, 95% CI: 1.59–2.17, P<0.001). The results of the subgroup analyses confirmed the overall outcomes.

Conclusion: GPS or mGPS is an accurate prognostic predictor in patients with CRC. Patients with elevated pretreatment GPS or mGPS have a poor prognosis. Subgroup analyses confirmed the overall outcomes. Pretreatment GPS is a useful biomarker in the management of CRC.

Keywords: colorectal cancer, Glasgow prognostic score, modified Glasgow prognostic score, systematic review, meta-analysis

Introduction

Colorectal cancer (CRC) is one of the most common gastrointestinal malignancies and the fourth leading cause of cancer-related mortality worldwide.^{1,2} CRC accounts for ~10% of all newly diagnosed cancers each year.³ Although diagnostic technologies and therapeutic strategies for CRC have markedly improved, the prognosis of patients remains poor, which is attributed to the high rate of tumor recurrence and metastasis.^{2,4} The treatment strategies for CRC are based on the biological characteristics of the tumor and the systemic condition of patients. Surgery remains the optimal curative treatment for resectable cancer and the optional strategy for many patients with advanced cancer,⁵ while chemotherapy, immunotherapeutic strategies, and targeted therapy are optional for unresectable cancers.^{4,5} Therefore, an accurate prediction model which can predict the prognosis of CRC patients would be useful for the selection of therapeutic modalities.

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In previous studies, the tumor, node, metastasis (TNM) stage, which was proposed by the American Joint Committee on Cancer, was considered an effective system for predicting CRC recurrence and patient prognosis.^{6,7} However, the TNM stage alone was demonstrated to be inadequate in evaluating prognostic outcomes as tumor progression may be determined by the tumor characteristics as well as systemic inflammation and nutritional status.^{8,9} Recently, an increasing number of studies have focused on the prognostic role of inflammation biomarkers in predicting the prognosis of malignancies.¹⁰⁻¹² The Glasgow prognostic score (GPS), an inflammationbased model, has been shown to be an accurate predictor of prognosis in CRC patients in several studies.^{13–17} This score is based on the combination of C-reactive protein (CRP) and serum albumin (ALB) levels. It was first reported by Forrest et al in 2003 for its prognostic value in non-small-cell lung cancer.¹⁸ GPS was defined based on the presence of hypoalbuminemia (<35 g/L) and elevated CRP (>10 mg/L): if both were abnormal, the score was 2; if either was abnormal, the score was 1; if neither was abnormal, the score was 0.19-21Subsequently, more studies have evaluated the prognostic role of the GPS in a variety of cancers, such as pancreatic cancer, esophageal cancer, and hepatocellular carcinoma.^{12,22,23} In addition, some centers applied the modified Glasgow Prognostic Score (mGPS) to evaluate the prognostic outcomes of CRC patients. mGPS is also calculated using CRP and ALB levels. Patients with CRP <10 mg/L were scored 0, those with CRP > 10 mg/L were scored 1, and those with CRP > 10 mg/Land ALB <35 g/L were scored 2.20 However, the role of the GPS in CRC remains controversial. Ishizuka et al verified the accurate predictive value of GPS,24 while other researchers showed no association between the GPS and the prognosis of CRC patients.13,19,25,26

In this study, we investigated the prognostic value of pretreatment GPS in CRC patients by searching available relevant studies and conducting a meta-analysis. We also investigated the predictive role of the GPS in patients in different subgroups by subgroup analysis.

Methods

Literature search strategy

A comprehensive medical literature search was performed in May 2018 using the online databases PubMed, Embase, Web of Science, and the Cochrane Library. Studies which focused on the association between GPS and the prognostic outcomes of CRC patients were retrieved. There were no restrictions on language, publication region, and type. Search terms were confined to the following freetext words and Medical Subject Headings: ((C-reactive protein) or (CRP) or (albumin) or (Glasgow prognostic score) or (GPS)) and ((colorectal) or (colon) or (rectum) or (rectal)) and ((cancer) or (cancers) or (tumor) or (tumors) or (carcinoma)). A backward search was also conducted using cross-references from the bibliographies of primary selected studies and relevant studies to ensure a comprehensive search. Two reviewers (Lu X and Guo WY) completed searching for titles and abstracts independently.

Inclusion and exclusion criteria

Two reviewers (Lu X and Guo WY) selected eligible studies independently based on the prespecified inclusion and exclusion criteria. When there were disagreements, a final decision was made by a senior reviewer (Zhao WZ). Inclusion and exclusion criteria were established by all authors.

The inclusion criteria were as follows: 1) studies evaluating patients with CRC; 2) studies evaluating either GPS or mGPS in patients prior to treatment; and 3) studies with a clear presentation of the main outcomes including overall survival (OS) and cancer-specific survival (CSS).

The exclusion criteria were as follows: 1) studies not focusing on the prognosis of CRC patients; 2) studies without survival data; 3) studies not focusing on either pretreatment GPS or mGPS; 4) review articles/editorials; and 5) conference abstracts/case reports.

For duplicate publications by the same authors or departments, only the publications with most representative patient cohorts were included in this meta-analysis. If two or more independent sample sets such as training cohorts and validation cohorts were analyzed in the same study, the cohorts were analyzed independently. Moreover, if the researches were repetitive, only one was included. A flow diagram of study retrieval and selection is shown in Figure 1.

Data management and statistical analyses

EndNote software (version X7, Thomson Reuters, USA) was used for sorting and preliminary screening. Data from the included studies were extracted by two authors (Xu W and Zhang XL) by reading the full text independently. Baseline information including the full list of authors, year of publication, regions of the research, research centers, sample size, follow-up period, TNM stages, and therapeutic strategies was summarized. The endpoints of OS and CSS were characterized by HRs with 95% CIs.

Data were extracted from tables or the text of the included studies. In some studies, the HRs and 95% CIs were not presented in the tables or text. These values were then computed from the Kaplan–Meier graph using the Engauge Digitizer



Figure I Flow diagram showing study retrieval and selection process.

Abbreviations: CRC, colorectal cancer; GPS, Glasgow prognostic score; mGPS, modified Glasgow prognostic score.

software (version 4.1, M Mitchell, Engauge Digitizer, http:// digitizer.sourceforge.net).^{27,28} All data from the included studies were pooled using the Cochrane Collaboration's Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). A fixed effects model was used when there was no obvious heterogeneity (I²=0); otherwise, a random effects model was used. Statistical heterogeneity among the studies was determined using the chi-squared test with a significance level of P=0.10, and heterogeneity was quantified using the I² statistic. A sensitivity analysis of OS was performed using Stata software (version 12.0; StataCorp LP, College Station, TX, USA).²⁹ Funnel plots were used to evaluate publication bias. Symmetry of the funnel plots was analyzed using Egger and Begg tests (Stata, version 12.0).

Risk of bias assessment

All the included studies were critically assessed for methodological quality by two researchers independently (Lu X and Guo WY) by using the Quality In Prognosis Studies tool.³⁰ Each study was graded for the following domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. The risk of bias for each domain is graded as low (–), moderate (\pm), or high (+).

Subgroup analyses

Subgroup analyses were performed according to the models used to predict the prognostic outcomes of CRC patients as the scoring of the GPS and mGPS models was different. Subgroups were set according to therapeutic strategies, score cutoff values, sample size, region of publication, and TNM stages of patients in the included studies. The treatment modalities included surgical resection (SR) and chemotherapy. The cutoff value for sample size in the studies was a total of 300 patients. The region subgroups were defined as Asian countries and countries out of Asia taking into consideration the differences between the epidemiologic features and clinicopathological characteristics of CRC. Subgroups of TNM stages were divided into patients with advanced tumors of TNM stage IV and patients with TNM stage 0–III.

Results

Characteristics of the included studies

The comprehensive literature search identified a total of 14,359 studies from the above four databases. A flow diagram of study identification and selection is shown in Figure 1. Of these studies, 3,138 were duplicates. The titles and abstracts of the remaining 11,221 studies were then screened. Among the 11,125 studies excluded, 4,732 were not related to CRC, 3,192 were irrelevant studies, 268 were case reports, 71 were reviews or editorials, and 2,862 did not evaluate GPS or mGPS. The full texts of the remaining 96 articles were carefully reviewed, 56 articles were excluded, and 41 articles were finally included in the present study. Of the 56 excluded studies, 18 studies were published by the same center, 18 included duplicate sample sets, 14 did not include survival outcomes, and six were conference abstracts. Two studies were published by the same author in the same year.³¹ However, the patients enrolled in these studies received different treatment modalities (SR and chemotherapy). As a result, both studies were included in this meta-analysis. Two other studies were published by the same center^{13,24} and both were included as independent cohorts due to their different endpoints. Patient cohorts in these studies were analyzed independently. Hence, 43 independent cohorts from 41 studies were included in this study. $^{13-17,19-21,24-26,31-59}$ The methodological quality of the included studies is summarized in Table S1.

The characteristics of the included studies are summarized in Table 1. A total of 9,839 patients were enrolled. Thirty-three independent cohorts of 8,006 CRC patients analyzed the correlation between GPS or mGPS and OS, and 26 independent cohorts of 7,616 patients focused on the correlation between GPS or mGPS and CSS. The overall outcomes showed that patients with elevated GPS or mGPS were associated with poor OS (HR: 2.20, 95% CI: 1.88–2.57, P<0.001). In addition, higher GPS or mGPS resulted in worse CSS (HR: 1.86, 95% CI: 1.59-2.17, *P*<0.001).

Subgroup analysis

The results of the subgroup analyses are shown in Table 2. In the model subgroups, elevated GPS resulted in worse OS (HR: 2.08, 95% CI: 1.69-2.55, P<0.001) and CSS (HR: 2.38, 95% CI: 1.63-3.46, P<0.001). Patients in the mGPS subgroup with elevated mGPS were associated with a worse OS (HR: 2.23, 95% CI: 1.79-2.78, P<0.001) and CSS (HR: 1.73, 95% CI: 1.47–2.03, P<0.001) (Figure 2). Patients with increased GPS or mGPS who underwent SR had a poor OS (HR: 2.30, 95% CI: 1.90–2.79, P<0.001) and CSS (HR: 2.06, 95% CI: 1.67-2.53, P<0.001). The chemotherapy subgroup confirmed that elevated GPS or mGPS was associated with a worse OS (HR: 1.95, 95% CI: 1.46–2.62, P<0.001) and CSS (HR: 1.47, 95% CI: 1.24-1.74, P<0.001) (Figure 3). The pooled outcomes of studies which used 1 as the cutoff value demonstrated that

Fable I Cha	racterist	ics of include	ed studies										
Study	Year	Country	Design,	Models	Endpoint	HRs	Sample	Cutoff	Age (years)	Male	TNM	Follow-up	Therapies
			center				size			(%)	stages	(months)	
Adachi et	2014	Japan	Prospective,	mGPS	SO	Reported	65	2	64 (17–38)	59.6	≥I⊣	N/A	Resection
al ²⁰			one center										
Chan et	2017	Australia	Retrospective,	mGPS	SO	Reported	386	_	≤70: 107; >70:	44	≡	52 (27–92)	Resection
al ³³			database						279				
Choi et	2014	Korea	Retrospective,	GPS	CSS	Reported	105	2	63 (32–86)	60	≥⊣	44 (2–81)	Resection
al ¹⁷			one center										
Dréanic et	2013	France	Retrospective,	GPS	OS and	Reported	49	_	<65: 29; ≥65: 20	63	≥	35 (16.5–	Chemotherapy
al ³⁴			one center		CSS							74.7)	
Eren et al ³⁵	2015	Turkey	Retrospective,	GPS	CSS	Reported	115	2	66 (32–91)	56	≥⊣	20 (7-41)	Resection
			one center										
Furukawa	2011	Japan	Retrospective,	GPS	SO	Reported	40	2	66.1±9.6	75	≥	N/A	Chemotherapy
et al ³⁶			one center										
Ghanim et	2015	Austria	Retrospective,	mGPS	SO	Reported	52	_	62.7±11.4	53.8	II, I<	N/A	Resection
al ³⁷			one center										
Hong et	2017	China	Retrospective,	mGPS	CSS	Reported	571	_	62.99±11.78	52		Median: 42	Resection
al ³⁸			one center										

		herapy				F		herapy						۶			ï	erapy					F		herapy		F		F		۶		herapy		F				tinued)
Resection	ī	Chemotr		Kesection		Resection		Chemoth		Resection		Resection		Resection			Resection	chemoth			Resection		Resection		Chemoth		Resection		Resection		Resection		Chemoth		Resection		Resection		(con
65 (2–189)		621±145 dave		1,536±898 طميرة	cybu	I,091±828	days	Median:	17.6	32 (I–66)		38 (30.5–	45.6)	50 (2.2–	177.6)		R: 48	(36–73); U:	12 (6–73)		60		Median: 30		I4 (I–58)		25 (8–78)		44.4	(1.2–81.6)	N/A		12 (0.4–67)		N/A		43 (5–155)		
		2		>		>0		≥		≥		≥		≥			R: ⊢III;	⊂ N			=		≥		≥		=		≡⊥		≥		≥		≥⊣		≥		
71		60		66.4		63.8		63		53.2		69.8		62.8			R: 54.4;	U: 57.I			35.4		54.3		56.3		54.3		55.3		63.8		65.5		58.8		67		
64 (33–83)		64 (29–85)		67.4±11.1		67.7±11.7		62 (18–88)		≤70: 43; >70: 36		<70: 41; ≥70: 22		65 (32–87)			R: <65: 48; 65–74:	52; >74: 49; U:	<65: 34; 65–74:	27; >74: 23	62.6±10.7		<70: 62; ≥70: 32		65 (36–83)		<65: 33; 65–74:	29; >74: 8	69.9±10.6		62.83±3.85		60.2 (20–74)		70.4 (24–90)		63 (30–87)		
_	_	_	_	_		2		2		2		_		_			2				2		2		2		_		_		_		_		2		_		
115		163	120	1/7		627		503		79		63		492			R: 149;	U: 84			66		94		80		70		206		343		148		272		134		
Reported	-	Keported		Keported		Reported		Reported		Reported		Reported		Reported			Reported				Reported		Reported		Extracted from	survival plots	Reported		Reported		Reported		Reported		Reported		Reported		
OS and	CSS	S		ŝ		SO		OS and	CSS	CSS		SO		SO			OS and	CSS			SO		SO		OS and	CSS	CSS		SO		CSS		SO		SO		OS and	CSS	
mGPS		mGPS		۲J		GPS		mGPS		mGPS		GPS		GPS			mGPS				GPS		GPS		GPS		mGPS		mGPS		mGPS		GPS		mGPS		GPS		
Retrospective,	one center	Ketrospective, one center		Ketrospective, one center		Retrospective,	one center	Retrospective,	one center	Retrospective,	one center	Retrospective,	one center	Retrospective,	multiple centers		Retrospective,	one center			Retrospective,	one center	Retrospective,	one center	Retrospective,	one center	Retrospective,	one center	Retrospective,	two centers	Retrospective,	one center	Retrospective,	one center	Retrospective,	one center	Retrospective,	one center	
Japan	-	Japan		Japan		Japan		Korea		Japan		Japan		Sweden;	Finland;	Norway	Š				China		Japan		France		ž		ž		Japan		China		Japan		Japan		
2017		5103		7117		2016		2017		2013		2010		2016			2007				2015		2013		2014		2017		2010		2014		2016		2014		2017		
lde et al ³⁹		Inoue et	а 	Isnizuka et	a	Ishizuka et	al ²⁴	Kim et al ⁴¹		Kishiki et	al ²¹	Kobayashi	et al ⁴²	Køstner et	al ⁴³		Leitch et	al ¹⁴			Lin et al ⁴⁴		Maeda et	al ⁴⁵	Maillet et	al ⁴⁶	McSorley	et al ⁴⁷	Moug et	al ⁴⁸	Nakagawa	et al ⁴⁹	Ni et al ⁵⁰		Nozoe et	al ¹⁵	Okimoto	et al ²⁵	

Table I (cor	ntinued)												
Study	Year	Country	Design,	Models	Endpoint	HRs	Sample	Cutoff	Age (years)	Male	TNM	Follow-up	Therapies
			center				size			(%)	stages	(months)	
Okugawa	2018	Japan	Retrospective,	mGPS	OS	Reported	T: I25;	2	T: 72.7±11.9; V:	T: 56.8;	≥⊥	N/A	Resection
et al ⁵¹			two centers				V: 545		66.9±11.3	V: 58.9			
Read et	2006	Australia	Retrospective,	GPS	SO	Extracted from	51	_	64 (40–79)	58.8	≥	Median:	Chemotherapy
al ¹⁹			two centers			survival plots						29.8	
Sharma et	2008	Australia	Retrospective,	GPS	SO	Extracted from	52	2	Median: 70.5	64	≥	N/A	Chemotherapy
al ⁵²			multiple centers			survival plots							
Shibutani	2015	Japan	Retrospective,	GPS	OS and	Extracted from	011	_	64 (27–86)	57.3	≥	N/A	Chemotherapy
et al $(1)^{31}$			one center		CSS	survival plots							
Shibutani	2015	Japan	Retrospective,	GPS	SO	Reported	254	_	66 (26–86)	54.7	II, III	N/A	Resection
et al (2) ³¹			one center										
Shimura et	2017	Japan	Retrospective,	mGPS	SO	Reported	92	2	65 (31–90)	61.9	≥	16.2	Resection
al ³²			one center									(0.2–110.4)	
Sirniö et	2018	Finland	Prospective,	mGPS	OS and	Reported	271	_	69.5±11.6	50.9	≥⊢	Median:	Resection
al ²⁶			one center		CSS							64.3	
Son et al ⁵³	2013	Korea	Retrospective,	mGPS	SO	Reported	624	2	<60: 295; ≥60:	58.9	≣⊥	42 (1–66)	Resection
			one center						329				
Song et	2015	Korea	Retrospective,	mGPS	SO	Reported	177	_	52 (25–81)	46.9	≥	3.1	Chemotherapy
al ⁵⁴			one center									(0.1–33.3)	
Sugimoto	2012	Japan	Retrospective,	GPS	CSS	Reported	366	2	≤70: 240; >70:	57.1		Median:	Resection
et al ⁱ⁶			one center						126			70.8	
Sun et al ⁵⁵	2014	China	Retrospective,	mGPS	OS and	Reported	255	_	59.47±12.63	52.9		N/A	Resection
			one center		CSS								
Toiyama	2011	Japan	Retrospective,	mGPS	OS and	Reported	219	_	66 (29–91)	62.I	II, III	56.9 ±63.8	Resection
et al ⁵⁶			one center		CSS								
Tokunaga	2017	Japan	Retrospective,	mGPS	OS and	Reported	468	_	68 (19–93)	59.2	≡⊥	48.5	Resection
et al ⁵⁷			one center		CSS							(2–124)	
Watt et	2016	ž	Retrospective,	mGPS	OS and	Reported	813	_	<65: 268; 65–74:	54.6	III−0	T: 116	Resection
al ⁵⁸			one center		CSS				286; >74: 259			(72–180); V: 31 (10–71)	
Yamamoto	2012	Japan	Retrospective,	mGPS	CSS	Reported	42	2	<70: 12; ≥70: 30	61.9	≥	Median:	Chemotherapy
et al ⁵⁹			two centers									424 days	
Note: Age and 1	ollow-up p	eriods were exp	ressed as mean ± SD o	ır median (range	.(1								
Abbreviations: V validation	CSS, cance	er-specific surviv	al; GPS, Glasgow progr	nostic score; m(GPS, modified Glas	sgow prognostic score	e; N/A, not avai	ilable; OS, ov	erall survival; R, resectabl	le; T, training	TNM, tumo	r, node, metastase	s; U, unresectable;
1) 1411444011													

Subgroups	Independent	Sample	HR (95% CI)	P-value	Study he	terogen	eity	
	cohorts	size	(H/L)		χ ²	df	l ² (%)	P-value
Overall survival	32	7,714	2.20 (1.88, 2.57)	<0.00001	91.05	31	66	<0.00001
Models								
GPS	14	2,293	2.08 (1.69, 2.55)	<0.00001	19.95	13	35	0.10
mGPS	18	5,421	2.23 (1.79, 2.78)	<0.00001	70.68	17	76	<0.00001
Therapies								
Resection	23	6,504	2.30 (1.90, 2.79)	<0.00001	70.01	22	69	<0.00001
Chemotherapy	9	1,210	1.95 (1.46, 2.62)	<0.00001	19.36	8	59	0.01
Cutoff value								
I	18	4,263	1.85 (1.58, 2.16)	<0.00001	37.66	17	55	0.003
2	14	3,451	3.02 (2.21, 4.13)	<0.00001	39.04	13	67	0.0002
Regions								
Asia	21	5,113	2.44 (1.98, 3.02)	<0.00001	56.26	20	64	<0.0001
Others	11	2,601	1.79 (1.47, 2.18)	<0.00001	20.44	10	51	0.03
Age, years								
Mean/median <65	11	1,709	1.91 (1.50, 2.43)	<0.00001	21.98	10	55	0.02
Mean/median ≥65	17	5,091	2.46 (1.93, 3.13)	<0.00001	67.21	16	76	<0.00001
Sample size								
Sample <300	24	3,256	2.43 (1.97, 3.00)	<0.00001	60.13	23	62	<0.0001
Sample ≥300	8	4,458	1.86 (1.50, 2.31)	<0.00001	21.04	7	67	0.004
TNM stages								
0–111	12	3,588	1.95 (1.57, 2.42)	<0.00001	31.86	10	69	0.0004
IV	14	2,085	1.95 (1.56, 2.42)	<0.00001	26.46	13	51	0.01
Cancer-specific survival	23	5,375	1.86 (1.59, 2.17)	<0.00001	45.42	22	52	0.002
Models								
GPS	8	1,230	2.38 (1.63, 3.46)	<0.00001	12.75	7	45	0.08
mGPS	15	4,145	1.73 (1.47, 2.03)	<0.00001	28.10	14	50	0.01
Therapies								
Resection	16	4,344	2.06 (1.67, 2.53)	<0.00001	35.67	15	58	0.002
Chemotherapy	7	1,031	1.47 (1.24, 1.74)	<0.00001	6.06	6	1	0.42
Cutoff value								
I	14	3,852	1.74 (1.48, 2.05)	<0.00001	21.26	13	39	0.07
2	9	1,523	2.34 (1.61, 3.40)	<0.00001	24.07	8	67	0.002
Regions								
Asia	15	3,744	2.01 (1.65, 2.44)	<0.00001	27.86	14	50	0.01
Others	8	1,631	1.56 (1.24, 1.96)	<0.00001	10.65	7	34	0.15
Age, years								
Mean/median <65	9	2,299	1.83 (1.47, 2.27)	<0.00001	16.28	8	51	0.04
Mean/median ≥65	10	2,512	1.73 (1.34, 2.24)	<0.00001	17.68	9	49	0.04
Sample size								
Sample <300	17	2,311	2.02 (1.64, 2.49)	<0.00001	27.01	16	41	0.04
Sample ≥300	6	3,064	1.61 (1.32, 1.96)	<0.00001	10.35	5	52	0.07
TNM stages								
0–111	9	3,026	2.01 (1.57, 2.58)	<0.00001	19.29	8	59	0.01
IV	10	1,587	1.80 (1.43, 2.27)	<0.00001	15.76	9	43	0.07

Table 2 Results of subgroup analyses of overall survival and cancer-specific survival

Abbreviations: df, degrees of freedom; GPS, Glasgow prognostic score; H, high group; L, low group; mGPS, modified Glasgow prognostic score; TNM, tumor, node, metastases.

CRC patients with elevated GPS or mGPS had a worse OS (HR: 1.85, 95% CI: 1.58–2.16, P<0.001) and CSS (HR: 1.74, 95% CI: 1.48–2.05, P<0.001). Studies which used 2 as the cutoff value also demonstrated that elevated GPS resulted in poor OS (HR: 3.02, 95% CI: 2.21–4.13, P<0.001) and CSS (HR: 2.34, 95% CI: 1.61–3.40, P<0.001) (Figure 4). The pooled outcomes of 21 independent cohorts

published in Asia showed that increased GPS or mGPS was associated with worse OS (HR: 2.44, 95% CI: 1.98–3.02, P<0.001) and CSS (HR: 2.01, 95% CI: 1.65–2.44, P<0.001) (Figure 5). The subgroup analysis based on geographical regions showed that Asian patients with increased GPS or mGPS level had a poor OS (HR: 2.44, 95% CI: 1.98–3.02, P<0.001) and CSS (HR: 2.01, 95% CI: 1.65–2.44, P<0.001)

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(Figure 6). For elderly patients with a mean/median age >65 years, elevated GPS or mGPS was also associated with worse OS (HR: 2.46, 95% CI: 1.93–3.13, *P*<0.001) and CSS (HR: 1.73, 95% CI: 1.34–2.24, *P*<0.001) (Figure 7). The subgroup of patients with CRC TNM stage 0–III demonstrated the prognostic value of GPS or mGPS in

predicting OS (HR: 2.13, 95% CI: 1.66–2.73, P<0.001) and CSS (HR: 2.01, 95% CI: 1.57–2.58, P<0.001) (Figure 8). The subgroup of patients with CRC TNM stage IV indicated that elevated GPS or mGPS was associated with poor OS (HR: 1.95, 95% CI: 1.56–2.42, P<0.001) and CSS (HR: 1.80, 95% CI: 1.43–2.27, P<0.001).

Α						В								
Study or subgroup	log (HR)	SE	Weight (%	HR W random 95% Cl	HR IV random 95% CI						HR		HR	
1.1.1 GPS	log (FIR)		Weight (70	TV, Tandoni, 3378 Of	TV, Tandolit, 3578 Ci		Study or subgroup	log (HR)	SE V	/eight (%) I\	V, random, 95% CI		IV, random, 95%	CI
Dreanic 2013	0.7472	0.2873	3.5	2.11 (1.20, 3.71)			1.2.1 GPS							
Furukawa 2011	2.0285	0.7078	1.1	7.60 (1.90, 30.44)			Choi 2014	1.6425	0.5496	1.8	5.17 (1.76, 15.18)			
Ishizuka 2016	0.5928	0.2176	4.3	1.81 (1.18, 2.77)			Dreanic 2013	0.4035	0.287	4.5	1.50 (0.85, 2.63)			
Kobayashi 2010	1.1217	0.4878	1.9	3.07 (1.18, 7.99)	-		Eren 2015	1.4115	0.5412	1.8	4.10 (1.42, 11.85)			
Lin 2015	0.4886	0.1605	5.1	1.63 (1.19, 2.23)			Ishizuka 2012	0.3155	0.3761	3.2	1.37 (0.66, 2.87)		+	
Madea 2013	0.6678	0.3158	3.2	1.95 (1.05, 3.62)			Maillet 2014	2.0605	0.841	0.8	7.85 (1.51, 40.81)			
Maillet 2014	1.6506	0.7407	1.0	5.21 (1.22, 22.25)			Okimoto 2017	1.0543	0.359	3.4	2.87 (1.42, 5.80)			_
Ni 2016	0.4662	0.1127	5.7	1.59 (1.28, 1.99)	-		Shibutani 2015 (1)	0.3716	0.3229	3.9	1.45 (0.77, 2.73)		+	
Okimolo 2017	0.4996	0.2757	3.6	1.65 (0.96, 2.83)			Sugimoto 2012	1.1282	0.3201	4.0	3.09 (1.65, 5.79)			_
Read 2009	0.2199	0.7898	0.9	1.25 (0.26, 5.86)			Subtotal (95% CI)			23.4	2 38 (1 63 3 46)		•	
Sharma 2008 Shikutani 2015 (1)	1.9906	0.5/9/	1.5	7.32 (2.35, 22.80)			Hotorogonoitu: -2=0.12: -2=12.7E	- d=7 (D=0	00) F=4E0		,,		·	
Shibutani 2015 (1) Shibutani 2015 (2)	1.0702	0.2913	3.5	2.40 (1.39, 4.30) 7.24 (1.18, 44.30)			Test for suprell effect: 7=4.61 /D	5, ar=7 (P=0.	J6); / =45%	D				
Subtotal (95% CI)	1.9793	0.9234	37.5	2 08 (1 69, 2 55)	•		Test for overall effect. 2=4.51 (F	<0.00001)						
Heterogeneity: r ² =0.04;	r ² =19.95, df=	13 (P=0.1	0); r ² =35%	,,	-									
Test for overall effect: Z=	6.93 (P<0.00	0001)					1.2.2 mGPS							
110-000							Hong 2017	0.5008	0.2306	5.7	1.65 (1.05, 2.59)			
1.1.2 mGPS	0.0000		0.0	0.00 (4.54.40.05)			Ide 2017	0.5766	0.421	2.7	1.78 (0.78, 4.06)			
Adachi 2014 Chan 2017	2.0903	0.8555	0.8	0.09 (1.01, 43.20)			Inoue 2013	0.6195	0.2176	6.0	1.86 (1.21, 2.85)			
Ghanim 2015	1 1145	0.2143	1.4	3.05 (0.93, 9.96)			Kim 2017	0.2624	0.1318	8.3	1.30 (1.00, 1.68)		-	
Ide 2017	0.6098	0.5803	1.5	1.84 (0.59, 5.74)			Kishiki 2013	1.311	0.3441	3.6	3.71 (1.89, 7.28)			
Kim 2017	0.4187	0.1388	5.4	1.52 (1.16, 2.00)			Leitch 2007 (resectable)	0.6981	0.3265	3.9	2.01 (1.06, 3.81)			
Leitch 2007 (resectable)	0.7275	0.2181	4.3	2.07 (1.35, 3.17)			Leitch 2007 (unresectable)	0.3784	0.1682	7.3	1 46 (1 05 2 03)			
Moug 2010	0.4447	0.1424	5.3	1.56 (1.18, 2.06)			McSorley 2017	0.6575	0.5102	2.0	1.93 (0. 71, 5.25)			-
Nozeo 2014	2.0028	0.3599	2.8	7.41 (3.66, 15.00)			Nakanawa 2014	0.4669	0 1642	74	1 60 (1 16 2 20)			
Okugawa 2018 (training Okugawa 2018 (validatir	n) 1.0900	0.3616	2.0	3 15 (2.06, 11.01)			Sirnio 2018	0.0296	0.3201	4.0	1.03 (0.55, 1.93)			
Shimura 2017	0.8587	0.423	2.3	2.36 (1.03, 5.41)			Sun 2014	0.8755	0 1471	7.9	2 40 (1 80 3 20)			
Sirnio 2018	0.3148	0.2619	3.8	1.37 (0.82, 2.29)	+		Teixeme 2011	1 6114	0.5924	1.6	E 01 (1 60 15 60)			
Son 2013	0.7962	0.5767	1.5	2.22 (0.72, 6.87)			Tolyana 2011	0.7000	0.0405	1.0	0.44 (4.40.0.07)			
Song 2015	0.1266	0.2343	4.1	1.13 (0.72, 1.80)	+-		Tokunaga 2017	0.7608	0.2105	0.0	2.14 (1.40, 3.27)		_	
Sun 2014	1.0879	0.1676	5.0	2.97 (2.14, 4.12)			Watt 2016	0.3075	0.0945	9.4	1.36 (1.13, 1.64)		· · · ·	
Tolyama 2011	1.0296	0.3428	2.9	2.80 (1.43, 5.48)			Yamamoto 2012	0.1931	0.7878	0.9	1.21 (0.26, 5.68)			-
Watt 2016	0.8901	0.2402	4.1	2.40 (1.03, 3.92)	-		Subiotal (95% CI)			/0.0	1.73 (1.47, 2.03)		•	
Subtotal (95% CI)	0.5075	0.0724	62.5	2.23 (1.79, 2.78)	•		Heterogeneity: τ ² =0.04; χ ² =28.10), <i>df</i> =14 (<i>P</i> =0	0.01); <i>l</i> *=50	%				
Heterogeneity: r ² =0.14;	2=70.68, df=	17 (P<0.0	10001); f=76	5%			Test for overall effect: Z=6.58 (P-	<0.00001)						
Test for overall effect: Z=	7.11 (P<0.00	0001)												
T-1-1 (059/ 01)			400.00/	0.00 (4.00, 0.57)			Total (95% CI)			100.0%	1.86 (1.59, 2.17)		•	
Hotorogonolity =2=0.10	2=01 05 df=	21 /0~0.0	100.0%	2.20 (1.00, 2.57)			Heterogeneity: r ² =0.10: v ² =91.05	5 df=31 (P<0	$(0001) \cdot \hat{f} =$	66%		—		
Test for overall effect: 7=	(-91.05, 0/= 9.87 (P<0.00	3 i (≓≪0.0)001)	1001), 7 = 66	0.01	0.1 1 10 10	0	Test for overall effect: Z=9.87 (P	<0.00001)		0070		0.01	0.1 1	10 100
Test for subgroup differe	nces: y ² =0 2	2 df=1 (P	=0.64) f=0	%	Favors HG Favors LG		Test for subgroup differences: v2	=2 35 df=1	P=0 13) P	=57.5%			Favors HG Favors L	G
rost is: subgroup differe		., ., ., ., .,	0.04), 1 =0				rost ion subgroup unterendes. 2	2.00, 01-11	, ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	01.070				

Figure 2 Subgroup analysis showing correlation between GPS and prognosis of CRC patients according to models. Note: (A) Overall survival and (B) cancer-specific survival.

Abbreviations: CRC, colorectal cancer; df, degrees of freedom; GPS, Glasgow prognostic score; mGPS, modified Glasgow prognostic score; LG, low group; HG, high group; SE, standard error.

Δ									R									
~	Study or subgroup	log (HR)	SE V	Weight (%) IV. random.	95% CI	IV. random. 9	95% CI	D					HR		HF	2	
	1.3.1 Resection				, , ,		,			Study or subgroup	log (HR)	SE	Weight (%)	V, random, 95% (IV, random	i, 95% Cl	
	Adachi 2014	2.0903	0.8555	0.8	8.09 (1.51, 4	(3.25)				1.4.1 Resection								
	Chan 2017	0.7948	0.2145	4.4	2.21 (1.45,	3.37)	-	-		Choi 2014	1.6425	0.5496	1.8	5.17 (1.76, 15.18	3)			_
	Ghanim 2015	1.1145	0.604	1.4	3.05 (0.93,	9.96)				Eren 2015	1.4115	0.5412	1.8	4.10 (1.42, 11.85	5)			-
	lde 2017	0.6098	0.5803	1.5	1.84 (0.59,	5.74)				Hong 2017	0.5008	0.2306	5.7	1.65 (1.05, 2.59	a)			
	Ishizuka 2016	0.5928	0.2176	4.3	1.81 (1.18	,2.77)				Ide 2017	0.5766	0.421	27	1 78 (0 78 4 06	s)	+		
	Kostpor 2016	0.4996	0.4676	1.9 E 1	3.07 (1.18,	7.99)	_	-		Isbizuka 2012	0 3155	0 3761	3.2	1 37 (0 66 2 8	ń	-		
	Leith 2007 (recectable)	0.4000	0.1005	4.3	2.07 (1.15)	3 17)		-		Kiebiki 2013	1 3 1 1	0.3441	3.6	3 71 (1 80 7 2	2)			
	Lin 2015	1 1681	0.5203	1.7	3.22 (1.16	8.92)				Laitab 2007 (assessed	0.0004	0.0005	3.0	0.04 (4.00, 0.04	<i>''</i>			
	Madea 2013	0.6678	0.3158	3.2	1.95 (1.05.	3.62)		_		Leitch 2007 (resectable)	0.6961	0.3205	3.9	2.01 (1.06, 3.8)			
	Moug 2010	0.4447	0.1424	5.3	1.56 (1.18,	2.06)	-			McSorley 2017	0.6575	0.5102	2.0	1.93 (0.71, 5.25)		•	
	Nozoe 2014	2.0028	0.3599	2.8	7.41 (3.66, 1	15.00)				Nakagawa 2014	0.4669	0.1642	7.4	1.60 (1.16, 2.20))			
	Okimoto 2017	0.4996	0.2757	3.6	1.65 (0.96,	2.83)	-	_		Okimoto 2017	1.0543	0.359	3.4	2.87 (1.42, 5.80))		-	
	Okugawa 2018 (training)	1.6956	0.3816	2.6	5.45 (2.58, 1	11.51)				Simio 2018	0.0296	0.3201	4.0	1.03 (0.55, 1.93	3)			
	Okugawa 2018 (validation) Shihutoni 2015 (2)	1.14/4	0.2167	4.3	3.15 (2.06.	4.82)				Sugimoto 2012	1.1282	0.3201	4.0	3.09 (1.65, 5.79	3)			
	Shimura 2017	0.8587	0.9234	2.3	2 36 (1.10, 4	5.41)				Sun 2014	0.8755	0.1471	7.9	2.40 (1.80, 3.20))			
	Simio 2018	0.3148	0.2619	3.8	1.37 (0.82	2.29)		_		Toiyama 2011	1.6114	0.5824	1.6	5.01 (1.60, 15.69	a)			_
	Son 2013	0.7962	0.5767	1.5	2.22 (0.72.	6.87)	+			Tokunaga 2017	0 7608	0 2165	6.0	2 14 (1 40 3 2)	ń		_	
	Sun 2014	1.0879	0.1676	5.0	2.97 (2.14,	4.12)				Watt 2016	0.3075	0.0945	9.4	1 36 (1 13 1 64	n i		-	
	Toiyama 2011	1.0296	0.3428	2.9	2.80 (1.43,	5.48)	-			Subtotal (95% CI)	0.0070	0.0010	68.2	2.06 (1.67, 2.5)	*)		.	
	Tokunaga 2017	0.8961	0.2402	4.1	2.45 (1.53,	3.92)	-			Subtotal (35% CI)			00.2	2.00 (1.07, 2.00	,		•	
	Watt 2016	0.3075	0.0724	6.1	1.36 (1.18,	1.57)	-	•		Heterogeneity: τ'=0.08; χ'=35.67, df	=15 (P=0.0	02); ľ°=5	8%					
	Subiotal (95% CI)			/ 3.5	2.30 (1.90,	2.79)	· ·	•		Test for overall effect: Z=6.81 (P<0.0	10001)							
	Heterogeneity: τ'=0.12; χ'=70.71	, df=22 (P<	< 0.00010	0); <i>I</i> °=69%														
	Test for overall effect: Z=8.51 (P-	<0.00001)								1.4.2 Chemotherapy								
	1.3.2 Chemotherapy									Dreanic 2013	0.4035	0287	4.5	1.50 (0.85, 2.63	5)	+		
	Dreanic 2013	0 7472	0 2673	3.6	2 11 (1 20	3 71)				Inoue 2013	0.6195	0.2176	6.0	1.86 (1.21, 2.85	á			
	Furukawa 2011	2.0285	0.7078	1.1	7.60 (1.90, 3	30.44)	· · ·			Kim 2017	0 2624	0.1318	8.3	1.30(1.00.1.68	ń	-	-	
	Kim 2017	0.4187	0.1386	5.4	1.52 (1.16,	2.00)	-			Leitch 2007 (unresectable)	0 3784	0 1682	73	1 46(1 05 2 03	n)		-	
	Maillet 2014	1.6506	0.7407	1.0	5.21 (1.22, 2	22.25)	-			Maillet 2014	2 0605	0.841	0.8	7 85(1 51 40 81	·/			
	Ni 2016	0.4662	0.1127	5.7	1.59 (1.28,	1.99)	-			Shihutani 2015 (1)	0.2716	0.0011	2.0	1 45(0 77 0 73	, 	_		
	Read 2009	0.2199	0.7896	0.9	1.25 (0.26,	5.86)				Shibutani 2015 (1)	0.3710	0.3229	3.9	1.43(0.77, 2.73	9			
	Shibutani 2005 (1)	0.0002	0.2013	3.6	2 46 (1 30	4 35)				ramamoto 2012	0.1931	0.7676	0.9	1.21 (0.20, 5.00	9		•	
	Song 2015	0.3002	0.2343	4.1	1 13 (0 72	1.80)				Subtotal (95% CI)			31.8	1.47(1.24, 1.74	-)		•	
	Subtotal (95% CI)	0.1200	0.2010	26.5	1.95 (1.46	2.62)	•	•		Heterogeneity: τ ² =0.00; χ ² =6.06, df=	6 (P=0.42);	<i>l°</i> =1%						
	Heterogeneity: 72=0.09: 72=19.36	df=8 (P<0	(0.01) f =	-59%	,	,				Test for overall effect: Z=4.48 (P<0.0	0001)							
	Test for overall effect: Z=4.48 (P-	<0.00001)	,, .															
	`	,								Total (95% CI)		1	00.0%	1.86 (1.59, 2.17)			•	
	Total (95% CI)		1	00.0%	2.20 (1.88, 1	2.57)		•		Heterogeneity: $\tau^2=0.06$: $\chi^2=45.42$ df	=22 (P=0 0)2): f=5:	2%		+	+		+
	Heterogeneity: τ ² =0.10; χ ² =91.05	, df=31 (P<	<0.00001	1); ľ=66%		0 02	01 1	10 50		Test for overall effect: 7=7 75 (Pc0 (0001	,,, 0.			0.02 0).1 1 [°]	10) 50
	Test for overall effect: Z=9.87 (P-	< 0.00001)					Favors HG Fa	ivors LG		Toot for outparoun differences: u ² =6 (0001) 00 df=1 (D	0.01) 6	-02 50/			Favors HG	Favors LG	
	Test for subgroup differences: 22	=0.86 df=1	I (P=0.3	5): $f=0\%$						rest for subgroup differences: X =0.0	io, ui≓1 (P=	0.01); 1	-03.3%					

Figure 3 Subgroup analysis showing correlation between GPS and prognosis of CRC patients according to therapeutic strategies.

Note: (A) Overall survival and (B) cancer-specific survival.

Abbreviations: CRC, colorectal cancer; df, degrees of freedom; GPS, Glasgow prognostic score; LG, low group; HG, high group; SE, standard error.

Α

			HR	HR								
Study or subgroup	log (HR) SE \	Neight (%) IV, random, 95% CI	IV, random, 95% CI	Study or subgroup	log (HR)	SE We	iaht (%)	HR IV random 95% CI	HR IV random 95% C	1	
1.5.1 1					1.6.1.1	log (LIIV)	OL WG	ignic (70)	IV, Tandoin, 3376 Of	Tv, Tandoni, 3376 C		
Chan 2017	0.7948 0.2145	4.4	2.21 (1.45, 3.37)		1.0.1 1							
Dreanic 2013	0.7472 0.2873	3.5	2.11 (1.20, 3.71)		Dreanic 2013	0.4035	0.287	4.5	1.50 (0.85, 2.63)			
Ghanim 2015	1.1145 0.604	1.4	3.05 (0.93, 9.96)		Hong 2017	0.5008	0.2306	5.7	1.65 (1.05, 2.59)		-	
lde 2017	0.6098 0.5803	1.5	1.84 (0.59, 5.74)		Ide 2017	0.5766	0.421	2.7	1.78 (0.78, 4.06)		· · ·	
Kobayashi 2010	1.1217 0.4878	1.9	3.07 (1.18, 7.99)		Inoue 2013	0.6195	0.2176	6.0	1.86 (1.21, 2.85)			
Kostner 2016	0.4886 0.1605	5.1	1.63 (1.19, 2.23)	<u> </u>	Ishizuka 2012	0.3155	0.3761	3.2	1 37 (0 66 2 87)	-		
Moug 2010	0.4447 0.1424	5.3	1.56 (1.18, 2.06)	-	McSoney 2017	0.6575	0.5102	2.0	1 03 (0 71 5 25)	-		
Ni 2016	0.4662 0.1127	5.7	1.59 (1.28, 1.99)		Nekagawa 2014	0.0070	0.1642	7.4	1.60 (1.16, 0.20)			
Okimoto 2017	0.4996 0.2757	3.6	1.65 (0.96, 2.83)		Nakagawa 2014	0.4009	0.1042	7.4	1.00 (1.10, 2.20)		-	
Read 2009	0.2199 0.7898	0.9	1.25 (0.26, 5.86)		Okimoto 2017	1.0543	0.359	3.4	2.87 (1.42, 5.80)			
Shibutani 2015 (1)	0.9002 0.2913	3.5	2.46 (1.39, 4.35)		Shibutani 2015 (1)	0.3716	0.3229	3.9	1.45 (0.77, 2.73)			
Shibutani 2015 (2)	1.9793 0.9254	0.7	7.24 (1.18, 44.39)	+	Sirnio 2018	0.0296	0.3201	4.0	1.03 (0.55, 1.93)	_	-	
Simio 2018	0.3148 0.2619	3.8	1.37 (0.82, 2.29)	+-	Sun 2014	0.8755	0.1471	7.9	2.40 (1.80, 3.20)		-	
Song 2015	0.1200 0.2343	4.1	1.13 (0.72, 1.60)	-	Toiyama 2011	1.6114	0.5824	1.6	5.01 (1.60, 15.69)		·	
Sun 2014 Toiwama 2011	1.00/9 0.10/0	5.0	2.97 (2.14, 4.12)		Tokunaga 2017	0 7608	0 2165	6.0	2 14 (1 40 3 27)			
Tolyania 2011	0.9061 0.3420	2.9	2.60 (1.43, 3.46)		Watt 2016	0 3075	0.0945	9.4	1 36 (1 13, 1 64)		-	
Watt 2016	0.0901 0.2402	6.1	1 36 (1 18 1 57)		Subtotal (05% CI)	0.0070	0.0010	67.6	1 74 (1 48, 2.05)		•	
Subtotal (95% CI)	0.3073 0.0724	63.3	1.85 (1.58, 2.16)	•				07.0	1.74 (1.40, 2.00)		•	
Heterogeneity: -2=0.05: -2=37	66 df-17 (P-0.003)	P=55%	1.00 (1.00, 2.10)		Heterogeneity: r=0.03; y=21.26	6, df=13 (P=0	07); 7=39%					
Test for overall effect: 7=7.63	(P<0.0001)	1-3370			Test for overall effect: Z=0.02 (P	~0.0001)						
1.5.2 2	(1 -0.0001)											
Adachi 2014	2.0903 0.8555	0.8	8.09 (1.51, 43.25)		1.6.2 2							
Furukawa 2011	2.0285 0.7078	1.1	7.60 (1.90, 30.44)		Choi 2014	1.6425	0.5496	1.8	5.17 (1.76, 15.18)			
Ishizuka 2016	0.5928 0.2176	4.3	1.81 (1.18,2.77)		Eren 2015	1.4115	0.5412	1.8	4.10 (1.42, 11.85)			
Kim 2017	0.4187 0.1388	5.4	1.52 (1.16, 2.00)	-	Kim 2017	0 2624	0 1318	8.3	1.30 (1.00, 1.68)		L	
Leitch 2007 (resectable)	0.7275 0.2181	4.3	2.07 (1.35. 3.17)		Kichiki 2013	1 3 1 1	0.3441	3.6	3 71 (1 80 7 28)			
Madea 2013	0.6678 0.3158	3.2	1.05 (1.05, 3.62)		Leitch 2007 (resectable)	0.6981	0.3265	3.0	2.01 (1.06, 3.81)			
Maillet 2013	1 6506 0 7407	1.0	5 21 (1 22 22 25)		Leitch 2007 (resocrable)	0.0301	0.3203	7.0	2.01 (1.00, 3.01)			
Nozoe 2014	2 0028 0 3599	2.8	7 41 (3 66, 15 00)		Leitch 2007 (unresectable)	0.3764	0.1662	1.3	1.46 (1.05, 2.03)		-	
Okugawa 2018 (training)	1.6956 0.3816	2.6	5.45 (2.58, 11.51)		Maillet 2014	2.0605	0.841	0.8	7.85 (1.51, 40.81)			_
Okugawa 2018 (validation)	1.1474 0.2167	4.3	3.15 (2.06, 4.82)		Sugimoto 2012	1.1282	0.3201	4.0	3.09 (1.65, 5.79)			
Sharma 2008	1.9906 0.5797	1.5	7.32 (2.35, 22.80)		Yamamoto 2012	0.1931	0.7878	0.9	1.21 (0.26, 5.68)			
Shimura 2017	0.8587 0.423	2.3	2.36 (1.03, 5.41)		Subtotal (95% CI)			32.4	2.34 (1.61, 3.40)		•	
Son 2013	0.7962 0.5767	1.5	2.22 (0.72, 6.87)		11-t	7	001 6-070					
Subtotal (95% CI)		36.7	3.02 (2.21, 4.13)	•	Test for overall effect: 7=4.47 (P	7, 01=6 (P=0.0	02); 1=61%					
Heterogeneity: r ² =0.20; x ² =39	.04, df=13 (P=0.0002)	; ľ=67%			103c 101 Overall Bliect. Z-4.47 (P	-0.00001)						
Test for overall effect: Z=6.89	(P<0.0001)				T-1-1 (05% OI)			0.00/	4 00 (4 50 0 47)			
Total (95% CI)	10	0.0%	2 20 (1 88 2 57)		IOIBI (95% CI)		10	10.0%	1.00 (1.59, 2.17)		•	
Heterogeneity: r ² =0 10: v ² =91	05 df=31 (P<0.0000)	1): f=66%			Heterogeneity: τ ² =0.06; χ ² =45.42	2, df=22 (P<0	002); / ² =529	%	H 1	+		
Test for overall effect: 7=9.87	(P<0.0001)	1, 1 -00 %	0.01	0.1 1 10 100	Test for overall effect: Z=7.75 (P	<0.00001)			0.0	J1 0.1	1 10	100
Toot ion overall effect. 2-3.07			70/	Eavors HG Eavors I G	Test for subgroup differences: x ²	=2.06 df=1 (P=0 15) / =	51.5%		Eavors HG	Favors I G	

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Figure 4 Subgroup analysis showing correlation between GPS and prognosis of CRC patients according to cutoff values. Note: (A) Overall survival and (B) cancer-specific survival.

Abbreviations: CRC, colorectal cancer; df, degrees of freedom; GPS, Glasgow prognostic score; LG, low group; HG, high group; SE, standard error.

Α	Study or subgroup	log (HR) S	E Weight (%)	HR IV. random, 95% CI	HR IV. random, 95% CI	в	0	I (UD)	05 1	Malah (0/)	HR	D.(-	HR OF C	
	1.7.1 Asia						1 8 1 Asia	log (HR)	SE V	veight (%)	IV, random, 95% CI	IV, 6	andom, 95% CI	
	Adachoi 2014	2.0903 0.85	56 0.8	8.09 (1.51, 43.25)			Ob-1 2011	4.0405	0.5400	4.0	5 47 (4 70 45 40)			
	Furokawa 2011	2.0285 0.70	78 1.1	7.60 (1.90, 30.44)			Choi 2014	1.6425	0.5496	1.0	5.17 (1.76, 15.16)			
	lde 2017 Jebizuka 2016	0.5028 0.2	03 1.5 76 4.3	1.84 (0.59, 5.74)			Hong 2017	0.5008	0.2306	5.7	1.00 (1.00, 2.09)			
	Kim 2017	0.4187 0.13	88 54	1.52 (1.16, 2.00)	-		Ide 2017	0.5766	0.421	2.1	1.78 (0.78, 4.06)			
	Kobayashi 2010	1.1217 0.48	78 1.9	3.07 (1.18, 7.99)			Inoue 2013	0.6195	0.2176	6.0	1.86 (1.21, 2.85)			
	Lin 2015	1.1681 0.52	03 1.7	3.22 (1.16, 8.92)			Isnizuka 2012	0.3155	0.3761	3.2	1.37 (0.66, 2.87)			
	Madea 2013	0.6678 0.31	58 3.2	1.95 (1.05, 3.62)			Kim 2017	0.2624	0.1318	8.3	1.30 (1.00, 1.68)		-	
	Ni 2016	0.4662 0.11	27 5.7	1.59 (1.28, 1.99)			Kishiki 2013	1.311	0.3441	3.6	3.71 (1.89, 7.28)			
	Okimoto 2017	2.0028 0.35	99 2.8 57 3.6	1.65 (0.96, 15.00)	·		Nakagawa 2014	0.4669	0.1642	7.4	1.60 (1.16, 2.20)		-	
	Okygawa 2018 (training)	1.6956 0.38	16 2.6	5.45 (2.58, 11.51)			Okimoto 2017	1.0543	0.359	3.4	2.87 (1.42, 5.80)			
	Okugawa 2018 (validation)	1.1474 0.21	67 4.3	3.15 (2.06, 4.82)			Shibutani 2015 (1)	0.3716	0.3229	3.9	1.45 (0.77, 2.73)		+	
	Shibutani 2015 (1)	0.9002 0.29	13 3.5	2.46 (1.39, 4.35)			Sugimoto 2012	1.1282	0.3201	4.0	3.09 (1.65, 5.79)			
	Shibutani 2015 (2)	1.9793 0.92	54 0.7	7.24 (1.18, 44.39)			Sun 2014	0.8755	0.1471	7.9	2.40 (1.80, 3.20)		-	
	Shimura 2017	0.8567 0.4	23 2.3	2.36 (1.03, 5.41)			Toiyama 2011	1.6114	0.5824	1.6	5.01 (1.60, 15.69)			
	Song 2015	0.1266 0.23	43 4.1	1 13 (0.72, 1.80)			Tokunaga 2017	0.7608	0.2165	6.0	2.14 (1.40, 3.27)			
	Sun 2014	1.0879 0.16	76 5.0	2.97 (2.14, 4.12)			Yamamoto 2012	0.1931	0.7878	0.9	1.21 (0.26, 5.68)	-		
	Toiyama 2011	1.0296 0.34	28 2.9	2.80 (1.43, 5.48)			Subtotal (95% CI)			66.4	2.01 (1.65, 2.44)		•	
	Tokunaga 2017	0.8961 0.24	02 4.1	2.45 (1.53, 3.92)	—		Hotorogonoitu: -2=0.06: -2=27.96	df=14 (D=0)	01) C=50	10/			· ·	
	Subtotal (95% CI)		62.8	2.44 (1.98, 3.02)	•		Test for overall effect: Z=7.03 (P<	0.0001)	51), 7 = 30	J 70				
	Test for overall effect: 7=8.28 (I	8, ar=20 (P<0.	JUUT); / =64%					, , ,						
	163t 101 0Verall effect. 2=0.20 (/	~0.0001)					1.8.2 Others							
	1.7.2 Others						Dreanic 2013	0.4035	0.287	4.5	1 50 (0 85 2 63)			
	Chan 2017	0.7948 0.21	45 4.4	2.21 (1.45, 3.37)			Eren 2015	1 4115	0.5412	1.0	4 10 (1 42 11 85)			
	Dreanic 2013	0.7472 0.28	73 3.5	2.11 (1.20, 3.71)			Leitch 2007 (resectable)	0.6981	0.3265	3.0	2.01 (1.06 3.81)			
	Gnanim 2015 Keetner 2016	0.4886_0.16	04 1.4	3.05 (0.93, 9.96)			Leiteh 2007 (upresenteble)	0.0301	0.3203	7.2	2.01 (1.00, 3.01) 1.46 (1.05, 3.03)			
	Leitch 2007 (resectable)	0.7275 0.21	81 4.3	2 07 (1.35, 3.17)			Moillot 2014	2.0605	0.1002	7.3	7 95 (1 51 40 91)			_
	Maillet 2014	1.6506 0.74	07 10	5.21 (1.22, 22.25)			Mallet 2014	2.0005	0.041	0.0	1.00 (0.74 5.05)			
	Moug 2010	0.4447 0.14	24 5.3	1.56 (1.18, 2.06)	-		McSoney 2017	0.6575	0.5102	2.0	1.93 (0.71, 5.25)			
	Read 2009	0.2199 0.78	98 0.9	1.25 (0.26, 5.86)			Simio 2018	0.0296	0.3201	4.0	1.03 (0.55, 1.93)			
	Sharma 2008 Sirpio 2018	1.9906 0.5/	9/ 1.5	1 37 (0 82 2 20)			Watt 2016	0.3075	0.0945	9.4	1.30 (1.13, 1.04)			
	Watt 2016	0.3075 0.07	24 6.1	1.36 (1.18, 1.57)	÷		Subtotal (95% CI)			33.6	1.56 (1.24, 1.96)		•	
	Subtotal (95% CI)		37.2	1.79 (1.47, 2.18)	•		Heterogeneity: τ ² =0.06; χ ² =45.42,	df=22 (P=0.	002); <i>ľ</i> =5	52%				
	Heterogeneity: r2=0.04; 2=20.4	4, df=10 (P=0.	03); <i>f</i> =51%				Test for overall effect: Z=7.75 (P<0	0.00001)						
	Test for overall effect: Z=5.77 (#	P<0.00001)												
	Total (05% CI)		100.0%	2 20 /1 99 2 57)			Total (95% CI)			100.0%	1.86 (1.59, 2.17)		•	
	Heterogeneity: -2=0.10: -2=01.0	5 df=31 (Pc0	100.0%	2.20 (1.00, 2.07)			Heterogeneity: τ ² =0.06; χ ² =45.42,	df=22 (P=0.	002); <i>ľ</i> =5	52%	F			
	Test for overall effect: Z=9.87 (F	P<0.00001)	50001), 7 = 00%	' Ò.01	0.1 1 10 100		Test for overall effect: Z=7.75 (P<0	0.00001)			0	1.01 0.1 Favors	HG Favors I G	100
	Test for subgroup differences:	2=4.45. df=1 (A	=0.03); f=77 f	5%	Pavors HG Pavors LG		Test for subgroup differences: $\chi^2 = 2$	2.69, <i>df</i> =1 (F	P=0.10); f	°=62.8%		1 87018		
			, ,											

Figure 5 Subgroup analysis showing correlation between GPS and prognosis of CRC patients according to the region of publication. Note: (A) Overall survival and (B) cancer-specific survival.

Abbreviations: CRC, colorectal cancer; df, degrees of freedom; GPS, Glasgow prognostic score; LG, low group; HG, high group; SE, standard error.

Sensitivity analysis and publication bias

Sensitivity analysis was conducted by omitting the included studies in sequence to investigate the stability of HR for OS. The results showed that several studies deviated from the center line (Figure 9A).^{15,51,52,55,58} After eliminating these studies, the pooled HRs did not alter significantly (Figure 9B).

associated with publication bias (Figure 9D). In addition, statistical tests were carried out to evaluate dissymmetry of the funnel plot using Begg (z=1.86, P=0.132) and Egger (bias coefficient -0.905, standard error 0.405, t=1.91, P=0.070) tests.

The funnel plot showed publication bias in the included studies (Figure 9C). The studies were almost symmetrically distributed around the center line after removing the studies

Discussion

CRC is one of the most common gastrointestinal malignancies and accounts for ~10% of all newly diagnosed Α

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				HR	HR
Study or subgroup	log (HR)	SE	Weight (%)	IV, random, 95% CI	IV, random, 95% CI
1.9.1 Mean/median <65					
Adachi 2014	2.0903	0.8555	0.9	8.09 (1.51, 43.25)	
Ghanim 2015	1 1145	0 604	16	3.05 (0.93, 9.96)	
Ide 2017	0 6098	0.5803	1.0	1 84 (0 59 5 74)	
Kim 2017	0.0000	0.0000	5.9	1.52 (1.16, 2.00)	-
Lin 2015	1 1681	0.5203	2.0	3 22 (1 16 8 02)	
LII 2015	1.1001	0.5205	2.0	1 50 (1 20 1 00)	-
NI 2016	0.4662	0.1127	6.2	1.59 (1.28, 1.99)	
Okimoto 2017	0.4996	0.2757	4.1	1.65 (0.96, 2.83)	
Read 2009	0.2199	0.7898	1.0	1.25 (0.26, 5.86)	
Shibutani 2015 (1)	0.9002	0.2913	3.9	2.46 (1.39, 4.35)	
Song 2015	0.1266	0.2343	4.6	1.13 (0.72, 1.80)	+-
Sun 2014	1.0879	0.1676	5.5	2.97 (2.14, 4.12)	
Subtotal (95% CI)			37.2	1.91 (1.50, 2.43)	◆
Heterogeneity: τ^2 =0.07; χ^2 =21.98 Test for overall effect: Z=5.23 (P<	, <i>df</i> =10 (<i>P</i> =0.02) 0.00001)	; / ²=55%			
1 9 2 Mean/median >65	0.00001)				
Chop 2017	0 70 40	0.2145	10	2 21 (1 /5 2 27)	
	0.7948	0.2145	4.0	2.21 (1.40, 0.01)	
Furukawa 2011	2.0285	0.7078	1.2	7.60 (1.90, 30.44)	
Ishizuka 2016	0.5928	0.2176	4.8	1.81 (1.18, 2.77)	
Kostner 2016	0.4886	0.1605	5.6	1.63 (1.19, 2.23)	-
Leitch 2007 (resectable)	0.7275	0.2181	4.8	2.07 (1.35, 3.17)	
Maillet 2014	1.6506	0.7407	1.1	5.21 (1.22, 22.25)	· · · · · · · · · · · · · · · · · · ·
Moua 2010	0.4447	0.1424	5.8	1.56 (1.18. 2.06)	-
Nozoe 2014	2 0028	0.3599	3.1	7.41(3.66. 15.00)	·
Okugawa 2018 (training)	1 6056	0.3816	29	5 45 (2 58 11 51)	
	1.0900	0.0010	2.3	0.40 (2.00, 11.01)	
Okugawa 2018 (Validation)	1.1474	0.210/	4.8	3.15 (2.00, 4.82)	
sharma 2008	1.9906	0.5797	1.7	1.32 (2.35, 22.80)	
Shibutani 2015 (2)	1.9793	0.9254	0.8	7.24 (1.18, 44.39)	· · · · · · · · · · · · · · · · · · ·
Shimura 2017	0.8587	0.423	2.6	2.36 (1.03, 5.41)	
Sirnio 2018	0.3148	0.2619	4.2	1.37 (0.82, 2.29)	+
Toivama 2011	1.0296	0.3428	3.3	2.80 (1.43, 5.48)	— . —
Tokunaga 2017	0 8961	0.2402	4.5	2 45 (1 53 3 92)	
Watt 2016	0.3075	0.0724	6.6	1.36 (1.18, 1.57)	-
Subtotal (95% CI)	0.0010		62.8	2 46 (1 93, 3 13)	•
Total (95% CI)		104) R-	100.0	2.21 (1.86, 2.62)	•
Total (95% Cl) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (P< Test for subgroup differences: χ^2 =	, df=27 (P<0.000 0.00001) :2.15, df=1 (P=0.	001); <i>I</i> ²= .14), <i>I</i> ²={	100.0 70% 53.4%	2.21 (1.86, 2.62) –––– 0.01	0.1 1 10 100 Favors HG Favors LG
Total (95% CI) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (<i>P</i> < Test for subgroup differences: χ^2 =	, <i>df=27 (P<</i> 0.000 0.00001) :2.15, <i>df=</i> 1 (<i>P</i> =0.	001); I ² =' .14), I ² =!	100.0 70% 53.4%	2.21 (1.86, 2.62) 0.01	0.1 1 10 100 Favors HG Favors LG
Total (95% CI) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (P <i Test for subgroup differences: χ^2= Study or subgroup</i 	, df=27 (P<0.000 0.00001) :2.15, df=1 (P=0. log (HR)	001); /²=' 14), /²=; SE	100.0 70% 53.4% Weight (%)	2.21 (1.86, 2.62) 0.01 HR IV, random, 95% CI	0.1 1 10 100 Favors HG Favors LG HR IV, random, 95% CI
Total (95% CI) Heterogeneity: τ ² =0.11; χ ² =89.22, Test for overall effect: Z=9.15 (P< Test for subgroup differences: χ ² = Study or subgroup 1.10.1 Mean/median <65	, df=27 (P<0.000 0.00001) :2.15, df=1 (P=0. log (HR)	001);	100.0 70% 53.4% Weight (%)	2.21 (1.86, 2.62) 0.01 HR IV, random, 95% CI	0.1 1 10 100 Favors HG Favors LG HR IV, random, 95% CI
Total (95% CI) Heterogeneitly: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (P <i Test for subgroup differences: χ^2= Study or subgroup 1.10.1 Mean/median <65 Choi 2014</i 	, df=27 (P<0.000 0.00001) :2.15, df=1 (P=0. log (HR) 1.6425	001); P= .14), P= .5E 0.5496	100.0 70% 53.4% Weight (%) 1.9	2.21 (1.86, 2.62) 0.01 HR IV, random, 95% CI 5.17 (1.76, 15.18)	0.1 1 10 100 Favors HG Favors LG HR IV, random, 95% CI
Total (95% CI) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (P< Test for subgroup differences: χ^2 = Study or subgroup 1.10.1 Mean/median <65 Choi 2014 Hong 2017	, df=27 (P<0.000 0.00001) :2.15, df=1 (P=0. log (HR) 1.6425 0.5008	001); / ² = .14), / ² = .5E 0.5496 0.2306	100.0 70% 53.4% Weight (%) 1.9 6.6	2.21 (1.86, 2.62) 	0.1 1 10 100 Favors HG Favors LG HR IV, random, 95% CI
Total (95% CI) Heterogeneity: τ ² =0.11; χ ² =89.22, Test for overall effect: Z=9.15 (<i>P</i> Test for subgroup differences: χ ² = Study or subgroup 1.10.1 Mean/median <65	, df=27 (P<0.000 0.00001) 2:15, df=1 (P=0. log (HR) 1.6425 0.5008 0.5766	001); P= 14), P= SE 0.5496 0.2306 0.421	100.0 70% 53.4% Weight (%) 1.9 6.6 3.0	2.21 (1.86, 2.62) HR IV, random, 95% CI 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06)	0.1 1 10 100 Favors HG Favors LG HR IV, random, 95% CI
Total (95% CI) Heterogeneitly: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (P <i Test for subgroup differences: χ^2= Study or subgroup 1.10.1 Mean/median <65 Choi 2014 Hong 2017 Ide 2017 Incure 2013</i 	, df=27 (P<0.000 0.00001) :2.15, df=1 (P=0 log (HR) 1.6425 0.5008 0.5766	$\begin{array}{c} 001); \ P=\\ 14), \ P=\\ \\ \hline \\ SE\\ 0.5496\\ 0.2306\\ 0.421\\ 0.2176\end{array}$	100.0 70% 53.4% Weight (%) 1.9 6.6 3.0 7.0	2.21 (1.86, 2.62) 0.01 HR IV, random, 95% CI 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06) 1.86 (1.2, 2.85)	0.1 1 10 100 Favors HG Favors LG HR IV, random, 95% CI
Total (95% CI) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (P< Test for subgroup differences: χ^2 = Study or subgroup 1.10.1 Mean/median <65 Choi 2014 Hong 2017 Ide 2017 Inoue 2013	, df=27 (P<0.000 0.00001) :2.15, df=1 (P=0. log (HR) 1.6425 0.5008 0.5766 0.6195	(001); P = 14), P =	100.0 70% 53.4% Weight (%) 1.9 6.6 3.0 7.0 40.0	2.21 (1.86, 2.62) 	0.1 1 10 100 Favors HG Favors LG HR IV, random, 95% CI
Total (95% CI) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (P <i Test for subgroup differences: χ^2= Study or subgroup 1.10.1 Mean/median <65 Choi 2014 Hong 2017 Inoue 2013 Kim 2017</i 	, df=27 (P<0.000 0.00001) 2.15, df=1 (P=0. log (HR) 1.6425 0.5008 0.5766 0.6195 0.2624	001); <i>P</i> = 14), <i>P</i> = SE 0.5496 0.2306 0.421 0.2176 0.1318	100.0 70% 53.4% <u>Weight (%)</u> 1.9 6.6 3.0 7.0 10.0	2.21 (1.86, 2.62) HR IV, random, 95% CI 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06) 1.86 (1.21, 2.85) 1.30 (1.00, 1.68) 	0.1 1 10 100 Favors HG Favors LG HR IV, random, 95% CI
Total (95% CI) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (P <i Test for subgroup differences: χ^2= Study or subgroup 1.10.1 Mean/median <65 Choi 2014 Hong 2017 Ide 2017 Inoue 2013 Kim 2017 Nakagawa 2014</i 	, df=27 (P<0.000 0.00001) :2.15, df=1 (P=0. log (HR) 1.6425 0.5008 0.5766 0.6195 0.2624 0.4669	001); P= 14), P= SE 0.5496 0.2306 0.421 0.2176 0.1318 0.1642	100.0 70% 53.4% Weight (%) 1.9 6.6 3.0 7.0 10.0 8.8	2.21 (1.86, 2.62) 0.01 HR IV, random, 95% Cl 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06) 1.86 (1.21, 2.85) 1.30 (1.00, 1.68) 1.60 (1.16, 2.20)	0.1 1 10 100 Favors HG Favors LG HR IV, random, 95% CI
Total (95% CI) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (P< Test for subgroup differences: χ^2 = Study or subgroup 1.10.1 Mean/median <65 Choi 2014 Hong 2017 Ide 2017 Inoue 2013 Kim 2017 Nakagawa 2014 Okimoto 2017	, df=27 (P<0.000 0.00001) :2.15, df=1 (P=0. log (HR) 1.6425 0.5008 0.5766 0.6195 0.2624 0.4669 1.0543	001); P= 14), P= SE 0.5496 0.2306 0.421 0.2176 0.1318 0.1642 0.359	100.0 70% 53.4% Weight (%) 1.9 6.6 3.0 7.0 10.0 8.8 3.8	2.21 (1.86, 2.62) 0.01 HR IV, random, 95% CI 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06) 1.86 (1.21, 2.85) 1.30 (1.00, 1.86) 1.60 (1.16, 2.20) 2.87 (1.42, 5.80)	0.1 1 10 100 Favors HG Favors LG HR IV, random, 95% CI
Total (95% CI) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (P <i Test for subgroup differences: χ^2= Study or subgroup 1.10.1 Mean/median <65 Choi 2014 Hong 2017 Inoue 2013 Kim 2017 Nakagawa 2014 Okimoto 2017 Shibulani 2015 (1)</i 	, df=27 (P<0.000 0.00001) :2.15, df=1 (P=0 1.6425 0.5008 0.5766 0.6195 0.2624 0.4669 1.0543 0.3716	001); $P=$ 14), $P=$ SE 0.5496 0.2306 0.421 0.2176 0.1318 0.1642 0.359 0.3229	100.0 70% 53.4% <u>Weight (%)</u> 1.9 6.6 3.0 7.0 10.0 8.8 3.8 4.4	2.21 (1.86, 2.62) 	0.1 1 10 100 Favors HG Favors LG HR IV, random, 95% CI
Total (95% CI) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (<i>P</i> <i Test for subgroup differences: χ^2= Study or subgroup 1.10.1 Mean/median <65 Choi 2014 Hong 2017 Ide 2017 Inoue 2013 Kim 2017 Nakagawa 2014 Okimoto 2017 Shibulani 2015 (1) Sun 2014</i 	, df=27 (P<0.000 0.00001) :2.15, df=1 (P=0 log (HR) 1.6425 0.5008 0.5766 0.6195 0.2624 0.4669 1.0543 0.3716 0.3716	001); ℓ ² = 14), ℓ ² = <u>SE</u> 0.5496 0.2306 0.421 0.2176 0.1642 0.3529 0.3229 0.1471	100.0 70% 53.4% Weight (%) 1.9 6.6 3.0 7.0 10.0 8.8 3.8 4.4 9.5	2.21 (1.86, 2.62) 0.01 HR IV, random, 95% Cl 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06) 1.86 (1.21, 2.85) 1.30 (1.00, 1.68) 1.60 (1.16, 2.20) 2.87 (1.42, 5.80) 1.45 (0.77, 2.73) 2.40 (1.80, 3.20)	0.1 1 10 100 Favors HG Favors LG HR IV, random, 95% CI
Total (95% CI) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (<i>P</i> Test for subgroup differences: χ^2 = Study or subgroup 1.10.1 Mean/median <65	, df=27 (P<0.000 0.00001) 2.15, df=1 (P=0. log (HR) 1.6425 0.5008 0.5766 0.6195 0.2624 0.4669 1.0543 0.3716 0.8755	001); P ² = 14), P ² = <u>SE</u> 0.5496 0.2306 0.421 0.2176 0.1642 0.359 0.3229 0.1471	100.0 70% 53.4% Weight (%) 1.9 6.6 3.0 7.0 10.0 8.8 3.8 4.4 9.5 54.9	2.21 (1.86, 2.62) U.0.1 HR IV, random, 95% Cl 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06) 1.86 (1.21, 2.85) 1.30 (1.00, 1.68) 1.60 (1.16, 2.20) 2.87 (1.42, 5.80) 1.46 (0.77, 2.73) 2.40 (1.80, 3.20) 1.83 (1.47, 2.27)	0.1 1 10 100 Favors HG Favors LG
Total (95% CI) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (P< Test for subgroup differences: χ^2 = Study or subgroup 1.10.1 Mean/median <65 Choi 2014 Hong 2017 Ide 2017 Inoue 2013 Kim 2017 Nakagawa 2014 Okimoto 2017 Shibulani 2015 (1) Sun 2014 Subtotal (95% CI) Heterogeneity: τ^2 =0.05; χ^2 =16.28 Test for overall effect: Z=5.46 (P<	, df=27 (P<0.000 0.00001) :2.15, df=1 (P=0. log (HR) 1.6425 0.5008 0.5766 0.6195 0.2624 0.4669 1.0543 0.3716 0.8755 , df=8 (P=0.04); 0.00001)	001); <i>P</i> = 14), <i>P</i> = SE 0.5496 0.2306 0.421 0.2176 0.1318 0.1642 0.359 0.3229 0.1471 <i>P</i> =51%	100.0 70% 53.4% <u>Weight (%)</u> 1.9 6.6 3.0 7.0 10.0 8.8 3.8 4.4 9.5 54.9	2.21 (1.86, 2.62) 0.01 HR IV, random, 95% CI 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06) 1.86 (1.21, 2.85) 1.30 (1.00, 1.68) 1.60 (1.16, 2.20) 2.87 (1.42, 5.80) 1.45 (0.77, 2.73) 2.40 (1.80, 3.20) 1.83 (1.47, 2.27)	0.1 1 10 100 Favors HG Favors LG HR IV, random, 95% CI
Total (95% CI) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (<i>P</i> Test for subgroup 11 1.10.1 Mean/median <65	, df=27 (P<0.000 0.00001) 22.15, df=1 (P=0. 1.6425 0.5008 0.5766 0.6195 0.2624 0.4669 1.0543 0.3716 0.8755 , df=8 (P=0.04); 0.00001)	001); ℓ= 14), ℓ= SE 0.5496 0.2306 0.421 0.421 0.359 0.3229 0.1471 ℓ=51%	100.0 70% 53.4% Weight (%) 1.9 6.6 3.0 7.0 10.0 8.8 3.8 4.4 9.5 54.9	2.21 (1.86, 2.62) 0.01 HR IV, random, 95% Cl 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06) 1.86 (1.21, 2.85) 1.30 (1.00, 1.68) 1.60 (1.16, 2.20) 2.87 (1.42, 5.80) 1.45 (0.77, 2.73) 2.40 (1.80, 3.20) 1.83 (1.47, 2.27)	0.1 1 10 100 Favors HG Favors LG HR IV, random, 95% Cl
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Total (95% CI) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (<i>P</i> Test for subgroup 11.10.1 Mean/median <65	, df=27 (P<0.000 0.00001) :2.15, df=1 (P=0. log (HR) 1.6425 0.5008 0.5766 0.6195 0.2624 0.4669 1.0543 0.3716 0.8755 , df=8 (P=0.04); 0.00001) 1.4115	001); ℓ= 14), ℓ= SE 0.5496 0.2306 0.421 0.2176 0.359 0.1471 ℓ=51% 0.5412	100.0 70% 53.4% Weight (%) 1.9 6.6 3.0 7.0 10.0 8.8 3.8 4.4 9.5 54.9 2.0	2.21 (1.86, 2.62) 0.01 HR IV, random, 95% Cl 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06) 1.86 (1.21, 2.85) 1.30 (1.00, 1.68) 1.60 (1.16, 2.20) 2.87 (1.42, 5.80) 1.45 (0.77, 2.73) 2.40 (1.80, 3.20) 1.83 (1.47, 2.27) 4.10 (1.42, 11.85)	0.1 1 10 100 Favors HG Favors LG
Total (95% CI) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (<i>P</i> Test for subgroup 11.0.1 Mean/median <65	, df=27 (P<0.000 0.00001) 22.15, df=1 (P=0. 1.6425 0.5008 0.5766 0.6195 0.2624 0.4669 1.0543 0.3716 0.8755 , df=8 (P=0.04); 0.00001) 1.4115 0.3155	001); ℓ= 14), ℓ= SE 0.5496 0.2306 0.421 0.2176 0.359 0.3229 0.1471 ℓ=51% 0.5412 0.3761	100.0 70% 53.4% Weight (%) 1.9 6.6 3.0 7.0 10.0 8.8 3.8 4.4 9.5 54.9 2.0 3.5	2.21 (1.86, 2.62) 0.01 HR IV, random, 95% Cl 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06) 1.86 (1.21, 2.85) 1.30 (1.00, 1.68) 1.60 (1.16, 2.20) 2.87 (1.42, 5.80) 1.45 (0.77, 2.73) 2.40 (1.80, 3.20) 1.83 (1.47, 2.27) 4.10 (1.42, 11.85) 1.37 (0.66, 2.87)	0.1 1 10 100 Favors HG Favors LG HR IV, random, 95% CI
Total (95% CI) Heterogeneity: r^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (P <i Test for subgroup differences: χ^2= Study or subgroup 1.10.1 Mean/median <65 Choi 2014 Hong 2017 Ide 2017 Inoue 2013 Kim 2017 Nakagawa 2014 Okimoto 2017 Shibulani 2015 (1) Sun 2014 Subtotal (95% CI) Heterogeneity: τ^2=0.05; χ^2=16.28 Test for overall effect: Z=5.46 (P<i 1.10.2 Mean/median ≥65 Eren 2015 Ishizuka 2012 Leilch 2007 (reseclable)</i </i 	, df=27 (P<0.000 0.00001) :2.15, df=1 (P=0. 1.6425 0.5008 0.5766 0.6195 0.2624 0.4669 1.0543 0.3716 0.8755 , df=8 (P=0.04); 0.00001) 1.4115 0.3155 0.6981	001); ℓ= 14), ℓ= SE 0.5496 0.2306 0.421 0.2176 0.359 0.3229 0.1471 ℓ=51% 0.5412 0.3761 0.3265	100.0 70% 53.4% Weight (%) 1.9 6.6 3.0 7.0 10.0 8.8 3.8 4.4 9.5 54.9 2.0 3.5 4.3	2.21 (1.86, 2.62) 0.01 HR IV, random, 95% CI 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06) 1.86 (1.21, 2.85) 1.30 (1.00, 1.68) 1.60 (1.16, 2.20) 2.87 (1.42, 5.80) 1.45 (0.77, 2.73) 2.40 (1.80, 3.20) 1.83 (1.47, 2.27) 4.10 (1.42, 11.85) 1.37 (0.66, 2.87) 2.01 (1.06, 3.81)	0.1 1 10 100 Favors HG Favors LG
Total (95% CI) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (<i>P</i> <i Test for overall effect: Z=9.15 (<i>P</i><i Test for subgroup 1.10.1 Mean/median <65 Choi 2014 Hong 2017 Inoue 2013 Kim 2017 Nakagawa 2014 Okimoto 2017 Shibulani 2015 (1) Sun 2014 Subtotal (95% CI) Heterogeneity: τ^2=0.05; χ^2=16.28 Test for overall effect: Z=5.46 (<i>P</i></i </i 	, df=27 (P<0.000 0.00001) :2.15, df=1 (P=0. log (HR) 1.6425 0.5008 0.5766 0.6195 0.2624 0.4669 1.0543 0.3716 0.8755 0.2624 0.4669 1.0543 0.3716 0.8755 0.4f=8 (P=0.04); 0.00001) 1.4115 0.3155 0.6981	001); ℓ= 14), ℓ=; SE 0.5496 0.2306 0.421 0.2176 0.359 0.3229 0.1318 0.1642 0.359 0.3229 0.1471 ℓ=51% 0.5412 0.3761 0.3265 0.3265 0.3265	100.0 70% 53.4% Weight (%) 1.9 6.6 3.0 7.0 10.0 8.8 3.8 4.4 9.5 54.9 2.0 3.5 54.9	2.21 (1.86, 2.62) 0.01 HR IV, random, 95% Cl 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06) 1.86 (1.21, 2.85) 1.30 (1.00, 1.68) 1.60 (1.16, 2.20) 2.87 (1.42, 5.80) 1.45 (0.77, 2.73) 2.40 (1.80, 3.20) 1.83 (1.47, 2.27) 4.10 (1.42, 11.85) 1.37 (0.66, 2.87) 2.01 (1.05, 2.03)	0.1 1 10 100 Favors HG Favors LG
Total (95% CI) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect. Z=9.15 (<i>P</i> Test for subgroup differences: χ^2 = Study or subgroup differences: χ^2 = Study or subgroup differences: χ^2 = Choi 2014 Hong 2017 Ide 2017 Inoue 2013 Kim 2017 Nakagawa 2014 Okimoto 2017 Shibulani 2015 (1) Subtotal (95% CI) Heterogeneitly: τ^2 =0.05; χ^2 =16.28 Test for overall effect: Z=5.46 (<i>P</i> <	, df=27 (P<0.000 0.00001) 22.15, df=1 (P=0. 1.6425 0.5008 0.5766 0.6195 0.2624 0.4669 1.0543 0.3716 0.8755 , df=8 (P=0.04); 0.00001) 1.4115 0.3155 0.6881 0.3784 2.0605	001); ℓ= 14), ℓ=! SE 0.5496 0.2306 0.421 0.2176 0.359 0.3229 0.1471 ℓ=51% 0.5412 0.3761 0.3265 0.1682 0.3841	100.0 70% 53.4% Weight (%) 1.9 6.6 3.0 7.0 10.0 8.8 3.8 4.4 9.5 54.9 2.0 3.5 4.3 8.6 0.9	2.21 (1.86, 2.62) 0.01 HR IV, random, 95% Cl 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06) 1.86 (1.21, 2.85) 1.30 (1.00, 1.68) 1.60 (1.16, 2.20) 2.87 (1.42, 5.80) 1.45 (0.77, 2.73) 2.40 (1.80, 3.20) 1.83 (1.47, 2.27) 4.10 (1.42, 11.85) 1.37 (0.66, 2.87) 2.01 (1.06, 3.81) 1.46 (1.05, 2.03) 7.85 (1.51, 4.08.1)	0.1 1 10 100 Favors HG Favors LG HR IV, random, 95% Cl
Total (95% CI) Heterogeneity: r^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (<i>P</i> <4 Test for subgroup differences: χ^2 = Study or subgroup 1.10.1 Mean/median <65 Choi 2014 Hong 2017 Ide 2017 Inoue 2013 Kim 2017 Nakagawa 2014 Okimoto 2017 Shibulani 2015 (1) Sun 2014 Subtotal (95% CI) Heterogeneity: r^2 =0.05; χ^2 =16.28 Test for overall effect: Z=5.46 (<i>P</i> <- 1.10.2 Mean/median ≥65 Eren 2015 Ishibuka 2012 Leilch 2007 (resectable) Leilch 2007 (unresectable) Maillet 2014 Simio 2018	, df=27 (P<0.000 0.00001) :2.15, df=1 (P=0. 1.6425 0.5008 0.5766 0.6195 0.2624 0.4669 1.0543 0.3716 0.8755 , df=8 (P=0.04); 0.00001) 1.4115 0.3155 0.6681 0.3784 2.0605	001); ℓ= 14), ℓ=; 14), ℓ=; 0.5496 0.2306 0.421 0.2176 0.3229 0.1471 ℓ=51% 0.5412 0.3761 0.3265 0.1682 0.8301	100.0 70% 53.4% Weight (%) 1.9 6.6 3.0 7.0 10.0 8.8 3.8 4.4 9.5 54.9 2.0 3.5 4.3 8.6 0.9 9 4.4	2.21 (1.86, 2.62) 0.01 HR IV, random, 95% CI 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06) 1.86 (1.21, 2.85) 1.30 (1.00, 1.68) 1.60 (1.16, 2.20) 2.87 (1.42, 5.80) 1.45 (0.77, 2.73) 2.40 (1.80, 3.20) 1.83 (1.47, 2.27) 4.10 (1.42, 11.85) 1.37 (0.66, 2.87) 2.01 (1.06, 3.81) 1.46 (1.05, 2.03) 7.85 (1.51, 40.81) 1.03 (0.55 1.93)	0.1 1 10 100 Favors HG Favors LG
Total (95% CI) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (<i>P</i> <i Test for overall effect: Z=9.15 (<i>P</i><i Test for subgroup differences: χ^2= Study or subgroup 1.10.1 Mean/median <65 Choi 2014 Hong 2017 Ide 2017 Inoue 2013 Kim 2017 Nakagawa 2014 Okimoto 2017 Shibulani 2015 (1) Sun 2014 Subtotal (95% CI) Heterogeneity: τ^2=0.05; χ^2=16.28 Test for overall effect: Z=5.46 (<i>P</i> 1.10.2 Mean/median ≥65 Eren 2015 Ishizuka 2012 Leiich 2007 (resectable) Leiich 2007 (urresectable) Maillet 2014 Sirnio 2018 Toixama 2011</i </i 	, df=27 (P<0.000 0.00001) :2.15, df=1 (P=0. log (HR) 1.6425 0.5008 0.5766 0.6195 0.2624 0.4669 1.0543 0.3716 0.8755 0.2624 0.4669 1.0543 0.3716 0.8755 0.6195 0.3755 0.6195 0.3755 0.61981 1.4115 0.3155 0.6981	001); ℓ= 14), ℓ=; SE 0.5496 0.2306 0.421 0.2176 0.1318 0.1642 0.359 0.13471 ℓ=51% 0.5412 0.3265 0.3265 0.3265 0.3265 0.3265 0.3265 0.3265 0.5242	100.0 70% 53.4% Weight (%) 1.9 6.6 3.0 7.0 10.0 8.8 3.8 4.4 9.5 54.9 2.0 3.5 54.9 2.0 3.5 4.3 8.6 0.9 4.4 7	2.21 (1.86, 2.62) 0.01 HR IV, random, 95% Cl 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06) 1.80 (1.21, 2.85) 1.30 (1.00, 1.68) 1.60 (1.16, 2.20) 2.87 (1.42, 5.80) 1.45 (0.77, 2.73) 2.40 (1.80, 3.20) 1.83 (1.47, 2.27) 4.10 (1.42, 11.85) 1.37 (0.66, 2.87) 2.01 (1.05, 2.03) 7.85 (1.51, 40.81) 1.03 (0.55, 1.93)	0.1 1 10 100 Favors HG Favors LG
Total (95% CI) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (<i>P</i> Test for subgroup 11 11.0.1 Mean/median <65	, df=27 (P<0.000 0.00001) 22.15, df=1 (P=0. 1.6425 0.5008 0.5766 0.6195 0.2624 0.4669 1.0543 0.3716 0.8755 , df=8 (P=0.04); 0.00001) 1.4115 0.3155 0.6881 0.3784 2.0605 0.0296 1.6114	001); ℓ= 14), ℓ= SE 0.5496 0.2306 0.421 0.2176 0.359 0.3229 0.1471 ℓ=51% 0.5412 0.3761 0.3265 0.1682 0.3841 0.3201 0.3841 0.3201 0.3841 0.3201 0.3841 0.3201 0.3841 0.3201 0.3841 0.3201 0.3841 0.3201 0.3841 0.3201 0.3841 0.3201 0.3841 0.3201 0.3841 0.3201 0.3841 0.3201 0.3841 0.3859 0	100.0 70% 53.4% Weight (%) 1.9 6.6 3.0 7.0 10.0 8.8 3.8 4.4 9.5 54.9 2.0 3.5 4.3 8.6 0.9 4.4 1.7 -	2.21 (1.86, 2.62) 0.01 HR IV, random, 95% CI 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06) 1.86 (1.21, 2.85) 1.30 (1.00, 1.68) 1.60 (1.16, 2.20) 2.87 (1.42, 5.80) 1.45 (0.77, 2.73) 2.40 (1.80, 3.20) 1.83 (1.47, 2.27) 4.10 (1.42, 11.85) 1.37 (0.66, 2.87) 2.01 (1.06, 3.81) 1.46 (1.05, 2.03) 7.85 (1.51, 4.08.1) 1.03 (0.55, 1.93) 5.01 (1.60, 15.69) 2.41 (1.60, 7.72)	0.1 1 10 100 Favors HG Favors LG
Total (95% CI) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (P <i Test for subgroup differences: χ^2= Study or subgroup 1.10.1 Mean/median <65 Choi 2014 Hong 2017 Ide 2017 Inoue 2013 Kim 2017 Nakagawa 2014 Okimoto 2017 Shibulani 2015 (1) Sun 2014 Subtotal (95% CI) Heterogeneity: τ^2=0.05; χ^2=16.28 Test for overall effect: Z=5.46 (P<i 1.10.2 Mean/median ≥65 Eren 2015 Ishizuka 2012 Leilch 2007 (unresectable) Leilch 2007 (unresectable) Maillet 2014 Sirnio 2018 Toiyama 2011 Toiyama 2011</i </i 	, df=27 (P<0.000 0.00001) :2.15, df=1 (P=0 log (HR) 1.6425 0.5008 0.5766 0.6195 0.2624 0.4669 1.0543 0.3716 0.8755 0.8755 0.8755 0.6981 0.3784 2.0605 0.2926 0.3784 2.0605 0.0296 1.6114 0.7608	001); ℓ= 14), ℓ=; SE 0.5496 0.2306 0.2276 0.1318 0.1642 0.359 0.1329 0.1471 ℓ=51% 0.5412 0.3761 0.3265 0.1682 0.3411 0.3261	100.0 70% 53.4% Weight (%) 1.9 6.6 3.0 7.0 10.0 8.8 3.8 4.4 9.5 54.9 2.0 3.5 4.3 8.6 0.9 4.4 1.7 7.0	2.21 (1.86, 2.62) 0.01 HR IV, random, 95% Cl 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06) 1.86 (1.21, 2.85) 1.30 (1.00, 1.68) 1.60 (1.16, 2.20) 2.87 (1.42, 5.80) 1.45 (0.77, 2.73) 2.40 (1.80, 3.20) 1.83 (1.47, 2.27) 4.10 (1.42, 11.85) 1.37 (0.66, 2.87) 2.01 (1.06, 3.81) 1.46 (1.05, 2.03) 7.85 (1.51, 40.81) 1.03 (0.55, 193) 5.01 (1.60, 15.69) 2.14 (1.40, 3.27)	0.1 1 10 100 Favors HG Favors LG
Total (95% CI) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (<i>P</i> Test for subgroup 11.0.1 Mean/median <65	, df=27 (P<0.000 0.00001) 22.15, df=1 (P=0. log (HR) 1.6425 0.5008 0.5766 0.6195 0.2624 0.4669 1.0543 0.3716 0.8755 , df=8 (P=0.04); 0.00001) 1.4115 0.3155 0.6981 0.3784 2.0605 0.0296 1.6114 0.7608 0.3075	001); ℓ= 14), ℓ= SE 0.5496 0.2306 0.421 0.2176 0.359 0.3229 0.1471 ℓ=51% 0.5412 0.3761 0.3265 0.3201 0.3201 0.3201 0.3201 0.3201 0.3201 0.3201 0.3201 0.3201 0.3202 0.3412 0.3201 0.3201 0.3201 0.3202 0	100.0 70% 53.4% Weight (%) 1.9 6.6 3.0 7.0 10.0 8.8 3.8 4.4 9.5 54.9 2.0 3.5 4.3 8.6 0.9 4.4 1.7 7.0 11.5	2.21 (1.86, 2.62) U, 0.01 HR IV, random, 95% Cl 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06) 1.86 (1.21, 2.85) 1.30 (1.00, 1.68) 1.60 (1.16, 2.20) 2.87 (1.42, 5.80) 1.45 (0.77, 2.73) 2.40 (1.80, 3.20) 1.83 (1.47, 2.27) 4.10 (1.42, 11.85) 1.37 (0.66, 2.87) 2.01 (1.06, 3.20) 1.45 (1.05, 2.03) 7.85 (1.51, 40.81) 1.03 (0.55, 1.93) 5.01 (1.60, 15.69) 2.14 (1.40, 3.27) 1.36 (1.13, 1.64)	0.1 1 10 100 Favors HG Favors LG
Total (95% CI) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (P <i Test for subgroup differences: χ^2= Study or subgroup 1.10.1 Mean/median <65 Choi 2014 Hong 2017 Ide 2017 Inoue 2013 Kim 2017 Nakagawa 2014 Okimoto 2017 Shibulani 2015 (1) Sun 2014 Subtotal (95% CI) Heterogeneity: τ^2=0.05; χ^2=16.28, Test for overall effect: Z=5.46 (P<i 1.10.2 Mean/median ≥65 Eren 2015 Ishizuka 2012 Leilch 2007 (resectable) Leilch 2007 (unresectable) Maillet 2014 Toiyama 2011 Tokunaga 2017 Watt 2016 Yamamdo 2012</i </i 	, df=27 (P<0.000 0.00001) ;2.15, df=1 (P=0. 1.6425 0.5008 0.5766 0.6195 0.2624 0.4669 1.0543 0.3716 0.8755 , df=8 (P=0.04); 0.00001) 1.4115 0.3155 0.6981 0.3784 2.0605 0.0296 1.6114 0.7608 0.3075 0.1931	001); ℓ= 14), ℓ= SE 0.5496 0.2306 0.421 0.2176 0.359 0.3229 0.1471 ℓ=51% 0.5412 0.3761 0.3265 0.1682 0.3201 0	100.0 70% 53.4% Weight (%) 1.9 6.6 3.0 7.0 10.0 8.8 3.8 4.4 9.5 54.9 2.0 3.5 4.3 8.6 0.9 4.4 1.7 7.0 11.5 1.0	2.21 (1.86, 2.62) 0.01 HR IV, random, 95% Cl 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06) 1.86 (1.21, 2.85) 1.30 (1.00, 1.68) 1.30 (1.00, 1.68) 1.45 (0.77, 2.73) 2.40 (1.80, 3.20) 1.83 (1.47, 2.27) 4.10 (1.42, 11.85) 1.37 (0.66, 2.87) 2.01 (1.06, 3.81) 1.46 (1.05, 2.03) 7.85 (1.51, 40.81) 1.03 (0.55, 1.93) 5.01 (1.60, 15.69) 2.14 (1.40, 3.27) 1.36 (1.13, 1.64) 1.21 (0.26, 5.68)	0.1 1 10 100 Favors HG Favors LG
Total (95% CI) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (<i>P</i> <4 Test for subgroup differences: χ^2 = Study or subgroup 1.10.1 Mean/median <65 Choi 2014 Hong 2017 Ide 2017 Inoue 2013 Kim 2017 Nakagawa 2014 Okimoto 2017 Shibulani 2015 (1) Sun 2014 Subtotal (95% CI) Heterogeneity: τ^2 =0.05; χ^2 =16.28 Test for overall effect: Z=5.46 (<i>P</i> <4 1.10.2 Mean/median ≥65 Eren 2015 Ishizuka 2012 Leiich 2007 (unresectable) Leiich 2007 (unresectable) Maillet 2014 Simio 2018 Toiyama 2011 Tokunaga 2017 Watt 2016 Yamamolo 2012 Subtotal (95% CI)	, df=27 (P<0.000 0.00001) -2.15, df=1 (P=0 	001); ℓ= 14), ℓ=; SE 0.5496 0.2306 0.421 0.2176 0.359 0.1318 0.1642 0.359 0.1329 0.1471 ℓ=51% 0.5412 0.3761 0.3265 0.1682 0.341 0.3265 0.1682 0.341 0.3265 0.5824 0.2165 0.5824 0.5878	100.0 70% 53.4% Weight (%) 1.9 6.6 3.0 7.0 10.0 8.8 3.8 4.4 9.5 54.9 2.0 3.5 4.3 8.6 0.9 4.4 1.7 7.0 11.5 1.0 145.1	2.21 (1.86, 2.62) 0.01 HR IV, random, 95% Cl 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06) 1.86 (1.21, 2.85) 1.30 (1.00, 1.68) 1.60 (1.16, 2.20) 2.87 (1.42, 5.80) 1.45 (0.77, 2.73) 2.40 (1.80, 3.20) 1.83 (1.47, 2.27) 4.10 (1.42, 11.85) 1.37 (0.66, 2.87) 2.01 (1.06, 3.81) 1.46 (1.05, 2.03) 7.85 (1.51, 40.81) 1.03 (0.55, 1.93) 5.01 (1.60, 15.69) 2.14 (1.40, 3.27) 1.36 (1.13, 1.64) 1.73 (1.34, 2.24)	0.1 1 10 100 Favors HG Favors LG
Total (95% CI) Heterogeneity: $\tau^{2}=0.11$; $\chi^{2}=89.22$, Test for overall effect: Z=9.15 (P <i Test for subgroup differences: $\chi^{2}=$ Study or subgroup 1.10.1 Mean/median <65 Choi 2014 Hong 2017 Ide 2017 Inoue 2013 Kim 2017 Nakagawa 2014 Okimoto 2017 Shibulani 2015 (1) Sun 2014 Subtotal (95% CI) Heterogeneity: $\tau^{2}=0.05$; $\chi^{2}=16.28$, Test for overall effect: Z=5.46 (P<i 1.10.2 Mean/median ≥65 Eren 2015 Ishizuka 2012 Leilch 2007 (resectable) Leilch 2007 (unresectable) Maillet 2014 Tokunaga 2017 Watt 2018 Toiyama 2011 Tokunaga 2017 Watt 2016 Yamamolo 2012 Subtotal (95% CI)</i </i 	, df=27 (P<0.000 0.00001) 22.15, df=1 (P=0. 1.6425 0.5008 0.5766 0.6195 0.2624 0.4669 1.0543 0.3716 0.8755 , df=8 (P=0.04); 0.00001) 1.4115 0.3155 0.6981 0.3784 2.0605 0.0296 1.6114 0.3768 0.3075 0.1931 1.414	001); ℓ= 14), ℓ= SE 0.5496 0.2306 0.421 0.2176 0.359 0.359 0.3229 0.1471 ℓ=51% 0.5412 0.3761 0.3265 0.1642 0.3761 0.3265 0.1642 0.3761 0.3265 0.1642 0.3761 0.3265 0.1642 0.3761 0.3265 0.1642 0.3761 0.3265 0.1642 0.3761 0.3265 0.1642 0.359 0.1642 0.3682 0.1642 0.3682 0.7878 0.7878 0.7878 0.7878	100.0 70% 53.4% Weight (%) 1.9 6.6 3.0 7.0 10.0 8.8 3.8 4.4 9.5 54.9 2.0 3.5 4.3 8.6 0.9 4.4 1.7 7.0 11.5 1.0 45.1	2.21 (1.86, 2.62) 0.01 HR IV, random, 95% Cl 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06) 1.86 (1.21, 2.85) 1.30 (1.00, 1.68) 1.30 (1.00, 1.68) 1.30 (1.00, 1.68) 1.45 (0.77, 2.73) 2.40 (1.80, 3.20) 1.83 (1.47, 2.27) 4.10 (1.42, 11.85) 1.37 (0.66, 2.87) 2.01 (1.06, 3.81) 1.46 (1.05, 2.03) 7.85 (1.51, 14.08.1) 1.03 (0.55, 1.93) 5.01 (1.60, 15.69) 2.14 (1.40, 3.27) 1.36 (1.13, 1.64) 1.21 (0.26, 5.68) 1.73 (1.34, 2.24)	0.1 1 10 100 Favors HG Favors LG
Total (95% CI) -leterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (<i>P</i> Test for subgroup 1.10.1 Mean/median <65	, df=27 (P<0.000 0.00001) :2.15, df=1 (P=0. log (HR) 1.6425 0.5008 0.5766 0.6195 0.2624 0.4669 1.0543 0.3716 0.8755 0.2624 0.4669 1.0543 0.3716 0.8755 0.6981 1.4115 0.3155 0.6981 0.3784 2.0605 0.0296 1.6114 0.3784 2.0605 0.0296 1.6114 0.3784 2.0605 0.0296 1.6114 0.3784 2.0605 0.0296	001); <i>P</i> = 14), <i>P</i> = SE 0.5496 0.2306 0.421 0.2176 0.359 0.1318 0.1642 0.359 0.1347 0.359 0.1471 <i>P</i> =51% 0.5412 0.3265 0.3279 0.3265 0.3265 0.3265 0.3265 0.3278 0.3265 0.3265 0.3265 0.3278 0.3265 0.3265 0.3265 0.3278 0.3265 0.3265 0.3265 0.3265 0.3278 0.3265 0.3278 0.327	100.0 70% 53.4% Weight (%) 1.9 6.6 3.0 7.0 10.0 8.8 3.8 4.4 9.5 54.9 2.0 3.5 4.3 8.6 0.9 4.4 1.7 7.0 11.5 1.0 45.1	2.21 (1.86, 2.62) U, 0.01 HR IV, random, 95% Cl 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06) 1.86 (1.21, 2.85) 1.30 (1.00, 1.68) 1.60 (1.16, 2.20) 2.87 (1.42, 5.80) 1.45 (0.77, 2.73) 2.40 (1.80, 3.20) 1.83 (1.47, 2.27) 4.10 (1.42, 11.85) 1.37 (0.66, 2.87) 2.01 (1.05, 2.03) 7.85 (1.51, 40.81) 1.03 (0.55, 1.93) 5.01 (1.60, 15.68) 1.73 (1.34, 2.24) 1.73 (1.34, 2.24)	0.1 1 10 100 Favors HG Favors LG
Total (95% CI) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (<i>P</i> Test for subgroup 11.0.1 Mean/median <65	, df=27 (P<0.000 0.00001) 22.15, df=1 (P=0. log (HR) 1.6425 0.5008 0.5766 0.6195 0.2624 0.4669 1.0543 0.3716 0.8755 0.2624 0.4669 1.0543 0.3716 0.8755 0.6981 1.4115 0.3155 0.6981 0.3784 2.0605 0.0296 1.6114 0.3784 2.0605 0.0296 1.6114 0.3768 0.3075 0.1931 0.3075	001); <i>P</i> = 14), <i>P</i> =1 SE 0.5496 0.2306 0.421 0.2176 0.359 0.1421 0.359 0.1421 0.359 0.1471 <i>P</i> =51% 0.5412 0.3761 0.3265 0.3761 0.3265 0.3761 0.3201 0.3201 0.3201 0.3201 0.3201 0.3229 0.1471 0.3265 0.3261 0.3265 0.3261 0.3265 0.36	100.0 70% 53.4% Weight (%) 1.9 6.6 3.0 7.0 10.0 8.8 3.8 4.4 9.5 54.9 2.0 3.5 4.3 8.6 0.9 4.4 1.7 7.0 11.5 1.0 45.1	2.21 (1.86, 2.62) 0.01 HR IV, random, 95% Cl 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06) 1.86 (1.21, 2.85) 1.30 (1.00, 1.68) 1.60 (1.16, 2.20) 2.87 (1.42, 5.80) 1.45 (0.77, 2.73) 2.40 (1.80, 3.20) 1.83 (1.47, 2.27) 4.10 (1.42, 11.85) 1.37 (0.66, 2.87) 2.01 (1.06, 3.81) 1.46 (1.05, 2.03) 7.85 (1.51, 40.81) 1.03 (0.55, 1.93) 5.01 (1.60, 15.69) 2.14 (1.40, 3.27) 1.36 (1.13, 1.64) 1.21 (0.26, 5.68) 1.73 (1.34, 2.24)	0.1 1 10 100 Favors HG Favors LG
Total (95% CI) Heterogeneity: τ^2 =0.11; χ^2 =89.22, Test for overall effect: Z=9.15 (<i>P</i> Test for subgroup differences: χ^2 = Study or subgroup 11.0.1 Mean/median <65	, df=27 (P<0.000 0.00001) 2.15, df=1 (P=0. 1.6425 0.5008 0.5766 0.6195 0.2624 0.4669 1.0543 0.3716 0.8755 0.2624 0.4669 1.0543 0.3716 0.8755 0.2624 0.4669 1.0543 0.3716 0.3755 0.2624 0.4669 1.0543 0.3716 0.3755 0.2624 1.0543 0.3755 0.2626 1.6114 0.3784 2.0605 0.0296 1.6114 0.7608 0.3075 0.1931 0.3075 0.1931 0.3075	 001); <i>P</i>= 14), <i>P</i>=! SE 0.5496 0.2306 0.421 0.2176 0.1318 0.369 0.3229 0.1471 <i>P</i>=51% 0.5412 0.3761 0.3265 0.6841 0.3201 0.5824 0.7878 <i>P</i>=49% <i>P</i>=500 	100.0 70% 53.4% Weight (%) 1.9 6.6 3.0 7.0 10.0 8.8 3.8 4.4 9.5 54.9 2.0 3.5 4.3 8.6 0.9 4.4 1.7 7.0 11.5 1.0 45.1	2.21 (1.86, 2.62) 0.01 HR IV, random, 95% Cl 5.17 (1.76, 15.18) 1.65 (1.05, 2.59) 1.78 (0.78, 4.06) 1.86 (1.21, 2.85) 1.30 (1.00, 1.68) 1.60 (1.16, 2.20) 2.87 (1.42, 5.80) 1.45 (0.77, 2.73) 2.40 (1.80, 3.20) 1.48 (1.47, 2.27) 4.10 (1.42, 11.85) 1.37 (0.66, 2.87) 2.01 (1.06, 3.81) 1.46 (1.05, 2.03) 7.85 (1.51, 40.81) 1.03 (0.55, 1.93) 5.01 (1.60, 15.69) 2.14 (1.40, 3.27) 1.36 (1.13, 1.64) 1.21 (0.26, 5.68) 1.73 (1.34, 2.24) 1.77 (1.51, 2.08) 0.01	0.1 1 10 100 Favors HG Favors LG

Test for subgroup differences: χ^2 =0.10, *df*=1 (*P*=0.75), *P*=0%

Figure 6 Subgroup analysis showing correlation between GPS and prognosis of CRC patients according to patient age.

Note: (A) Overall survival and (B) cancer-specific survival. **Abbreviations:** CRC, colorectal cancer; df, degrees of freedom; GPS, Glasgow prognostic score; LG, low group; HG, high group; SE, standard error.

Α		log (HP)			HR	HR
-	Study or subgroup	iog (LIIV)	SE	Weight (%	 IV, random, 95% CI 	IV, random, 95% CI
	1.11.1 Sample <300					
	Adachi 2014	2.0903	0.8555	0.8	8.09 (1.51 , 43.25)	
	Oreanic 2013	0.7472	0.2873	3.5	2.11 (1.20, 3.71)	
	Furukawa 2011	2.0285	0.7078	1.1	7.60 (1.90, 30.44)	
	Ghanim 2015	1.1145	0.604	1.4	3.05 (0.93, 9.96)	
	lde 2017	0.6098	0.5803	1.5	1.84 (0.59, 5.74)	
	Kobayashi 2010	1.1217	0.4878	1.9	3.07 (1.18, 7.99)	
	Leitch 2007 (resectable)	0.7275	0.2181	4.3	2.07 (1.35, 3.17)	
	Lin 2015	1.1681	0.5203	1.7	3.22 (1.16, 8.92)	
	Madea 2013	0.6678	0.3158	3.2	1.95 (1.05, 3.62)	
	Maillet 2014	1.6506	0.7407	1.0	5.21 (1.22, 22.25)	
	Moug 2010	0.4447	0.1424	5.3	1.56 (1.18, 2.06)	
	Ni 2016	0.4662	0.1127	5.7	1.59 (1.28, 1.99)	-
	Nozoe 2014	2.0028	0.3599	2.8	7.41 (3.66, 15.00)	
	Okimoto 2017	0.4996	0.2757	3.6	1.65 (0.96, 2.83)	
	Okugawa 2018 (training)	1 6956	0.3816	2.6	5 45 (2 58 11 51)	
	Read 2009	0 2199	0 7898	0.9	1 25 (0 26 5 86)	
	Sharma 2008	1 9906	0 5797	1.5	7 32 (2 35 22 80)	
	Shibutani 2015 (1)	0.9002	0.0101	3.5	2 46 (1 39 4 35)	
	Shibutani 2015 (2)	1 0703	0.2010	0.7	7 24 (1 18 44 39)	
	Shimura 2017	0.9597	0.92.04	2.2	2 36 (1 03 5 41)	
	Simia 2017	0.0307	0.423	2.3	1 37 (0 82 2 20)	
	Similio 2016	0.3140	0.2018	3.0	1.37 (0.02, 2.29)	
	Sun 2014	1 0970	0.2343	4.1	1.13(0.72, 1.00)	
	Sun 2014	1.00/9	0.10/0	5.0	2.97 (2.14, 4.12)	· · · ·
	Cubtatal (05% CI)	1.0296	0.3428	2.9	2.60 (1.43, 5.48)	
	Subiolal (95% CI)			64.9	2.43 (1.97, 3.00)	♥
	Heterogeneity: $\tau^2=0.13$; $\chi^2=60.13$, c	lf=23 (P<0	.0001);	<i>l</i> ²=62%		
		00001)				
	1.11.2 Sample ≥300					
	Chan 2017	0.7948	0.2145	4.4	2.21 (1.45, 3.37)	
	Ishizuka 2016	0.5928	0.2176	4.3	1.81 (1.18, 2.77)	
	Kim 2017	0.4187	0.1388	5.4	1.52 (1 .16, 2.00)	-
	Kostner 2016	0.4886	0.1605	5.1	1.63 (1 .19, 2.23)	
	Okugawa 2018 (validation)	1.1474	0.2167	4.3	3.15 (2.06, 4.82)	
	Son 2013	0.7962	0.5767	1.5	2.22 (0.72, 6.87)	
	Tokunaga 2017	0.8961	0.2402	4.1	2.45 (1.53, 3.92)	
	Watt 2016	0.3075	0.0724	6.1	1.36 (1.18, 1.57)	*
	Subtotal (95% CI)			35.1	1.86 (1.50, 2.31)	◆
	Heterogeneity: τ^2 =0.06; χ^2 =21.04, c Test for overall effect: Z=5.63 (<i>P</i> <0.	lf=7 (<i>P</i> =0.0 00001)	004); <i>I</i> ²=	67%	, · · ,	
	Total (95% CI)			100.0%	2.20 (1.88, 2.57)	♦
	Heterogeneity: τ^2 =0.10; χ^2 =91.05, σ Test for overall effect: Z=9.87 (<i>P</i> <0.10)	<i>lf</i> =31 (<i>P</i> <0 00001)	.00001)	; <i>I</i> ²=66%	0.01	0.1 1 10 100
	Test for subgroup differences: $\chi^2=2$.99, <i>df</i> =1 (P=0.08)	; <i>I</i> ²=66.6%		Favors HG Favors LG

в

				HR	HR
Study or subgroup	log (HR)	SE	Weight (%	b) IV, random, 95% Cl	IV, random, 95% CI
1.12.1 Sample <300					
Choi 2014	1.6425	0.5496	1.8	5.17 (1.76, 15.18)	
Dreanic 2013	0.4035	0.287	4.5	1.50 (0.85, 2.63)	+
Eren 2015	1.4115	0.5412	1.8	4.10 (1.42, 11.85)	———
lde 2017	0.5766	0.421	2.7	1.78 (0.78, 4.06)	+
Inoue 2013	0.6195	0.2176	6.0	1.86 (1.21, 2.85)	
lshizuka 2012	0.3155	0.3761	3.2	1.37 (0.66, 2.87)	—
Kishiki 2013	1.311	0.3441	3.6	3.71 (1.89, 7.28)	
Leitch 2007 (resectable)	0.6981	0.3265	3.9	2.01 (1.06, 3.81)	
Leitch 2007 (unresectable)	0.3764	0.1682	7.3	1.46 (1.05, 2.03)	
Maillet 2014	2.0605	0.841	0.8	7.85 (1.51, 40.81)	· · · · · · · · · · · · · · · · · · ·
McSorley 2017	0.6575	0.5102	2.0	1.93 (0.71, 5.25)	+
Okimoto 2017	1.0543	0.359	3.4	2.87 (1.42, 5.80)	
Shibutani 2015 (1)	0.3716	0.3229	3.9	1.45 (0.77, 2.73)	+ -
Simio 2018	0.0296	0.3201	4.0	1.03 (0.55, 1.93)	_
Sun 2014	0.8755	0.1471	7.9	2.40 (1.80, 3.20)	-
Toiyama 2011	1.6114	0.5824	1.6	5.01 (1.60, 15.69)	———
Yamamoto 2012	0.1931	0.7878	0.9	1.21 (0.26, 5.68)	
Subtotal (95% CI)			59.2	2.02 (1.64, 2.49)	◆
Heterogeneity: $\tau^2 = 0.07$; $\chi^2 = 27.01$,	df=16 (P=0	0.04); <i>I</i> ²=	41%		
Test for overall effect: Z=6.62 (P<0	.00001)				
1.12.2 Sample ≥300					
Hong 2017	0.5008	0.2306	5.7	1.65 (1.05, 2.59)	
Kim 2017	0.2624	0.1318	8.3	1.30 (1.00, 1.68)	-
Nakagawa 2014	0.4669	0.1642	7.4	1.60 (1.16, 2.20)	
Sugimoto 2012	1.1282	0.3201	4.0	3.09 (1.65, 5.79)	
Tokunaga 2017	0.7608	0.2165	6.0	2.14 (1.40, 3.27)	
Watt 2016	0.3075	0.0945	9.4	1.36 (1.13, 1.64)	
Subtotal (95% CI)			40.8	1.61 (1.32, 1.96)	◆
Heterogeneity: τ^2 =0.03; χ^2 =10.35, Test for overall effect: Z=4.72 (<i>P</i> <0	<i>df</i> =5 (<i>P</i> =0. 0.00001)	07); <i>I</i> ²=5	2%		
Total (95% CI)			100.0%	1.86 (1.59, 2.17)	♦
Heterogeneity: τ ² =0.60; χ ² =45.42, Test for overall effect: Z=7.75 (P<0	df=22 (P=0	0.002); <i>I</i> ²	=52%	0.01	0.1 1 10 100
Test for subgroup differences: $\chi^2=2$.49, <i>df</i> =1	(P=0.11)	<i>I</i> ² =59.9%		Favors HG Favors LG

Figure 7 Subgroup analysis showing correlation between GPS and prognosis of CRC patients according to sample size. Note: (A) Overall survival and (B) cancer-specific survival.

Abbreviations: CRC, colorectal cancer; df, degrees of freedom; GPS, Glasgow prognostic score; LG, low group; HG, high group; SE, standard error.

Study or subgroup	log (HR) SE	Weight (%)	IV, random, 95% CI	IV, random, 95% CI
1.13.1 TNM stage 0-III				
Chan 2017	0.7948 0.2145	5.7	2.21 (1.45, 3.37)	
de 2017	0.6098 0.5803	1.6	1.84 (0.59, 5.74)	
_eitch 2007 (resectable)	0.7275 0.2181	5.6	2.07 (1.35, 3.17)	
_in 2015	1.1681 0.5203	1.9	3.22 (1.16, 8.92)	
Moug 2010	0.4447 0.1424	7.4	1.56 (1.18, 2.06)	-
Shibutani 2015 (2)	1.9793 0.9254	0.7	7.24 (1.18, 44.39)	· · · · · · · · · · · · · · · · · · ·
Son 2013	0.7962 0.5767	1.6	2.22 (0.72, 6.87)	+ • • • • • • • • • • • • • • • • • • •
Sun 2014	1.0879 0.1676	6.7	2.97 (2.14, 4.12)	-
Foiyama 2011	1.0296 0.3428	3.5	2.80 (1.43, 5.48)	
Fokunaga 2017	0.8961 0.2402	5.1	2.45 (1.53, 3.92)	
Natt 2016	0.3075 0.0724	8.9	1.36 (1.18, 1.57)	· · · · · · · · · · · · · · · · · · ·
Subtotal (95% CI)		48.7	2.13 (1.66, 2.73)	•
Heterogeneity: τ^2 =0.09; χ^2 =31.86	, df=10 (P=0.0004); l ² =	69%		
Fest for overall effect: Z=5.94 (P-	<0.00001)			
12.2 TNM stage IV				
	0 7 1 7 0 0 0 7 0		0 44 (4 00 0 74)	
Dreanic 2013	0.7472 0.2873	4.3	2.11 (1.20, 3.71)	
-urukawa 2011	2.0285 0.7078	1.1	7.60 (1.90, 30.44)	
	0.4187 0.1388	1.4	1.52 (1.16, 2.00)	
Copayasni 2010	1.1217 0.4878	2.1	3.07 (1.18, 7.99)	
	0.4886 0.1605	6.9	1.63 (1.19, 2.23)	
viadea 2013	0.6678 0.3158	3.9	1.95 (1.05, 3.62)	
viailiet 2014	1.6506 0.7407	1.0	5.21 (1.22, 22.25)	
NI 2016	0.4662 0.1127	8.0	1.59 (1.28, 1.99)	
Okimoto 2017	0.4996 0.2757	4.5	1.65 (0.96, 2.83)	
Read 2009	0.2199 0.7898	0.9	1.25 (0.26, 5.86)	
Sharma 2008	1.9906 0.5797	1.6	7.32 (2.35, 22.80)	
Shibutani 2015 (1)	1.9906 0.5797	1.6	7.32 (2.35, 22.80)	
Shimura 2017	0.8587 0.423	2.6	2.36 (1.03, 5.41)	
Song 2015	0.1266 0.2343	5.3	1.13 (0.72, 1.80)	—
Subtotal (95% CI)		51.3	1.95 (1.56, 2.42)	▼
Heterogeneity: τ^2 =0.07; χ^2 =26.46	5, <i>df</i> =13 (<i>P</i> =0.01); <i>I</i> ² =51	%		
Fest for overall effect: Z=5.93 (P	<0.00001)			
Fest for overall effect: Z=8.74 (P Fest for subgroup differences: χ^2	<0.00001) =0.27, <i>df</i> =1 (<i>P</i> =0.60), <i>l</i> ² =	=0%	0.01	Favors HG Favors LG
Fest for overall effect: Z=8.74 (P- Fest for subgroup differences: χ^{2}	:0.00001) =0.27, <i>df</i> =1 (<i>P</i> =0.60), <i>l</i> ² :	=0%	HR	Favors HG Favors LG
Fest for overall effect: Z=8.74 (P- Fest for subgroup differences: χ^{2} : Study or subgroup	:0.00001) =0.27, <i>df</i> =1 (<i>P</i> =0.60), / ² : log (HR)	=0% SE We	HR ight (%) IV, random, S	Favors HG Favors LG HR 25% CI IV, random, 95% CI
Fest for overall effect: Z=8.74 (P× Fest for subgroup differences: ½ ² : Study or subgroup 1.14.1 TNM stage 0–III	:0.00001) =0.27, <i>df</i> =1 (<i>P</i> =0.60), <i>l</i> ² = log (HR)	=0% SE We	HR ight (%) IV, random, S	Favors HG Favors LG HR 15% CI IV, random, 95% CI
Fest for overall effect: Z=8.74 (P× Fest for subgroup differences: ½ ² : Study or subgroup I.14.1 TNM stage 0–III Hong 2017	:0.00001) =0.27, <i>df</i> =1 (<i>P</i> =0.60), <i>I</i> ² : log (HR) 0.5008 0.	=0% SE We 2306	6.6 1.65 (1.05, 2	Favors HG Favors LG HR 15% CI IV, random, 95% CI
Fest for overall effect: Z=8.74 (P- Fest for subgroup differences: χ ² - Study or subgroup 1.14.1 TNM stage 0–III Hong 2017 de 2017	:0.0001) =0.27, df=1 (P=0.60), P= log (HR) 0.5008 0. 0.5766 (=0% <u>SE We</u> 2306 0.421	HR ight (%) IV, random, 9 6.6 1.65 (1.05, 2 3.0 1.78 (0.78, 4	Favors HG Favors LG HR 95% CI IV, random, 95% CI .59)
Fest for overall effect: Z=8.74 (P Fest for subgroup differences: χ ² Study or subgroup I.14.1 TNM stage 0–III Hong 2017 de 2017 oitch 2007 (respectable)	0.00001) -0.27, df=1 (P=0.60), P= log (HR) 0.5008 0. 0.5766 (0 0.6981 0	=0% SE We 2306).421 2265	HR ight (%) IV, random, 9 6.6 1.65 (1.05, 2 3.0 1.78 (0.78, 4	59)
Fest for overall effect: Z=8.74 (P- Fest for subgroup differences: χ^2 : Study or subgroup I.14.1 TNM stage 0–III Hong 2017 de 2017 .eitch 2007 (resectable)	:0.00001) =0.27, df=1 (P=0.60), P= log (HR) 0.5008 0. 0.5766 (0.6981 0.	=0% SE We 2306 0.421 3265	HR ight (%) IV, random, 9 6.6 1.65 (1.05, 2 3.0 1.78 (0.78, 4 4.4 2.01 (1.06, 3	Eavors HG Favors LG HR 15% CI IV, random, 95% CI 159) 166) 17 IV 10 IV 1
Fest for overall effect: Z=8.74 (P* Fest for subgroup differences: ½ ² : 1.14.1 TNM stage 0–III Hong 2017 de 2017 Leitch 2007 (resectable) McSorley 2017	:0.00001) =0.27, df=1 (P=0.60), P= log (HR) 0.5008 0. 0.5766 (0.6981 0. 0.6575 0.	=0% SE We 2306 0.421 3265 5102	HR ight (%) IV, random, 9 6.6 1.65 (1.05, 2 3.0 1.78 (0.78, 4 4.4 2.01 (1.06, 3 2.2 1.93 (0.71, 5	Environ HG Favors LG Favors HG Favors LG HR HR IV, random, 95% CI .59) .06) .81) .25)
Fest for overall effect: $Z=8.74$ (P- rest for subgroup differences: χ^{22} Study or subgroup 1.14.1 TNM stage 0–III Hong 2017 de 2017 de 2017 exitch 2007 (resectable) McSorley 2017 Sugimoto 2012	0.00001) =0.27, df=1 (P=0.60), P= log (HR) 0.5008 0. 0.5766 (0.6981 0. 0.6575 0. 1.1282 0.	=0% SE We 2306 0.421 3265 5102 3201	HR ight (%) IV, random, 9 6.6 1.65 (1.05, 2 3.0 1.78 (0.78, 4 4.4 2.01 (1.06, 3 2.2 1.93 (0.71, 5 4.5 3.09 (1.65, 5	Favors HG Favors LG HR 95% Cl IV, random, 95% Cl .59) .66) .81) .25) .79)
Fest for overall effect: Z=8.74 (P Fest for subgroup I.14.1 TNM stage 0–III Hong 2017 de 2017 Leitch 2007 (resectable) McSorley 2017 Sugimoto 2012 Sun 2014	0.00001) 0.27, df=1 (P=0.60), P= 0.5008 0. 0.5766 0 0.6981 0. 0.6575 0. 1.1282 0. 0.8755 0.	=0% SE We 2306 0.421 3265 5102 3201 1471	HR ight (%) IV, random, 9 6.6 1.65 (1.05, 2 3.0 1.78 (0.78, 4 4.4 2.01 (1.06, 3 2.2 1.93 (0.71, 5 4.5 3.09 (1.65, 5 9.5 2.40 (1.80, 3	Favors HG Favors LG HR 95% CI IV, random, 95% CI .59) .06) .81) .25) .79) .20)
Fest for overall effect: Z=8.74 (P- Fest for subgroup I.14.1 TNM stage 0–III Hong 2017 de 2017 Leitch 2007 (resectable) McSorley 2017 Sugimoto 2012 Sun 2014 Foiyama 2011	0.00001) 0.27, df=1 (P=0.60), P= 0.5008 0. 0.5766 (0.6981 0. 0.6575 0. 1.1282 0. 0.8755 0. 1.6114 0.	=0% SE We 2306 0.421 3265 5102 3201 1471 5824	HR ight (%) IV, random, 9 6.6 1.65 (1.05, 2 3.0 1.78 (0.78, 4 4.4 2.01 (1.06, 3 2.2 1.93 (0.71, 5 4.5 3.09 (1.65, 5 9.5 2.40 (1.80, 3 1.8 5.01 (1.60, 15	Favors HG Favors LG HR 10/100/100 Favors HG Favors LG HR 10/100/100 HR 10/100/100 HR 10/100/100 HR 10/100/100 HR 10/100/100 HR 10/100/100 HR 10/100/100 HR 10/100/100 HR 10/100/100 10/100/100 10/100/100 10/100/10
Fest for overall effect: Z=8.74 (P- Fest for subgroup differences: χ^{2} : Study or subgroup 1.14.1 TNM stage 0–III Hong 2017 de 2017 de 2017 Leitch 2007 (resectable) McSorley 2017 Sugimoto 2012 Sun 2014 Foiyama 2011 Fokunana 2017	0.00001) 0.27, df=1 (P=0.60), P= 0.5008 0. 0.5766 (0.6981 0. 0.6575 0. 1.1282 0. 0.8755 0. 1.6114 0. 0.7608 0.	=0% SE We 2306 0.421 3265 5102 3201 1471 5824 2165	HR ight (%) IV, random, 9 6.6 1.65 (1.05, 2 3.0 1.78 (0.78, 4 4.4 2.01 (1.06, 3 2.2 1.93 (0.71, 5 4.5 3.09 (1.65, 5 9.5 2.40 (1.80, 3 1.8 5.01 (1.60, 15 7.0 2.14 (4.40, 2	Favors HG Favors LG HR 159) .06) .20) .20) .27)
Fest for overall effect: Z=8.74 (P× rest for subgroup differences: χ ²² Study or subgroup 1.14.1 TNM stage 0–III Hong 2017 de 2017 de 2017 exitch 2007 (resectable) McSorley 2017 Sugimoto 2012 Sun 2014 Fokunaga 2017 Nor 2016	0.00001) =0.27, df=1 (P=0.60), P= log (HR) 0.5008 0. 0.5766 (0.6981 0. 0.6575 0. 1.1282 0. 0.8755 0. 1.6114 0. 0.7608 0. 0.7608 0.	=0% SE We 2306 0.421 3265 5102 3201 1471 5824 2165 0045	HR ight (%) IV, random, 9 6.6 1.65 (1.05, 2 3.0 1.78 (0.78, 4 4.4 2.01 (1.06, 3 2.2 1.93 (0.71, 5 4.5 3.09 (1.65, 5 9.5 2.40 (1.80, 3 1.8 5.01 (1.60, 15 7.0 2.14 (1.40, 3 4.5 1.65 1.65 1.65 1.65 1.65 1.65 1.65 1.	Favors HG Favors LG Favors HG Favors LG HR 10, random, 95% Cl 159) 159 159 159 159 159 159 159 159
Fest for overall effect: Z=8.74 (P- Fest for subgroup differences: χ ²⁴ Study or subgroup 1.14.1 TNM stage 0–III Hong 2017 de 2017 Leitch 2007 (resectable) WeSorley 2017 Sugimoto 2012 Sun 2014 Foiyama 2011 Fokunaga 2017 Natt 2016 Discussion Comparison	0.00001) 0.27, df=1 (P=0.60), P= 0.5008 0. 0.5766 0 0.6981 0. 0.6975 0. 1.1282 0. 0.8755 0. 1.6114 0. 0.7608 0. 0.3075 0.	=0% SE We 2306 0.421 3265 5102 3201 1471 5824 2165 0945	HR ight (%) IV, random, 9 6.6 1.65 (1.05, 2 3.0 1.78 (0.78, 4 4.4 2.01 (1.06, 3 2.2 1.93 (0.71, 5 4.5 3.09 (1.65, 5 9.5 2.40 (1.80, 3 1.8 5.01 (1.60, 15 7.0 2.14 (1.40, 3 11.5 1.36 (1.13, 1	Favors HG Favors LG HR 95% CI IV, random, 95% CI .59) .06) .81) .25) .20) .27) .64) .27)
Fest for overall effect: Z=8.74 (P Fest for subgroup differences: χ ² Study or subgroup I.14.1 TNM stage 0–III Hong 2017 de 2017 Leitch 2007 (resectable) McSorley 2017 Sugimoto 2012 Sun 2014 Foiyama 2011 Fokunaga 2017 Natt 2016 Subtotal (95% CI)	0.00001) 0.27, df=1 (P=0.60), P= 0.5008 0. 0.5766 0 0.6981 0. 0.6575 0. 1.1282 0. 0.8755 0. 1.6114 0. 0.7608 0. 0.3075 0.	=0% SE We 2306 0.421 3265 5102 3201 1471 5824 2165 0945	HR ight (%) IV, random, 9 6.6 1.65 (1.05, 2 3.0 1.78 (0.78, 4 4.4 2.01 (1.06, 3 2.2 1.93 (0.71, 5 4.5 3.09 (1.65, 5 9.5 2.40 (1.80, 3 1.8 5.01 (1.60, 15 7.0 2.14 (1.40, 3 11.5 1.36 (1.13, 1 50.4 2.01 (1.57, 2	Favors HG Favors LG HR 10 HR 10 10 Favors LG HR 10 10 10 10 10 10 10 10 10 10
Fest for overall effect: $Z=8.74$ (P- rest for subgroup differences: χ^{22} Study or subgroup 1.14.1 TNM stage 0–III Hong 2017 de 2017 Leitch 2007 (resectable) WcSorley 2017 Sugimoto 2012 Sun 2014 Foiyama 2011 Fokunaga 2017 Vatt 2016 Subtotal (95% CI) Heterogeneity: $\tau^{2}=0.07; \chi^{2}=19$. Fest for overall effect: $Z=5.47$ (0.00001) 0.27, df=1 (P=0.60), P= 0.5008 0. 0.5766 0 0.6981 0. 0.6975 0. 1.1282 0. 0.8755 0. 1.6114 0. 0.7608 0. 0.3075 0. 29, df=8 (P=0.01); P= P<0 00001)	=0% SE We 2306 0.421 3265 5102 3201 1471 5824 2165 0945 59%	HR ight (%) IV, random, 9 6.6 1.65 (1.05, 2 3.0 1.78 (0.78, 4 4.4 2.01 (1.06, 3 2.2 1.93 (0.71, 5 4.5 3.09 (1.65, 5 9.5 2.40 (1.80, 3 1.8 5.01 (1.60, 15 7.0 2.14 (1.40, 3 11.5 1.36 (1.13, 1 50.4 2.01 (1.57, 2	Favors HG Favors LG HR 95% CI IV, random, 95% CI .59) .06) .81) .25) .20) .69) .27) .64) .58)
Test for overall effect: Z=8.74 (P- Test for subgroup differences: χ^{22} Study or subgroup I.14.1 TNM stage 0–III Hong 2017 de 2017 Leitch 2007 (resectable) McSorley 2017 Sugimoto 2012 Sun 2014 Toiyama 2017 Natt 2016 Subtotal (95% Cl) Heterogeneity: τ ² =0.07; χ^{2} =19. Fest for overall effect: Z=5.47 (0.00001) 0.27, df=1 (P=0.60), P= 0.5008 0. 0.5766 0 0.6981 0. 0.6575 0. 1.1282 0. 0.8755 0. 1.6114 0. 0.7608 0. 0.3075 0. 29, df=8 (P=0.01); P= P<0.00001)	=0% SE We 2306 0.421 3265 5102 3201 1471 5824 2165 0945 59%	HR ight (%) IV, random, 9 6.6 1.65 (1.05, 2 3.0 1.78 (0.78, 4 4.4 2.01 (1.06, 3 2.2 1.93 (0.71, 5 4.5 3.09 (1.65, 5 9.5 2.40 (1.80, 3 1.8 5.01 (1.60, 15 7.0 2.14 (1.40, 3 11.5 1.36 (1.13, 1 50.4 2.01 (1.57, 2	Favors HG Favors LG Favors HG Favors LG HR 10 10 HR 10 10 10 10 10 10 10 10 10 10
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Figure 8 Subgroup analysis showing correlation between GPS and prognosis of CRC patients according to TNM stages. Note: (A) Overall survival and (B) cancer-specific survival.

Abbreviations: CRC, colorectal cancer; df, degrees of freedom; GPS, Glasgow prognostic score; LG, low group; HG, high group; SE, standard error; TNM, tumor, node, metastases.



Figure 9 (Continued)



Figure 9 Sensitivity analysis and funnel plot of OS of patients with CRC.

Notes: Sensitivity analysis for (A) overall patients focusing on OS and (B) patients after removing studies with potential publication bias. Funnel plot for (C) overall patients focusing on OS and (D) patients after removing studies with potential publication bias.

Abbreviations: CRC, colorectal cancer; OS, overall survival; SE, standard error.

cancers. The development of therapeutic strategies and improvements in posttreatment quality of life remains a challenge as various factors influence prognosis. An increasing number of prognostic models or indicators have been used to predict the prognosis of patients with CRC. Inflammation-related models including the neutrophil to lymphocyte, platelet to lymphocyte, CRP, and the systemic inflammatory index were developed and demonstrated to be prognostic predictors in recent years. The GPS model was also designed to assess the prognosis of CRC patients. The present study attempted to identify the predictive role of GPS and mGPS by performing a meta-analysis based on the pooled outcomes of research worldwide.

This study included pooled survival outcomes from 43 independent cohorts involving 9,839 CRC patients. The

pooled outcomes showed that CRC patients with an increased level of pretreatment GPS or mGPS were associated with worse OS following SR or chemotherapy (HR: 2.20, 95% CI: 1.88–2.57, P<0.001). Moreover, elevated GPS or mGPS levels were also associated with poor CSS (HR: 1.86, 95% CI: 1.59–2.17, P<0.001). We also conducted subgroup analyses to reduce the heterogeneity. Subgroups were set according to models, therapeutic strategies, cutoff values, geographical regions, age, sample size, and TNM stages. The results of subgroup analyses confirmed the overall outcomes. By conducting the subgroup analyses, heterogeneity was reduced in the subgroups. Thus, the above-mentioned factors should be taken into consideration in future research.

CRC is one of the most common malignancies, and the prediction of prognosis is an important consideration in the

establishment of clinical treatment strategies. Recently, the prognostic role of inflammation factors in the management of CRC has been a focus of attention in surgeons.^{60,61} GPS is a prognostic score for cancer patients which calculates prognosis based on the combination of CRP and ALB levels. A growing number of studies have demonstrated the potential predictive value of GPS or mGPS in CRC patients. However, other studies found no correlation between the GPS or mGPS and the survival outcomes of CRC patients. Therefore, it was necessary to perform this systematic review and meta-analysis to draw credible conclusions on the controversial role of GPS in CRC.

As therapeutic strategy was one of the most important factors that influenced the prognostic outcomes of CRC patients, further subgroup analysis was performed to assess the effect of GPS or mGPS in CRC patients according to treatment. The results were consistent with the overall outcomes. Patients with low GPS or mGPS before undergoing SR had a better prognosis and longer CSS. GPS or mGPS was divided into three categories and there was no agreed conclusion on the cutoff values. Thus, subgroup analysis based on cutoff values was performed. The pooled outcomes obtained confirmed the accurate prognostic role of GPS and mGPS using either of the cutoff values. Moreover, patient age was considered another factor that influenced the overall outcomes. Tominaga et al demonstrated that the GPS was not correlated with patient prognosis as all the enrolled patients were over 65 years.62 We then conducted another subgroup analysis based on the mean/median patient age of 65 years as most of the patients included in this study were in the 65 years age group. In addition, 65 years was considered to be the dividing line between elderly and middle aged. Subgroup analyses of TNM stages, sample size, and publication regions were also carried out. The results of the subgroup analyses confirmed the overall outcomes and demonstrated the effective prognostic value of GPS or mGPS in predicting survival outcomes in CRC patients.

The results of the sensitivity analysis and funnel plot showed potential publication bias in several studies. After omitting these studies, the OS in the remaining studies was more symmetrically distributed. The reasons for this bias may be due to differences in the baseline characteristics of CRC patients and factors related to the study protocols. Moreover, the differences in detection methods and data storage may have resulted in heterogeneity. Although the random effects model reduced the effect of heterogeneity, the heterogeneity between studies was not abolished.

Two previous meta-analyses reported the prognostic value of GPS or mGPS in CRC patients.^{63,64} Dolan et al examined the evidence for the role of several systemic inflammationbased prognostic scores in patients who underwent SR.63 Only 12 studies with 4,739 CRC patients were included in the meta-analysis and no subgroup analyses were conducted. Liu et al performed a meta-analysis by pooling the outcomes of 25 retrospective studies.⁶⁴ The inclusion and exclusion criteria were not rigorous enough and several studies which focused on the prognostic value of GPS were not included. In their study, subgroup analyses were performed based on sample size, cutoff values, and geographical regions. However, they did not include therapeutic strategies, tumor clinical stages, and modifications of the GPS, which accounted for some of the heterogeneity. The present meta-analysis, to our knowledge, is the most comprehensive and included 41 studies. Furthermore, subgroup analyses were also performed.

GPS or mGPS is calculated based on serum CRP and ALB levels. CRP is an acute-phase protein produced in hepatocytes via activation of tumor necrosis factor-a and interleukin-6.51 Several studies have reported that increased serum CRP levels were associated with poor outcomes in a variety of solid tumors.^{65–67} In contrast, hypoalbuminemia is considered to be an indicator of malnutrition and cachexia. Two studies have shown that hypoalbuminemia was associated with poor outcomes in various cancers.68,69 The GPS or mGPS enables better appreciation of systemic inflammation or malnutrition in CRC patients. This study pooled outcomes and then drew reliable conclusions with regard to the prognostic value of the GPS or mGPS. Based on these conclusions, the GPS or mGPS should be highlighted in the clinical management of CRC. For patients with elevated GPS or mGPS, a management protocol for systemic inflammatory response via the tumor-host interaction during the postoperative course is urgently needed to improve their prognosis.⁵¹

The present meta-analysis was performed based on the largest patient sample available to date. However, the study had several limitations. Firstly, most of the included studies were retrospectively designed. This increased the risk of bias due to inadequate random blinding and sequencing. Secondly, even though subgroup analyses were performed, heterogeneity still existed among subgroups. This may have been due to a variety of baseline characteristics and follow-up information. Furthermore, the overall outcomes might be overvalued due to unpublished studies which had negative data. Finally, all included studies were written in English, and this may have resulted in publication bias. These limitations should be taken into consideration in further studies to confirm our results. Nevertheless, the present meta-analysis was conducted at an appropriate time based on sufficient studies with enough data to investigate the prognostic value of GPS or mGPS in CRC patients. A meta-analysis is a statistical inspection of scientific studies, and its level of evidence is considered to be superior to that of individual studies.⁷⁰ The results of this meta-analysis are encouraging although multiple strategies were used to identify relevant studies, with strict criteria used for study inclusion and evaluation. Subgroup analyses were performed to minimize heterogeneity due to different treatment modalities, cutoff values, regions, ages, and tumor stages. In addition, our study is the most comprehensive and up-to-date systematic review and meta-analysis which focused on the role of GPS or mGPS in predicting the prognosis of CRC.

Conclusion

The present study indicated that pretreatment GPS or mGPS was an accurate prognostic predictor in patients with CRC. Patients with elevated pretreatment GPS or mGPS were associated with worse prognosis. Subgroup analyses confirmed the overall outcomes. Pretreatment GPS or mGPS should be identified as an important parameter in the management of CRC.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

 Table SI Summary of risk of bias

Study	Study	Study	Prognostic	Outcome	Study	Statistical
	participation	attrition	factor	measurement	confounding	analysis and
			measurement			reporting
Adachi et al ^ı	-	-	±	-	-	±
Chan et al ²	-	-	-	-	±	±
Choi et al ³	-	-	±	-	±	-
Dréanic et al⁴	-	±	-	±	±	-
Eren et al⁵	-	-	±	-	±	-
Furukawa et al ⁶	±	±	-	-	-	-
Ghanim et al ⁷	±	±	-	-	-	-
Hong et al ⁸	-	-	-	-	±	-
Ide et al ⁹	-	-	±	-	±	-
Inoue et al ¹⁰	-	-	-	-	±	-
Ishizuka et al ¹¹	-	-	-	-	-	-
Ishizuka et al ¹²	-	-	-	-	±	±
Kim et al ¹³	-	-	-	-	±	-
Kishiki et al ¹⁴	-	-	-	-	±	-
Kobayashi et al ¹⁵	±	-	-	-	±	-
Køstner et al ¹⁶	-	-	-	-	±	-
Leitch et al ¹⁷	-	-	-	-	-	±
Lin et al ¹⁸	±	-	-	-	±	±
Maeda et al ¹⁹	±	-	-	-	±	-
Maillet et al ²⁰	±	-	-	-	±	-
McSorley et al ²¹	±	-	-	-	-	±
Moug et al ²²	-	-	-	±	±	±
Nakagawa et al ²³	-	±	-	-	±	-
Ni et al ²⁴	-	-	±	-	±	-
Nozoe et al ²⁵	-	±	-	-	±	±
Okimoto et al ²⁶	-	-	-	-	±	-
Okugawa et al ²⁷	-	±	-	-	-	-
Read et al ²⁸	±	-	-	-	-	-
Sharma et al ²⁹	±	±	-	-	±	-
Shibutani et al (I) ³⁰	-	±	-	-	±	-
Shibutani et al (2) ³⁰	-	-	-	-	±	-
Shimura et al ³¹	-	-	±	-	-	-
Sirniö et al ³²	-	-	-	-	±	-
Son et al ³³	-	-	-	-	±	-
Song et al ³⁴	-	-	-	-	-	±
Sugimoto et al ³⁵	±	-	-	-	±	-
Sun et al ³⁶	-	±	-	-	±	-
Toiyama et al ³⁷	-	-	-	-	-	±
Tokunaga et al ³⁸	-	-	_	_	±	-
Watt et al ³⁹	-	-	_	±	±	-
Yamamoto et al ⁴⁰	±	-	-	-	±	±

Note: The risk of bias for each domain is graded as low (–), moderate (\pm), or high (+).

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