### **Review** Article

# Incidence and Risk Factors for Postoperative Delirium in Patients Undergoing Spine Surgery: A Systematic Review and Meta-Analysis

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*Background*. The present study aims to investigate the incidence and risk factors associated with postoperative delirium in patients undergoing spine surgery. *Methods*. PubMed, EMBASE, Cochrane Library, and Science Citation Index were searched up to August 2019 for studies examining postoperative delirium following spine surgery. Incidence and risk factors associated with delirium were extracted. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for outcomes. The Newcastle–Ottawa Scale (NOS) was used for the study quality evaluation. *Results*. The final analysis includes a total of 40 studies. The pooled analysis reveals that incidence of delirium is 8%, and there are significant differences for developing delirium in age (OR 1.07; 95% CI 1.04–1.09), age more than 65 (OR 4.77; 95% CI 4.37–5.16), age more than 70 (OR 15.87; 95% CI 6.03–41.73), and age more than 80 (OR 1.91; 95% CI 1.78–2.03) years, male (OR 0.81; 95% CI 0.76–0.86), a history of alcohol abuse (OR 2.51; 95% CI 1.67–2.56), anxiety (OR 1.74; 95% CI 1.04–2.44), congestive heart failure (OR 1.4; 95% CI 1.21–1.6), depression (OR 2.5; 95% CI 1.52–3.49), hypertension (OR 1.12; 95% CI 1.04–1.2), kidney disease (OR 1.41; 95% CI 1.16–1.66), neurological disorder (OR 4.66; 95% CI 4.22–5.11), opioid use (OR 1.86; 95% CI 1.18–2.54), psychoses (OR 2.77; 95% CI 2.29–3.25), pulmonary disease (OR 1.81; 95% CI 0.5–0.89), preoperative pain (OR 1.88; 95% CI 1.11–2.64), and postoperative urinary tract infection (OR 5.68; 95% CI 2.41–13.39). *Conclusions*. A comprehensive understanding of incidence and risk factors of delirium can improve prevention, diagnosis, and management. Risk of postoperative delirium can be reduced based upon identifiable risk factors.

#### 1. Introduction

Postoperative delirium is a common complication after surgery in the elderly and causes difficulty in postoperative care [1, 2]. It is defined as an acute change in the cognitive status characterized by fluctuating consciousness, attention, memory, perceptions, and behavior postoperatively [3]. Postoperative delirium often brings out many adverse outcomes, such as functional disability, increased health care costs, and higher morbidity and mortality rates [4]. Thus, a further understanding and prevention of delirium may help reduce these problems and the associated costs. Some previous studies have reported the incidence and risk factors for delirium. However, incidences of postoperative delirium differ greatly, and risk factors of these studies are inconsistent. Therefore, we perform a systematic review and meta-analysis to explore incidence and risk factors for developing postoperative delirium following spine surgery.

#### 2. Materials and Methods

2.1. Search Strategy. The systematic review and meta-analysis were done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline and AMSTAR (assessing the methodological quality of systematic reviews) Guidelines [5, 6]. PubMed, EMBASE, Cochrane Library, and Science Citation Index were searched exhaustively with inception to August 2019.



FIGURE 1: Flow chart of the literature search and article selection.

The language was restricted to English, and only published articles were included. The search terms were combinations of epidemiology, prevalence, incidence, delirium, deliriums, deliria, delirious, confusion, transient mental disorder, spine, spinal cord, vertebrae, surgery, and operation. Papers from the reference lists of included studies and other metaanalyses were also searched.

2.2. Selection Criteria. Studies included in this systematic review and meta-analysis met the following criteria: (1) original articles on patients who underwent spine surgery, (2) observational, case series or cohort study design, (3) at least incidence reported or one risk factor identified as being associated with delirium, and (4) full text available. If the inclusion criteria were not met, the study was excluded. If the same study was published in different years or various journals, then the most frequently cited study was included for this meta-analysis. The potentially qualified studies were selected independently by 2 authors according to the inclusion and exclusion criteria. Any discrepancy was resolved by discussion to reach a consensus.

2.3. Data Extraction. Data were extracted by two independent authors. By discussion or by involving a third author, disagreements were addressed. The general features cover the first author, publication year, country, study type, sample size, patient characteristics, patients who underwent surgery, delirium diagnosis tool, incidence duration of delirium, and significant factors.

2.4. Quality Assessment. Two authors independently evaluated the quality of the studies, and the level of agreement between them was recorded. Any disagreements between the 2 authors were resolved by discussion with a third author. Newcastle–Ottawa Scale (NOS) was utilized to assess the quality of each study [7] since no studies were randomized controlled trials. Studies with 7–9 points could be identified as high quality, 5–6 points as moderate quality, and 0–4 as poor quality.

2.5. Statistical Analysis. The meta-analysis of comparable data was performed using Stata/SE version 15.0 software. All adjusted odds ratio (OR) with 95% confidence interval (CI)

TABLE 1: Study characteristics and quality assessment.

Study quality	∞	4	~	8	×	ø	~	8	~	4	М	~	~	9	8	8
Significant factors	Male, parkinsonism, lower baseline MMSE score	Age, PNI	Age, intraoperative ketamine use	CVD, dural tear	Low general health perception	Age >80	Parkinsonism	Blood loss	Cognitive impairment	CKD	Age, ASA physical status ≥3, METs <4, depression, nonelective surgery, invasiveness tier 3 or 4, BIS monitoring, mean pain score postoperative day 1	Preoperative hgb level <13.5 g/dl	Open laminectomy		Age, operative time ≥6 hours	Hyposmia (CCSIT score <9) and RBD (RBDSQ- K >4)
Duration of delirium (days)	2.6 (1-5)	I	I	Ι	<3	I	I	<5	Ι	I	I	Ι	I	I		I
Delirium incidence	12/83 (14.5%)	30/319 (9.4%)	(10.9%)	65/13188 (0.49%)	10/67 (14.9%)	4502/ 88370 (5.1%)	26/322 (8.1%)	59/532 (11.1%)	22/82 (18%)	28/293 (9.6%)	127/715 (17.8%)	25/204 (12.3%)	52/2712 (1.9%)	11/35 (31.43%)	34/304 (11.2%)	15/104 (14.4%)
Delirium diagnosis tool	CAM		I	I	CAM, DSM- IV	Ι		DSM-IV	CAM		I	I				CAM
Patients who underwent surgery	Lumbar spine	Spinal deformity	Complex spinal fusion (≥5 levels)	Lumbar spine	Cervical spine	Lumbosacral, thoracic, cervical, unspecified	Thoracic, lumbar spine	Spine	Thoracolumbar deformity	Lumbar spine	Cervical, lumbar spine	Elective complex spinal fusion (≥3 levels)	Lumbar spine	Cervical, thoracic, lumbar spine	Spinal deformity	Cervical, thoracic, lumbar spine
Sex ratio (M:F)	27:56	85:234	40:98	7174: 6014	49:18	47408: 40962	69:253	283: 249	33:49	105: 188	351: 400	204:0	1738: 974	14:21	64:240	36:68
Age mean (SD, range) years	71.4±4.6	>18	≥18	11-94	$69.6 \pm 12.0$	≥65	75.7 years (67–89)	64.2 (10-89)	≥65	≥18	73.6±6.0	≥60	≥20	91.3 (90–98)	62.9 (18-84)	71.7±4.7
Sample size	83	319	138	13188	67	88370	322	532	82	293	715	204	2712	35	304	104
Study type	Prospective	Retrospective	Retrospective	Prospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Prospective
Country	Korea	Japan	USA	Japan	Japan	Japan	Japan	Japan	USA	USA	Portugal	USA	Japan	Japan	Japan	Korea
Publication year	2019	2019	2019	2019	2019	2019	2019	2018	2018	2018	2018	2018	2018	2018	2018	2018
Author	Pan et al. [8]	Oe et al. [9]	Elsamadicy et al. [10]	Takenaka et al. [11]	Kin et al. [12]	Oichi et al. [13]	Watanabe et al. [14]	Morino et al. [15]	Adogwa et al. [16]	Adogwa et al. [17]	Susano et al. [18]	Elsamadicy et al. [19]	Oichi et al. [20]	Kobayashi et al. [21]	Yoshida et al. [22]	Kim et al. [23]

AuthorPublication yearCountryStuckRamos et al.2017USARetro[24]2017USARetro[25]2017USARetro[25]2017USARetroet al.2617USARetroet al.2017USARetroet al.2017USARetroet al.2017USARetroet al.2017USARetroet al.2017USARetrofadeliff2017USARetrofang et al.2017USARetro[30]2017ChinaRetroSoh et al.2017KoreaPros	c		A 200 200 200 0	c		:- :		ر ب ډ		
Ramos et al.2017USARetro[24](24]2017USARetro[25]2017JapanRetro[25]2017USARetroet al.[26]2017USARetroet al.[27]2017USARetroet al.[28]2017USARetrofisamadicy2017USARetroet al.[29]2017USARetrofiang et al.2017USARetrojang et al.2017ChinaRetroSoh et al.2017KoreaPros	dy type <sup>Sa</sup>	mple (	Age mean SD, range) years	ъех ratio (M:F)	Patients who underwent surgery	Delirium diagnosis tool	Delirium incidence	Duration of delirium (days)	Significant factors	Study quality
Oichi et al.2017JapanRetro[25]2017USARetroElsamadicy2017USARetroet al.[27]2017USARetroElsamadicy2017USARetroet al.[28]2017USARetrofadcliff2017USARetrofadcliff2017USARetrofadcliff2017USARetrofadcliff2017USARetrofads2017USARetrofood et al.2017ChinaRetrofood et al.2017KoreaPros	spective 1	1043	67±9	2981 : 8062	Spinal deformity	l	269/ 11043 (2.4%)	l	Movement disorder, parkinsonism	~
Elsamadicy 2017 USA Retro et al. [26] 2017 USA Retro Elsamadicy 2017 USA Retro et al. [28] 2017 USA Retro et al. [29] 2017 USA Retro f al. [29] 2017 USA Retro f al. [29] 2017 China Retro [30] soh et al. 2017 Korea Pros	ospective 6	5921	≥20	3324: 3597	Lumbosacral, thoracic, cervical, unspecified	l	670/6921 (9.7%)	l	Parkinsonism	2
Elsamadicy 2017 USA Retro et al. [27] 2017 USA Retro Elsamadicy 2017 USA Retro et al. [29] 2017 USA Retro et al. [29] 2017 China Retro [30] et al. 2017 China Retro	spective	453	≥65	211: 242	Spine	DSM-V	17/453 (3.75%)	l	Superficial surgical site infection, UTI, length of hospital stay	8
Elsamadicy 2017 USA Retro et al. [28] 2017 USA Retro et al. [29] 2017 USA Retro jang et al. 2017 China Retro [30] 2017 Korea Pros	ospective	923	≥18	333: 590	Spinal deformity	l	66/923 (7.15%)	l	Depression, age, operative time, postoperative UTI	
Radcliff 2017 USA Retro et al. [29] 2017 USA Retro Jiang et al. 2017 China Retro [30] Soh et al. 2017 Korea Pros	spective 8	839	≥18	329: 510	Elective complex spinal fusion (≥3 levels)	I	67/839 (7.98%)	I	I	9
Jiang et al. 2017 China Retro [30] Soh et al. 2017 Korea Pros	ospective 2	:792	≥65	1487: 1305	Cervical spine	Ι	157/2792 (5.6%)	I	Dementia, TIA/stroke, age≥ 85 in cervical decompression patients Intraoperative	
Soh et al. 2017 Korea Pros	spective	451 6	5.1 (45-84)	226: 225	Cervical and lumbar spine	I	42/451 (9.3%)	6.7 (4-10)	hypotension <80 mmHg, intraoperative use of dezocine	
[31]	spective	109	>70	56:53	Cervical, thoracic, lumbar spine	ICDSC; CAM-ICU	9/109 (8.2%)	I	Pulmonary disease	~
Adogwa 2017 USA Prosp et al. [32] 2017 USA Prosp	pective e	125	≥65	50:75	Spinal deformity	I	22/125 (17.6)	I	I	7
Adogwa 2017 USA Retro et al. [33] 2017 USA Retro	ospective	82	≥65	33:49	Spinal deformity	I	13/82 (15.9%)	I	Cognitive impairment	4
Kobayashi 2017 Japan Retro et al. [1]	ospective	262 8	2.7 (80–91)	142: 140	Cervical, thoracic, and lumbar spine	I	15/262 (5.72)	$\hat{\omega}$	Cervical lesion surgery, blood loss>300 mL Lower baseline MMSE	
Brown et al. 2016 USA Pros [34]	spective	195	74 (72–78)	47:42	Cervical, lumbar spine	CAM; CAM- ICU; DRS- 98-R	36/195 (18.5%)	I	score, higher average baseline pain, more intravenous fluid, baseline, antidepressant medication	<b>L</b>
Lee et al. 2016 Korea Retro [35]	spective	129	73.5 (70 to 85)	51:78	Lumbar spine	CAM; DSM- IV	18/129 (13.9%)	13.2 (1 to 92)	Cognitive impairment	~
Balabaud 2015 France Retro et al. [36] 2015	ospective	121	83.2 ± 2.4	48:73	Lumbar spine	Ι	16/(13%)	Ι	Instrumentation, blood loss	4

TABLE 1: Continued.

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TABLE	

	Study quality	7	9	œ	8	٥		9		6	►
	Significant factors	Age, male, head injury	I	Preoperative GDS, BIS measured intraoperatively under 40	CCI, dural tear	Age ≥65, teaching hospital, alcohol abuse, deficiency anemia, congestive heart failure, coagulopathy, depression, DM with end-organ damage, drug abuse, hypertension, fluid/electrolyte	disorders, metastatic neoplasm, neurological disorder, psychoses, pulmonary circulation disorders, renal failure, weight loss		Cerebral vascular disease, low hemoglobin and hematocrit levels at 1 day after surgery, bad	Age >70, high-dose methylprednisolone (>1000 mg), hearing impairment	Central nervous system disorder, surgical history, age> 65, DM, blood transfusion ≥800 ml, hemoglobin <100 g/L
	Duration of delirium (days)	I	I	I	I	I		I	13.2 (1 to 92)	I	3.1 (1 to 8)
	Delirium incidence	38/276 (13.8%)	21/101 (20.8)	17/70 (24.3%)	5/92 (5.4%)	4857/ 578457 (0.84%)		5/918 (0.54%)	11/81 (13.6%)	26/122 (21.3%)	18/549 (3.3%)
	Delirium diagnosis tool	I	I	ICDSC; CAM-ICU	I	I		I	CAM, DSM- IV	DOS, DSM- IV	DOS, DSM- IV
E 1: Continued.	Patients who underwent surgery	Thoracic, lumbar spine	Thoracic, lumbar, sacral spine	Cervical, lumbar spine	Lumbar spine	Lumbar spine		Lumbar spine	Lumbar spine	Cervical spine	Cervical, thoracic, lumbar, sacral spine
TABL	Sex ratio (M:F)	190:86	50:51	32:38		285520: 292937		521: 397	27:50	ĺ	302 : 247
	Age mean (SD, range) years	$42.9 \pm 18.8$	62 (33–85)	70.1 ± 5.8	$66.08 \pm 10.59$	>18		54 (11-87)	73.5 (70-85)	52-86	48.2 (10–83)
	Sample size	276	101	70	92	578457		918	87	122	549
	Study type	Retrospective	Prospective	Prospective	Prospective	Retrospective		Retrospective	Retrospective	Retrospective	Retrospective
	Country	Canada	Canada	Korea	Canada	USA		Japan	Korea	Japan	China
	Publication year	2015	2014	2014	2014	2013		2011	2010	2009	2008
	Author	Glennie et al. [37]	Dea et al. [38]	Seo et al. [39]	Kelly et al. [40]	Fineberg et al. [41]		Imagama et al. [42]	Lee et al. [43]	Ushida et al. [44]	Gao et al. [45]

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lor	Publication year	Country	Study type	Sample size	Age mean (SD, range) years	Sex ratio (M:F)	Patients who underwent surgery	Delirium diagnosis tool	Delirium incidence	Duration of delirium (days)	Significant factors	Study quality
aguchi . [46]	2006	Japan	Retrospective	341	59.2 (14–88)	186: 155	Cervical, thoracic, lumbar, sacral spine	CAM, DSM-III-R	13/341 (3.8%)	<∠7	Low concentrations of hemoglobin and hematocrit 1 day after surgery, ambulatory status at admission	œ
, delirium , chronic k itional Ind der; CCSI' lson Come	observation scr idney disease; ex; ASA, Amer F, cross-cultur; orbidity Index.	eening scale CAM-ICU, c ican Society 1 smell iden	;; DSM, diagnostic confusion assessm r of Anesthesiolog ntification test; RF	: and statist tent methoo jists physica DSQ-K, Ko	ical manual of me l for the intensive l status; BIS, Bisr prean version of l	ntal disorc care unit; oectral Ind 3BD screer	lers; CAM, confusion asse DRS-98-R, delirium ratin ex; METs, metabolic equiv ning questionnaire; TIA, t	ssment method; g scale revised-98 calents of task; U ransient ischemi	MMSE, mini- 8; ICDSC, inte 7TI, urinary tr: ic attack; GDS	mental state exan asive care deliriu act infection; RBI , global deteriora	ination; CVD, cardiovascul, n screening checklist; PNI, F J, rapid eye movement sleep tion scale; BIS, Bispectral In	r disease; rognostic behavior dex; CCI,

TABLE 1: Continued.

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Study ID			Incidence (95% CI)	% weight
Asia				
Pan et al. (2019)		•	0.14 (0.07, 0.22)	1.01
Oe et al. (2019)			0.09 (0.06, 0.13)	2.70
Takenaka et al. (2019)	• I		0.00 (0.00, 0.01)	4.26
Kin et al. (2019)		◆	0.15 (0.06, 0.23)	0.83
Oichi et al. (2019)	•		0.05 (0.05, 0.05)	4.26
Watanabe et al. (2019)			0.08 (0.05, 0.11)	2.84
Morino et al. (2018)			0.11 (0.08, 0.14)	3.04
Oichi et al. (2018)	•		0.02 (0.01, 0.02)	4.20
Kobayashi et al. (2018)		•	0.31 (0.16, 0.47)	0.30
Yoshida et al. (2018)		_	0.11 (0.08, 0.15)	2.50
Kim et al. (2018)		•	0.14 (0.08, 0.21)	1.19
Oichi et al. (2017)	•		0.10 (0.09, 0.10)	4.15
Jiang et al. (2017)			0.09 (0.07, 0.12)	3.03
Soh et al. (2017)	•		0.08 (0.03, 0.13)	1.70
Kobayashi et al. (2017)		_	0.06 (0.03, 0.09)	2.95
Lee et al. (2016)		•	0.14 (0.08, 0.20)	1.41
Seo et al. (2014)		•	0.24 (0.14, 0.34)	0.64
Imagama et al. (2011)	•	_	$0.01\ (0.00,\ 0.01)$	4.21
Lee et al. (2010)		<u> </u>	0.14 (0.06, 0.21)	1.03
Ushida et al. (2009)		<b>•</b>	0.21 (0.14, 0.29)	1.07
Gao et al. (2008)	-		0.03 (0.02, 0.05)	3.79
Kawaguchi et al. (2006)	-		0.04 (0.02, 0.06)	3.46
Subtotal ( $I^2 = 99.3\%$ , $P = 0.000$ )	$ \qquad \qquad$		0.08 (0.07, 0.10)	54.57
Amorico				
Flsamadicy et al. (2019)			0.11 (0.06, 0.16)	1.69
Adogwa et al. (2018)	•		0.27(0.17, 0.36)	0.69
Adogwa et al. (2018)		•	0.10(0.06, 0.13)	2.60
Elsamadicy et al. (2018)		L	0.12(0.08, 0.17)	1.99
Ramos et al. (2017)			0.02(0.02, 0.03)	4.24
Elsamadicy et al. (2017)	· · ·		0.04 (0.02, 0.06)	3.63
Elsamadicy et al. (2017)	· •		0.07 (0.05, 0.09)	3.69
Elsamadicy et al. (2017)			0.08 (0.06, 0.10)	3.58
Radcliff et al. (2017)	•		0.06 (0.05, 0.06)	4.09
Adogwa et al. (2017)		•	0.18 (0.11, 0.24)	1.21
Adogwa et al. (2017)		•	0.16 (0.08, 0.24)	0.94
Brown et al. (2016)		· · · · · · · · · · · · · · · · · · ·	- 0.40 (0.30, 0.51)	0.62
Glennie et al. (2015)		-	0.14 (0.10, 0.18)	2.21
Dea et al. (2014)		•	0.21 (0.13, 0.29)	0.94
Kelly et al. (2014)			0.05 (0.01, 0.10)	1.93
Fineberg et al. (2013)	•		0.01 (0.01, 0.01)	4.26
Subtotal $(I^2 = 97.6\%, P = 0.000)$	$\diamond$		0.08 (0.07, 0.10)	38.33
Europe				
Susano et al. (2018)		-	0.18 (0.15, 0.21)	2.95
Balabaud et al. (2015)	•		0.01 (0.01, 0.02)	4.15
Subtotal ( $I^2 = 99.2\%, P = 0.000$ )			0.10 (-0.06, 0.26)	7.11
. Overall ( $I^2 = 99.2\%$ , $P = 0.000$ )	\$		0.08 (0.07, 0.09)	100.00
Note: weights are from random effects analysis				
	0	0.2 0.4		
	•			

(a) FIGURE 2: Continued.

Prospective Pan et al. (2019)       0.14 (0.07, 0.22)       1.01         Marchake at al. (2019)       0.04 (0.00, 0.01)       4.26         Kim et al. (2017)       0.04 (0.08, 0.21)       1.19         Adogwa et al. (2017)       0.04 (0.03, 0.22)       0.04 (0.03, 0.23)       0.64         Subto al (2014)       0.44 (0.13, 0.29)       0.94       0.44 (0.13, 0.29)       0.94         So et al. (2014)       0.24 (0.14, 0.33, 0.29)       0.94       0.24 (0.14, 0.33, 0.29)       0.94         Subto al (f <sup>2</sup> = 95.4%, P = 0.000)       0.15 (0.06, 0.13)       2.70       0.16 (0.08, 0.23)       1.3.00         Retrospective       0.09 (0.06, 0.13)       2.70       0.16 (0.08, 0.23)       1.3.30         Oct al. (2019)       0.15 (0.06, 0.13)       2.70       0.11 (0.06, 0.16)       1.69         Kin et al. (2019)       0.15 (0.06, 0.23)       0.83       0.05 (0.05)       4.26         Morino et al. (2018)       0.05 (0.05, 0.05)       4.26       0.08 (0.05, 0.05)       4.26         Susano et al. (2018)       0.16 (0.08, 0.17)       2.99       0.16 (0.08, 0.15)       2.50         Ramos et al. (2017)       0.04 (0.02, 0.06)       3.63       2.50       0.31 (0.16, 0.7)       2.50         Susano et al. (2017)       0.04 (0.02, 0.06)       3.63 </th <th>Study ID</th> <th>Incidence (95% CI)</th> <th>% weight</th>	Study ID	Incidence (95% CI)	% weight
Pan et al. (2019) Takenaka et al. (2019) Soh et al. (2017) Brown et al. (2017) Brown et al. (2016) Date et al. (2014) So et al. (2014) Sob et al. (2019) Correct al. (2019) Correct al. (2019) Correct al. (2019) Morino et al. (2018) Adogwa et al. (2018) Adogwa et al. (2018) Chichi et al. (2018) Chichi et al. (2017) Ramadicy et al. (2018) Chichi et al. (2017) Chichi et al. (2016)	Prospective		
Takenake et al. (2019)       0.00 (000, 001)       4.26         Sint et al. (2017)       0.08 (003, 013)       1.70         Adogwa et al. (2017)       0.08 (003, 013)       0.62         Prown et al. (2016)       0.01 (003, 013)       0.62         Dea et al. (2014)       0.21 (013, 0.29)       0.94         Soe et al. (2014)       0.21 (013, 0.29)       0.94         Soe et al. (2014)       0.21 (013, 0.29)       0.94         Soe et al. (2019)       0.16 (008, 0.23)       1.35.00         Fetrospective       0.09 (006, 0.13)       2.70         Elsamadicy et al. (2019)       0.15 (006, 0.23)       0.83         Oth et al. (2019)       0.15 (006, 0.23)       0.83         Oth et al. (2019)       0.15 (006, 0.23)       2.80         Morino et al. (2018)       0.010 (006, 0.13)       2.60         Susano et al. (2018)       0.11 (006, 0.13)       2.60         Susano et al. (2018)       0.11 (006, 0.13)       2.60         Oth et al. (2018)       0.11 (006, 0.13)       2.60         Susano et al. (2017)       0.86 (0.05, 0.13)       2.60         Susano et al. (2017)       0.86 (0.05, 0.13)       2.60         Susano et al. (2017)       0.60 (0.05, 0.05)       4.26         Sta	Pan et al. (2019)	• 0.14 (0.07, 0.22)	1.01
Kim et al. (2018) $0.44 (0.08, 0.21)$ 1.19 Adogwa et al. (2017) Adogwa et al. (2017) Adogwa et al. (2016) $0.60 (0.30, 0.51)$ 0.62 Date at al. (2014) $0.21 (0.13, 0.29)$ 0.94 Seo et al. (2014) $0.21 (0.13, 0.29)$ 0.94 Scottal ( $l^2 = 95.4\%, P = 0.000$ ) 0.16 (0.08, 0.23) 1.350 0.16 (0.08, 0.23) 0.351 0.09 (0.06, 0.13) 2.70 Elsamadicy et al. (2019) 0.05 (0.06, 0.13) 2.70 Elsamadicy et al. (2019) 0.05 (0.05, 0.05) 4.26 0.09 (0.06, 0.13) 2.60 0.05 (0.05, 0.05) 4.26 0.00 (0.06, 0.13) 2.60 0.02 (0.01, 0.02) 4.20 0.03 (0.05, 0.11) 2.84 0.03 (0.05, 0.11) 2.84 0.03 (0.05, 0.11) 2.84 0.03 (0.05, 0.13) 2.60 0.02 (0.01, 0.02) 4.20 0.02 (0.01, 0.02) 4.20 0.02 (0.02, 0.03) 4.24 0.02 (0.02, 0.03) 4.24 0.02 (0.01, 0.02) 4.20 0.02 (0.02, 0.03) 4.24 0.02 (0.02, 0.03) 4.24 0.04 (0.02, 0.06) 3.63 Elsamadicy et al. (2017) 0.06 (0.05, 0.06) 4.09 0.08 (0.06, 0.10) 3.58 Raddiff et al. (2017) 0.06 (0.03, 0.09) 2.95 Elsamadicy et al. (2017) 0.00 (0.00, 0.01) 4.21 0.01 (0.00,	Takenaka et al. (2019)	0.00 (0.00, 0.01)	4.26
Soh et al. (2017) Adagwa et al. (2017) Brown et al. (2016) Dra et al. (2014) Scot et al. (2014) Scot et al. (2014) Scot et al. (2014) Ce et al. (2019) Che et al. (2019) Che at al. (2018) Adagwa et al. (2018) Adagwa et al. (2018) Che at al. (2017) Che	Kim et al. (2018)	• 0.14 (0.08, 0.21)	1.19
$ \begin{array}{c} \operatorname{Adegwa}{\operatorname{et al}} (2017) \\ \operatorname{Dea et al} (2016) \\ \operatorname{Dea et al} (2014) \\ \operatorname{Seo et al} (2014) \\ \operatorname{Seo et al} (2014) \\ \operatorname{Seo et al} (2014) \\ \operatorname{Subtol} (f^2 - 95.4\%, P = 0.000) \\ \\ \operatorname{Retrospective} \\ \operatorname{Oe et al} (2019) \\ \operatorname{Elsamadicy}{\operatorname{et al}} (2019) \\ \operatorname{Elsamadicy}{\operatorname{et al}} (2019) \\ \operatorname{Sin et al} (2019) \\ \operatorname{Sin et al} (2019) \\ \operatorname{Subtol} (2019) \\ \operatorname{Sin et al} (2019) \\ \operatorname{Subtol} (2019) \\ \operatorname{Subtol} (2019) \\ \operatorname{Subtol} (2019) \\ \operatorname{Sin et al} (2019) \\ \operatorname{Subtol} (2019) \\ \operatorname{Sin et al} (2018) \\ \operatorname{Subsol} (2017) \\ \operatorname{Elsamadicy}{\operatorname{et al}} (2017) \\ \operatorname{Elsamadicy}{\operatorname{et al}} (2017) \\ \operatorname{Elsamadicy}{\operatorname{et al}} (2017) \\ \operatorname{Elsamadicy}{\operatorname{et al}} (2017) \\ \operatorname{Subsol} (2017) \\ S$	Soh et al. (2017)	0.08 (0.03, 0.13)	1.70
Brown et al. (2016) Dea et al. (2014) Seo et al. (2019) Cet et al. (2019) Cet et al. (2019) Cichi et al. (2019) Cichi et al. (2019) Cichi et al. (2019) Cichi et al. (2018) Adogwa et al. (2018) Adogwa et al. (2018) Cichi et al. (2018) Cichi et al. (2018) Cichi et al. (2018) Cichi et al. (2017) Cichi	Adogwa et al. (2017)	• 0.18 (0.11, 0.24)	1.21
Dea et al. (2014) Subtotal $(l^2 = 95.4\%, P = 0.000)$ Retrospective Oc et al. (2019) Elsamadicy et al. (2019) Obichi et al. (2019) Obichi et al. (2019) Morino et al. (2019) Morino et al. (2019) Morino et al. (2018) Adogwa et al. (2018) Adogwa et al. (2018) Adogwa et al. (2018) Obichi et al. (2018) Morino et al. (2018) Adogwa et al. (2018) Morino et al. (2018) Adogwa et al. (2018) Obichi et al. (2017) Elsamadicy et al. (2017) Chichi et al. (2017) Chichi et al. (2017) Elsamadicy et al. (2017) Chichi et al.	Brown et al. (2016)	• 0.40 (0.30, 0.51)	0.62
See et al. (2014) Kelly et al. (2019) Ce et al. (2019) Elsamadicy et al. (2019) Othi et al. (2018) Othi et al. (2017) Elsamadicy et al. (2017) Chi et al. (2017) Elsamadicy et al. (2017) Chi et al. (2017) Elsamadicy et al. (2017) Chi et al. (2017) Elsamadicy et al. (2017) Cothi et al. (2017) Elsamadicy et al. (2017) Cothi et al. (2015) Cothi et al. (2015) Cothi et al. (2015) Cothi et al. (2016) Cothi et al. (2008) Cothi et al. (2008) Coth	Dea et al. (2014)	• 0.21 (0.13, 0.29)	0.94
Kelly et al (2014) $0.05 (0.01, 0.10) 1.93$ Subtotal ( $l^2 = 95.4\%, P = 0.000$ ) $0.16 (0.08, 0.23) 13.50$ Rerospective Oc et al. (2019) $0.05 (0.01, 0.10) 1.93Elsamadicy et al. (2019) 0.05 (0.05, 0.05) 4.26Watanabe et al. (2019) 0.05 (0.05, 0.05) 4.260.08 (0.05, 0.11) 2.840.01 (0.06, 0.13) 2.60Susano et al. (2018) 0.12 (0.08, 0.14) 3.04Adogwa et al. (2018) 0.10 (0.06, 0.13) 2.600.18 (0.15, 0.21) 2.95Elsamadicy et al. (2018) 0.02 (0.01, 0.02) 4.20Kobsyashi et al. (2018) 0.02 (0.01, 0.02) 4.20Kobsyashi et al. (2017) 0.02 (0.02, 0.03) 4.240.01 (0.08, 0.15) 2.50Ramos et al. (2017) 0.02 (0.02, 0.03) 4.240.01 (0.09, 0.10) 4.15Elsamadicy et al. (2017) 0.04 (0.02, 0.06) 3.63Elsamadicy et al. (2017) 0.04 (0.02, 0.06) 3.63Elsamadicy et al. (2017) 0.06 (0.05, 0.01) 3.58Elsamadicy et al. (2017) 0.06 (0.05, 0.00) 4.240.04 (0.02, 0.06) 3.63Elsamadicy et al. (2017) 0.06 (0.05, 0.00) 4.240.04 (0.02, 0.06) 3.63Elsamadicy et al. (2017) 0.06 (0.05, 0.00) 4.240.04 (0.02, 0.06) 3.63Elsamadicy et al. (2017) 0.06 (0.05, 0.00) 3.68Elsamadicy et al. (2017) 0.06 (0.05, 0.00) 3.68Elsamadicy et al. (2017) 0.06 (0.05, 0.00) 4.240.04 (0.00, 0.00) 4.240.04 (0.00, 0.00) 4.240.04 (0.00, 0.00) 4.240.04 (0.00, 0.01) 4.250.01 (0.00, 0.01) 4.250.01 (0.00, 0.01) 4.260.01 (0.00, 0.01) 4.211.6 (0.08, 0.22) 0.111.6 (0.08, 0.22) 0.111.6 (0.08, 0.22) 0.111.6 (0.08, 0.23) 0.290.01 (0.00, 0.01) 4.211.6 (0.08, 0.21) 0.1030.01 (0.00, 0.01) 4.211.6 (0.04, 0.02) 0.5 (0.5) 3.790.04 (0.02, 0.05) 3.790.04 (0.02, 0.05) 3.760.04 (0.02, 0.05) 3.760.04 (0.02, 0.05) 3.460.04 (0.02, 0.05) 3.460.04 (0.02, 0.05) 3.460.04 (0.02, 0.05) 3.460.04 (0.02, 0.05) 3.460.04 (0.02, 0.05) 3.460.04 (0.02, 0.05) 3.460.04 (0.02, 0.05) 3$	Seo et al. (2014)	0.24 (0.14, 0.34)	0.64
Subicial $(l^2 = 95.4\%, P = 0.000)$ Retrospective Oc et al. (2019) Kin et al. (2019) Kin et al. (2019) Kin et al. (2019) Watanabe et al. (2019) Morino et al. (2018) Adogwa et al. (2018) Adogwa et al. (2018) Otchi et al. (2017) Elsamadicy et al. (2017) Elsamadicy et al. (2017) Elsamadicy et al. (2017) Elsamadicy et al. (2017) Chichi et al. (2017) Chichi et al. (2017) Adogwa et al. (2017) Chichi et al. (2018) Chichi et al. (2019) Chichi et al. (2019) Chichi et al. (2019) Chichi et al. (2016) Chichi et al. (2017) Chichi et al. (2018) Chichi et al. (2019) Chichi et al.	Kelly et al. (2014)	0.05 (0.01, 0.10)	1.93
Actrospective Oc et al. (2019) $0.09 (0.06, 0.13)$ $2.70$ Elsamadicy et al. (2019) $0.11 (0.06, 0.16)$ $1.69$ Kin et al. (2019) $0.15 (0.06, 0.23)$ $0.83$ Olchi et al. (2019) $0.15 (0.06, 0.23)$ $0.83$ Morino et al. (2018) $0.06 (0.05, 0.05)$ $4.26$ Morino et al. (2018) $0.11 (0.08, 0.14)$ $3.04$ Adogwa et al. (2018) $0.11 (0.06, 0.13)$ $2.60$ Susano et al. (2018) $0.12 (0.08, 0.17)$ $2.95$ Elsamadicy et al. (2017) $0.12 (0.08, 0.17)$ $0.29 (0.01, 0.02)$ $4.20$ Kobayashi et al. (2017) $0.02 (0.02, 0.03)$ $4.12$ Elsamadicy et al. (2017) $0.04 (0.02, 0.06)$ $3.63$ Elsamadicy et al. (2017) $0.06 (0.05, 0.06)$ $4.01$ Elsamadicy et al. (2017) $0.06 (0.05, 0.06)$ $4.02$ Iang et al. (2017) $0.06 (0.05, 0.06)$ $4.01$ Kobayashi et al. (2017) $0.06 (0.05, 0.06)$ $4.01$ Kobayashi et al. (2017) $0.06 (0.05, 0.06)$ $4.01$ Kobayashi et al. (2017) $0.06 (0.05, 0.06)$ $4.01$ Glennie et al. (2013) $0$	Subtotal ( $I^2 = 95.4\%$ , $P = 0.000$ )	0.16 (0.08, 0.23)	13.50
$\begin{array}{c} \text{Oe et al. (2019)} \\ \text{Elsamadicy et al. (2019)} \\ \text{Kin et al. (2019)} \\ \text{Watanabe et al. (2019)} \\ \text{Watanabe et al. (2019)} \\ \text{Worino et al. (2018)} \\ \text{Adogwa et al. (2018)} \\ \text{Susano et al. (2018)} \\ \text{Ochi t et al. (2018)} \\ \text{Susano et al. (2018)} \\ \text{Othi t et al. (2018)} \\ \text{Kobayashi et al. (2018)} \\ \text{Volti t et al. (2017)} \\ \text{Elsamadicy et al. (2017)} \\ \text{Radcliff et al. (2017)} \\ \text{Adogwa et al. (2017)} \\ \text{Raddliff et al. (2017)} \\ \text{Elsamadicy et al. (2017)} \\ \text{Raddliff et al. (2017)} \\ \text{Adogwa et al. (2017)} \\ \text{Raddliff et al. (2017)} \\ \text{Cobayashi et al. (2017)} \\ \text{Cobayashi et al. (2017)} \\ \text{Cobayashi et al. (2017)} \\ \text{Raddliff et al. (2017)} \\ \text{Cobayashi et al. (2015)} \\ \text{Core all (2016)} \\ \text{Colo (0.0.0, 0.00)} \\ \text{Colo (0.0.0, 0.00)} \\ \text{Colo (0.0.0, 0.01)} \\ \text{Colo (0.0.0, 0.02)} \\ \text{Colo (0.0.0, 0.01)} \\ \text{Colo (0.0.0, 0.01)} \\ \text{Colo (0.0.0, 0.01)} \\ \text{Colo (0.0.0, 0.01)} \\ \text{Colo (0.0.0, 0.02)} \\ Colo$	Retrospective		
Ekamadicy et al. (2019) (bith et al. (2018) Adogwa et al. (2018) Ekamadicy et al. (2018) (bith et al. (2018) (constrained by the second	Oe et al. (2019)	0.09 (0.06, 0.13)	2.70
Kin et al. (2019) Oichi et al. (2019) Watanabe et al. (2019) Morino et al. (2018) Adogva et al. (2018) Adogva et al. (2018) Susano et al. (2018) Oichi et al. (2018) Susano et al. (2018) Oichi et al. (2018) Sobient et al. (2018) Sobient et al. (2017) Sobient et al. (2017) Chick et al. (2017) Elsamadicy et al. (2017) Core all (2016) Balabad et al. (2015) Glennie et al. (2015) Glennie et al. (2015) Subtoul ( <i>L</i> = 99.4%, <i>P</i> = 0.000) Note: weights are from random effects analysis 0 0 0 0 0 0 0 0	Elsamadicy et al. (2019)	- 0.11 (0.06, 0.16)	1.69
Oichi et al. (2019)       0.05 (0.05, 0.05)       4.26         Watanabe et al. (2018)       0.08 (0.05, 0.11)       2.84         Adogwa et al. (2018)       0.27 (0.17, 0.36)       0.69         Susano et al. (2018)       0.10 (0.06, 0.13)       2.60         Susano et al. (2018)       0.12 (0.08, 0.17)       1.99         Oichi et al. (2018)       0.22 (0.01, 0.02)       4.20         Yoshida et al. (2018)       0.12 (0.08, 0.17)       1.99         Oichi et al. (2017)       0.02 (0.01, 0.02)       4.20         Yoshida et al. (2017)       0.02 (0.02, 0.03)       4.24         Elsamadicy et al. (2017)       0.02 (0.02, 0.03)       4.24         Elsamadicy et al. (2017)       0.04 (0.02, 0.06)       3.63         Elsamadicy et al. (2017)       0.06 (0.05, 0.09)       3.69         Radogwa et al. (2017)       0.06 (0.05, 0.06)       4.09         Jiang et al. (2017)       0.06 (0.05, 0.06)       4.09         Kobayashi et al. (2017)       0.06 (0.03, 0.09)       2.95         Lee et al. (2016)       0.14 (0.08, 0.20)       1.41         Balabaud et al. (2015)       0.14 (0.00, 0.01)       4.26         Ginenie et al. (2010)       0.14 (0.00, 0.01)       4.21         Unagamaet al. (2011)       0.01 (0.00, 0.01)<	Kin et al. (2019)	• 0.15 (0.06, 0.23)	0.83
Watanabe et al. (2019)       0.08 (0.05, 0.11)       2.84         Morino et al. (2018)       0.11 (0.08, 0.14)       3.04         Adogwa et al. (2018)       0.10 (0.06, 0.13)       2.60         Susano et al. (2018)       0.12 (0.08, 0.17)       1.99         Ochi et al. (2018)       0.02 (0.01, 0.02)       4.20         Kobayashi et al. (2018)       0.02 (0.01, 0.02)       4.20         Kobayashi et al. (2017)       0.02 (0.02, 0.03)       4.24         Ochi et al. (2017)       0.04 (0.02, 0.06)       3.63         Elsamadicy et al. (2017)       0.04 (0.02, 0.06)       3.63         Elsamadicy et al. (2017)       0.06 (0.05, 0.06)       4.09         Iang et al. (2017)       0.06 (0.05, 0.06)       4.09         Iang et al. (2017)       0.06 (0.05, 0.06)       4.09         Kobayashi et al. (2017)       0.06 (0.05, 0.06)       4.09         Iang et al. (2017)       0.06 (0.05, 0.06)       4.09         Kobayashi et al. (2017)       0.06 (0.03, 0.09)       2.55         Radeliff et al. (2017)       0.06 (0.03, 0.09)       2.50         Kobayashi et al. (2017)       0.06 (0.05, 0.06)       4.09         Balabaud et al. (2017)       0.06 (0.03, 0.09)       2.55         Imagama et al. (2015)       0.11 (0.08, 0.	Oichi et al. (2019)	0.05 (0.05, 0.05)	4.26
Morino et al. (2018) Adogwa et al. (2018) Adogwa et al. (2018) Susano et al. (2018) Ochi et al. (2018) Nobayashi et al. (2018) Ochi et al. (2017) Chi et al. (2015) Fineberg et al. (2015) Fineberg et al. (2013) Chi at al. (2015) Chi et al. (2010) Chi et al. (2008) Chi et al. (2009) Chi et al. (2008) Chi et al. (2008) Chi et al. (2008) Chi et al. (2009) Chi et al. (2008) Chi et al. (2008) C	Watanabe et al. (2019)	0.08 (0.05, 0.11)	2.84
Adogwa et al. (2018) Adogwa et al. (2018) Susano et al. (2018) Elsamadicy et al. (2018) Okiti et al. (2018) Noshida et al. (2018) Noshida et al. (2018) Noshida et al. (2017) Elsamadicy et al. (2017) Cover al. (2015) Fineberg et al. (2016) Balabaud et al. (2015) Glennie et al. (2015) Fineberg et al. (2016) Balabaud et al. (2017) Coverall ( $l^2 = 99.4\%$ , $P = 0.000$ ) Note: weights are from random effects analysis 0 $0.22$ $0.4$	Morino et al. (2018)	0.11 (0.08, 0.14)	3.04
Adogwa et al. (2018) Susano et al. (2018) Elsamadicy et al. (2018) Kobayashi et al. (2018) Noshida et al. (2018) Ramos et al. (2017) Oichi et al. (2017) Elsamadicy et al. (2017) Blaabadicy et al. (2017) Coverall ( $l^2 = 99.2\%, P = 0.000$ ) Note: weights are from random effects analysis 0 = 0.2 0.2 0.4	Adogwa et al. (2018)	0.27 (0.17, 0.36)	0.69
Susano et al. (2018) Elsamadicy et al. (2018) (Abdyashi et al. (2018) Substance et al. (2017) Elsamadicy et al. (2017) Radcliff et al. (2017) Adogwa et al. (2017) Adogwa et al. (2017) Elsamadicy et al. (2017) Biang et al. (2017) Adogwa et al. (2017) Cobe et al. (2017) Elsamadicy et al. (2017) Biang et al. (2017) Cobe et al. (2017) Elsamadicy et al. (2017) Cobe (10, 20, 00) Cobe (10, 00) Cobe (1	Adogwa et al. (2018)	0.10 (0.06, 0.13)	2.60
Elsamadicy et al. (2018) Oichi et al. (2018) Kobayashi et al. (2018) Noshida et al. (2018) Ramos et al. (2017) Elsamadicy et al. (2017) Kobayashi et al. (2017) Kobayashi et al. (2017) Glennie et al. (2015) Glennie et al. (2015) Glennie et al. (2015) Glennie et al. (2013) Ushida et al. (2010) Ushida et al. (2006) Subtotal ( $l^2 = 99.2\%, P = 0.000$ ) Note: weights are from random effects analysis 0 0, 2 0, 2 0, 4	Susano et al. (2018)	→ 0.18 (0.15, 0.21)	2.95
Oichi et al. (2018) $0.02 (0.01, 0.02)$ $4.20$ Kobayashi et al. (2018) $0.31 (0.16, 0.47)$ $0.30$ Yoshida et al. (2017) $0.02 (0.02, 0.03)$ $4.24$ Oichi et al. (2017) $0.04 (0.02, 0.03)$ $4.24$ Oichi et al. (2017) $0.04 (0.02, 0.06)$ $3.63$ Elsamadicy et al. (2017) $0.06 (0.05, 0.09)$ $3.69$ Badadicy et al. (2017) $0.06 (0.05, 0.06)$ $4.09$ Jiang et al. (2017) $0.06 (0.05, 0.06)$ $4.09$ Kobayashi et al. (2017) $0.06 (0.03, 0.09)$ $2.95$ Lee et al. (2016) $0.14 (0.08, 0.20)$ $1.41$ Balabaud et al. (2015) $0.14 (0.00, 0.01)$ $4.26$ Gan et al. (2010) $0.01 (0.00, 0.01)$ $4.26$ Ushida et al. (2000) $0.14 (0.06, 0.21)$ $1.03$ Ushida et al. (2006) $0.008 (0.07, 0.09)$ $0.008 (0.07, 0.09)$ <	Elsamadicy et al. (2018)	0.12 (0.08, 0.17)	1.99
Kobayashi et al. (2018)       0.31 (0.16, 0.47)       0.30         Yoshida et al. (2018)       0.11 (0.08, 0.15)       2.50         Ramos et al. (2017)       0.02 (0.02, 0.03)       4.24         Otchi et al. (2017)       0.04 (0.02, 0.06)       3.63         Elsamadicy et al. (2017)       0.07 (0.05, 0.09)       3.69         Elsamadicy et al. (2017)       0.06 (0.05, 0.06)       4.09         Jiang et al. (2017)       0.06 (0.05, 0.06)       4.09         Jiang et al. (2017)       0.06 (0.05, 0.06)       4.09         Kobayashi et al. (2017)       0.06 (0.05, 0.06)       4.09         Kobayashi et al. (2017)       0.06 (0.03, 0.09)       2.95         Lee et al. (2015)       0.14 (0.08, 0.24)       0.94         Glennie et al. (2015)       0.14 (0.08, 0.20)       1.41         Imagama et al. (2011)       0.01 (0.01, 0.01)       4.26         Lee et al. (2010)       0.14 (0.06, 0.21)       1.03         Ushida et al. (2006)       0.04 (0.02, 0.06)       3.46         Subtoral ( $l^2 = 99.2\%, P = 0.000$ )       0.86 (0.07, 0.09)       86.50         O       0.2       0.44       0.02       0.00         O       0.2       0.4       0.00       3.46	Oichi et al. (2018)	0.02 (0.01, 0.02)	4.20
Yoshida et al. (2018)       0.11 (0.08, 0.15)       2.50         Ramos et al. (2017)       0.02 (0.02, 0.03)       4.24         Oichi et al. (2017)       0.04 (0.02, 0.06)       3.63         Elsamadicy et al. (2017)       0.06 (0.05, 0.09)       3.69         Elsamadicy et al. (2017)       0.08 (0.06, 0.10)       3.58         Radciff et al. (2017)       0.08 (0.06, 0.10)       3.58         Radciff et al. (2017)       0.09 (0.07, 0.12)       3.03         Adogwa et al. (2017)       0.06 (0.05, 0.06)       4.09         Kobayashi et al. (2017)       0.06 (0.03, 0.09)       2.95         Lee et al. (2016)       0.14 (0.08, 0.24)       0.94         Balabaud et al. (2015)       0.14 (0.08, 0.20)       1.41         Balabaud et al. (2015)       0.14 (0.00, 0.01)       4.26         Imagama et al. (2010)       0.14 (0.00, 0.01)       4.26         Ushida et al. (2009)       0.03 (0.02, 0.05)       3.79         Gao et al. (2008)       0.08 (0.07, 0.09)       86.50         Kawaguchi et al. (2026)       0.08 (0.07, 0.09)       100.00         Note: weights are from random effects analysis       0       0.2       0.4	Kobayashi et al. (2018)	0.31 (0.16, 0.47)	0.30
Ramos et al. (2017) $0.02 (0.02, 0.03)$ $4.24$ Oichi et al. (2017) $0.01 (0.09, 0.10)$ $4.15$ Elsamadicy et al. (2017) $0.07 (0.05, 0.09)$ $3.69$ Elsamadicy et al. (2017) $0.08 (0.06, 0.10)$ $3.58$ Radcliff et al. (2017) $0.06 (0.03, 0.09)$ $3.69$ Jiang et al. (2017) $0.06 (0.05, 0.06)$ $4.09$ Jiang et al. (2017) $0.06 (0.03, 0.09)$ $2.95$ Lee et al. (2016) $0.16 (0.08, 0.24)$ $0.94$ Balabaud et al. (2015) $0.14 (0.08, 0.20)$ $1.41$ Balabaud et al. (2015) $0.01 (0.01, 0.02)$ $4.15$ Glennie et al. (2010) $0.14 (0.06, 0.21)$ $1.41$ Ushida et al. (2009) $0.14 (0.06, 0.21)$ $1.03$ Gao et al. (2008) $0.03 (0.02, 0.05)$ $3.79$ Kawaguchi et al. (2006) $0.08 (0.07, 0.09)$ $100.00$ Note: weights are from random effects analysis $0.22  0.4$ $0.4$	Yoshida et al. (2018)	0.11 (0.08, 0.15)	2.50
Oichi et al. (2017)       0.10 (0.09, 0.10)       4.15         Elsamadicy et al. (2017)       0.04 (0.02, 0.06)       3.63         Elsamadicy et al. (2017)       0.08 (0.06, 0.10)       3.58         Radcliff et al. (2017)       0.08 (0.06, 0.10)       3.58         Madgwa et al. (2017)       0.09 (0.07, 0.12)       3.03         Adogwa et al. (2017)       0.06 (0.05, 0.09)       2.95         Lee et al. (2016)       0.14 (0.08, 0.20)       1.41         Balabaud et al. (2015)       0.01 (0.01, 0.02)       4.15         Glennie et al. (2015)       0.01 (0.01, 0.02)       4.15         Glennie et al. (2013)       0.01 (0.01, 0.01)       4.26         Imagama et al. (2010)       0.01 (0.00, 0.01)       4.21         Ushida et al. (2009)       0.03 (0.02, 0.05)       3.79         Kawaguchi et al. (2006)       0.04 (0.02, 0.06)       3.46         Subtotal ( $I^2 = 99.2\%, P = 0.000$ )       0.08 (0.07, 0.09)       100.00         Note: weights are from random effects analysis       0       0.2       0.4	Ramos et al. (2017)	0.02 (0.02, 0.03)	4.24
Elsamadicy et al. (2017) Elsamadicy et al. (2017) Elsamadicy et al. (2017) Radcliff et al. (2017) Radcliff et al. (2017) Adogwa et al. (2017) Kobayashi et al. (2017) Lee et al. (2017) Lee et al. (2016) Balabaud et al. (2015) Glennie et al. (2015) Fineberg et al. (2013) Imagama et al. (2011) Lee et al. (2010) Ushida et al. (2009) Gao et al. (2009) Gao et al. (2008) Kawaguchi et al. (2006) Subtotal $(I^2 = 99.2\%, P = 0.000)$ Note: weights are from random effects analysis 0 $0.2$ $0.40$ $0.2$ $0.4$	Oichi et al. (2017)	0.10 (0.09, 0.10)	4.15
Elsamadicy et al. (2017) Elsamadicy et al. (2017) Elsamadicy et al. (2017) Radcliff et al. (2017) Adogwa et al. (2017) Adogwa et al. (2017) Kobayashi et al. (2017) Lee et al. (2016) Balabaud et al. (2015) Glennie et al. (2015) Glennie et al. (2015) Fineberg et al. (2013) Lee et al. (2010) Ushida et al. (2009) Gao et al. (2009) Gao et al. (2000) Note: weights are from random effects analysis 0 $0.2$ $0.40.07 (0.05, 0.09)$ $3.690.07 (0.05, 0.09)$ $3.690.08 (0.06, 0.10)$ $3.580.06 (0.05, 0.06)$ $4.090.09 (0.07, 0.12)$ $3.030.16 (0.08, 0.24)$ $0.940.01 (0.01, 0.02)$ $4.150.01 (0.01, 0.02)$ $4.150.01 (0.01, 0.01)$ $4.210.01 (0.01, 0.01)$ $4.210.01 (0.00, 0.01)$ $4.210.02 (0.04, 0.02, 0.05)$ $3.790.08 (0.07, 0.09)$ $100.00$	Elsamadicy et al. (2017)	0.04 (0.02, 0.06)	3.63
Elsamadicy et al. (2017) Radcliff et al. (2017) Radcliff et al. (2017) Adogwa et al. (2017) Adogwa et al. (2017) Adogwa et al. (2017) Lee et al. (2016) Balabaud et al. (2015) Glennie et al. (2015) Fineberg et al. (2013) Imagama et al. (2011) Lee et al. (2010) Ushida et al. (2009) Gao et al. (2008) Kawaguchi et al. (2006) Subtotal $(I^2 = 99.4\%, P = 0.000)$ Note: weights are from random effects analysis 0 $0.2$ $0.40.08 (0.07, 0.09)$ $100.00$	Elsamadicy et al. (2017)	0.07 (0.05, 0.09)	3.69
Radcliff et al. (2017) $0.06 (0.05, 0.06)$ $4.09$ Jiang et al. (2017) $0.09 (0.07, 0.12)$ $3.03$ Adogwa et al. (2017) $0.06 (0.03, 0.09)$ $2.95$ Lee et al. (2016) $0.14 (0.08, 0.24)$ $0.94$ Balabaud et al. (2015) $0.14 (0.08, 0.20)$ $1.41$ Glennie et al. (2013) $0.01 (0.01, 0.02)$ $4.15$ Fineberg et al. (2011) $0.01 (0.01, 0.01)$ $4.26$ Lee et al. (2010) $0.01 (0.00, 0.01)$ $4.21$ Lee et al. (2009) $0.14 (0.06, 0.21)$ $1.03$ Ushida et al. (2006) $0.03 (0.02, 0.05)$ $3.79$ Subtotal ( $I^2 = 99.4\%, P = 0.000$ ) $0.08 (0.07, 0.09)$ $100.00$ Note: weights are from random effects analysis $0.02$ $0.4$	Elsamadicy et al. (2017)	0.08 (0.06, 0.10)	3.58
Jiang et al. (2017) Adogwa et al. (2017) Kobayashi et al. (2017) Kobayashi et al. (2017) Lee et al. (2016) Balabaud et al. (2015) Glennie et al. (2015) Fineberg et al. (2013) Imagama et al. (2011) Lee et al. (2010) Ushida et al. (2009) Gao et al. (2009) Gao et al. (2009) Kawaguchi et al. (2006) Subtotal ( $I^2 = 99.4\%$ , $P = 0.000$ ) Note: weights are from random effects analysis 0 $0.2$ $0.40$ $0.2$ $0.40$ $0.2$ $0.4$	Radcliff et al. (2017)	0.06 (0.05, 0.06)	4.09
Adogwa et al. (2017) $0.16 (0.08, 0.24)$ $0.94$ Kobayashi et al. (2017) $0.06 (0.03, 0.09)$ $2.95$ Lee et al. (2016) $0.14 (0.08, 0.20)$ $1.41$ Balabaud et al. (2015) $0.01 (0.01, 0.02)$ $4.15$ Glennie et al. (2013) $0.01 (0.01, 0.01)$ $4.26$ Imagama et al. (2010) $0.01 (0.00, 0.01)$ $4.21$ Lee et al. (2009) $0.01 (0.00, 0.01)$ $4.21$ Gao et al. (2008) $0.03 (0.02, 0.05)$ $3.79$ Kawaguchi et al. (2006) $0.04 (0.02, 0.06)$ $3.46$ Subtotal $(I^2 = 99.4\%, P = 0.000)$ $0.08 (0.07, 0.09)$ $100.00$ Note: weights are from random effects analysis $0$ $0.22$ $0.4$	Jiang et al. (2017)	0.09 (0.07, 0.12)	3.03
Kobayashi et al. (2017)       0.06 (0.03, 0.09)       2.95         Lee et al. (2016)       0.14 (0.08, 0.20)       1.41         Balabaud et al. (2015)       0.01 (0.01, 0.02)       4.15         Glennie et al. (2013)       0.01 (0.01, 0.01)       4.26         Imagama et al. (2010)       0.01 (0.00, 0.01)       4.21         Lee et al. (2009)       0.01 (0.00, 0.01)       4.21         Gao et al. (2008)       0.03 (0.02, 0.05)       3.79         Kawaguchi et al. (2006)       0.04 (0.02, 0.06)       3.46         Subtotal ( $I^2 = 99.4\%, P = 0.000$ )       0.08 (0.07, 0.09)       100.00         Note: weights are from random effects analysis       0       0.22       0.4	Adogwa et al. (2017)	• 0.16 (0.08, 0.24)	0.94
Lee et al. (2016) Balabaud et al. (2015) Glennie et al. (2015) Fineberg et al. (2013) Imagama et al. (2011) Lee et al. (2010) Ushida et al. (2009) Gao et al. (2008) Kawaguchi et al. (2006) Subtotal $(I^2 = 99.4\%, P = 0.000)$ Note: weights are from random effects analysis 0 $0.2$ $0.40$ $0.2$ $0.40$ $0.2$ $0.40$ $0.2$ $0.40$ $0.4$ $(0.08, 0.20)$ $1.410.01$ $(0.08, 0.20)$ $1.410.01$ $(0.01, 0.02)$ $4.150.01$ $(0.01, 0.01)$ $4.260.01$ $(0.00, 0.01)$ $4.210.01$ $(0.06, 0.21)$ $1.030.14$ $(0.06, 0.21)$ $1.030.21$ $(0.14, 0.29)$ $1.070.08$ $(0.07, 0.09)$ $86.500.08$ $(0.07, 0.09)$ $100.00$	Kobayashi et al. (2017)	0.06 (0.03, 0.09)	2.95
Balabaud et al. (2015)       0.01 (0.01, 0.02)       4.15         Glennie et al. (2015)       0.14 (0.10, 0.18)       2.21         Fineberg et al. (2013)       0.01 (0.01, 0.01)       4.26         Imagama et al. (2011)       0.01 (0.00, 0.01)       4.21         Lee et al. (2009)       0.14 (0.06, 0.21)       1.03         Ushida et al. (2008)       0.03 (0.02, 0.05)       3.79         Kawaguchi et al. (2006)       0.04 (0.02, 0.06)       3.46         Subtotal ( $I^2 = 99.4\%, P = 0.000$ )       0.08 (0.07, 0.09)       86.50         Overall ( $I^2 = 99.2\%, P = 0.000$ )       0.08 (0.07, 0.09)       100.00	Lee et al. (2016)	• 0.14 (0.08, 0.20)	1.41
Glennie et al. (2015)       0.14 (0.10, 0.18)       2.21         Fineberg et al. (2013)       0.01 (0.01, 0.01)       4.26         Imagama et al. (2011)       0.01 (0.00, 0.01)       4.21         Lee et al. (2009)       0.14 (0.06, 0.21)       1.03         Ushida et al. (2008)       0.03 (0.02, 0.05)       3.79         Kawaguchi et al. (2006)       0.04 (0.02, 0.06)       3.46         Subtotal ( $I^2 = 99.4\%, P = 0.000$ )       0.08 (0.07, 0.09)       86.50         Overall ( $I^2 = 99.2\%, P = 0.000$ )       0.08 (0.07, 0.09)       100.00         Note: weights are from random effects analysis       0       0.2       0.4	Balabaud et al. (2015)	0.01 (0.01, 0.02)	4.15
Fineberg et al. (2013)       0.01 (0.01, 0.01)       4.26         Imagama et al. (2011)       0.01 (0.00, 0.01)       4.21         Lee et al. (2009)       0.14 (0.06, 0.21)       1.03         Ushida et al. (2008)       0.03 (0.02, 0.05)       3.79         Kawaguchi et al. (2006)       0.04 (0.02, 0.06)       3.46         Subtotal ( $I^2 = 99.4\%, P = 0.000$ )       0.08 (0.07, 0.09)       86.50         .       0       0.2       0.4	Glennie et al. (2015)	0.14 (0.10, 0.18)	2.21
Imagama et al. (2011)       0.01 (0.00, 0.01)       4.21         Lee et al. (2010)       0.14 (0.06, 0.21)       1.03         Ushida et al. (2009)       0.21 (0.14, 0.29)       1.07         Gao et al. (2008)       0.03 (0.02, 0.05)       3.79         Kawaguchi et al. (2006)       0.04 (0.02, 0.06)       3.46         Subtotal ( $I^2 = 99.4\%, P = 0.000$ )       0.08 (0.07, 0.09)       86.50         .       0       0.2       0.4	Fineberg et al. (2013)	0.01 (0.01, 0.01)	4.26
Lee et al. (2010) Ushida et al. (2009) Gao et al. (2008) Kawaguchi et al. (2006) Subtotal ( $I^2 = 99.4\%$ , $P = 0.000$ ) Overall ( $I^2 = 99.2\%$ , $P = 0.000$ ) Note: weights are from random effects analysis 0 0.2 0.4 0 0.2 0.4	Imagama et al. (2011)	0.01 (0.00, 0.01)	4.21
Ushida et al. (2009) $0.21 (0.14, 0.29)$ $1.07$ Gao et al. (2008) $0.03 (0.02, 0.05)$ $3.79$ Kawaguchi et al. (2006) $0.04 (0.02, 0.06)$ $3.46$ Subtotal ( $I^2 = 99.4\%$ , $P = 0.000$ ) $0.08 (0.07, 0.09)$ $86.50$ Overall ( $I^2 = 99.2\%$ , $P = 0.000$ ) $0.08 (0.07, 0.09)$ $100.00$ Note: weights are from random effects analysis $0$ $0.2$ $0.4$	Lee et al. (2010)	0.14 (0.06, 0.21)	1.03
Gao et al. (2008) $0.03 (0.02, 0.05) 3.79$ Kawaguchi et al. (2006) $0.04 (0.02, 0.06) 3.46$ Subtotal ( $I^2 = 99.4\%, P = 0.000$ ) $0.08 (0.07, 0.09) 86.50$ Overall ( $I^2 = 99.2\%, P = 0.000$ ) $0.08 (0.07, 0.09) 100.00$ Note: weights are from random effects analysis $0$ 0 $0.2$	Ushida et al. (2009)	0.21 (0.14, 0.29)	1.07
Kawaguchi et al. (2006) $0.04 (0.02, 0.06)$ $3.46$ Subtotal ( $I^2 = 99.4\%, P = 0.000$ ) $0.08 (0.07, 0.09)$ $86.50$ Overall ( $I^2 = 99.2\%, P = 0.000$ ) $0.08 (0.07, 0.09)$ $100.00$ Note: weights are from random effects analysis $0$ $0.2$ $0.4$	Gao et al. (2008)	0.03 (0.02, 0.05)	3.79
Subtotal $(I^2 = 99.4\%, P = 0.000)$ Overall $(I^2 = 99.2\%, P = 0.000)$ Note: weights are from random effects analysis 0 0.2 0.4	Kawaguchi et al. (2006)	0.04 (0.02, 0.06)	3.46
Overall ( $I^2 = 99.2\%$ , $P = 0.000$ )       0.08 (0.07, 0.09)       100.00         Note: weights are from random effects analysis       0       0.2       0.4	Subtotal ( $I^2 = 99.4\%, P = 0.000$ )	0.08 (0.07, 0.09)	86.50
Note: weights are from random effects analysis 0 0.2 0.4	. Overall $(I^2 = 99.2\%, P = 0.000)$	0.08 (0.07, 0.09)	100.00
	Note: weights are from random effects analysis		
0 0.2 0.4		- I - I	
	0	0.2 0.4	

(b) Figure 2: Continued.

Study ID	Incidence (95% CI)	% weight
Lumbar spine		
Pan et al. (2019)	- 0.14 (0.07, 0.22)	1.01
Takenaka et al. (2019)	0.00 (0.00, 0.01)	4.26
Adogwa et al. (2018)	0.10 (0.06, 0.13)	2.60
Oichi et al. (2018)	0.02 (0.01, 0.02)	4.20
Lee et al. (2016)	- 0.14 (0.08, 0.20)	1.41
Balabaud et al. (2015)	0.01 (0.01, 0.02)	4.15
Kelly et al. (2014)	0.05 (0.01, 0.10)	1.93
Fineberg et al. (2013)	0.01 (0.01, 0.01)	4.26
Imagama et al. (2011)	0.01 (0.00, 0.01)	4.21
Lee et al. (2010)	- 0.14 (0.06, 0.21)	1.03
Subtotal ( $I^2 = 92.8\%, P = 0.000$ )	0.01 (0.01, 0.02)	29.06
Spinal deformity		
Oe et al. (2019)	0.09 (0.06, 0.13)	2.70
Yoshida et al. (2018)	0.11 (0.08, 0.15)	2.50
Ramos et al. (2017)	0.02(0.02, 0.03)	4.24
Elsamadicy et al. (2017)	0.07 (0.05, 0.09)	3.69
Adogwa et al. (2017)	- 0.18 (0.11, 0.24)	1.21
Adogwa et al. (2017)	0.16 (0.08, 0.24)	0.94
Subtotal ( $I^2 = 95.0\%, P = 0.000$ )	0.10 (0.06, 0.14)	15.28
Mixed		
Elsamadicy et al. (2019)	0.11 (0.06, 0.16)	1.69
Oichi et al. (2019)	0.05(0.05, 0.05)	4.26
Watanabe et al (2019)	0.03(0.05, 0.03)	2.84
Morino et al. (2018)	0.00(0.03, 0.11) 0.11(0.08, 0.14)	3.04
Adogwa et al. (2018)		0.69
Susano et al. (2018)		2.95
Elsamadicy et al. (2018)	0.12(0.08, 0.17)	1.99
Kobavashi et al. (2018)		0.30
Kim et al. (2018)	- 0.14 (0.08, 0.21)	1.19
Oichi et al. (2017)	0.10(0.09, 0.10)	4.15
Elsamadicy et al. $(2017)$	0.04(0.02, 0.06)	3 63
Elsamadicy et al. (2017)	0.08(0.06, 0.10)	3.58
Jiang et al. (2017)	0.09(0.07, 0.12)	3.03
Soh et al. (2017)	0.03 (0.03, 0.12) 0.08 (0.03, 0.13)	1.70
Kobavashi et al. (2017)	0.06(0.03, 0.09)	2.95
Brown et al. (2017)		0.62
Glennie et al. (2015)		2 21
Dea et al. (2014)	0.21 (0.13, 0.29)	0.94
Seo et al. (2014)	0.21(0.13, 0.23)	0.64
Gao et al. (2008)		3 79
Kawaguchi et al. (2006)	0.03(0.02, 0.03)	3.46
Subtotal $(I^2 = 95.3\%, P = 0.000)$	0.11 (0.09, 0.13)	49.65
Cervical spine		
Kin et al. (2019)	0.15(0.06, 0.23)	0.83
Radcliff et al. (2017)	$0.15 (0.00, 0.25) \\ 0.06 (0.05, 0.06)$	4 00
Ushida et al. (2009)		1.07
Subtotal ( <i>I</i> <sup>2</sup> = 90.9%, <i>P</i> = 0.000)	0.13 (0.03, 0.24)	6.00
. Overall $(I^2 - 99.2\%, P - 0.000)$	0.09 (0.07, 0.00)	100.00
Note: weights are from random effects analysis	0.00 (0.07, 0.09)	100.00
0.506	0.500	
-0.500 0	0.506	
(c)		

FIGURE 2: Continued.



FIGURE 2: Pooled result of incidence of delirium: (a) subgroup analysis based on the factor of country; (b) subgroup analysis based on the factor of study type; (c) subgroup analysis based on the factor of surgical site; (d) result of sensitive analysis; (e) Begg's funnel plot.

were collected and pooled to evaluate the relationships between various risk factors and postoperative delirium in patients undergoing spine surgery. In addition, crude ORs with 95% CIs were calculated based on the frequency reported in the original literature. Inconsistency was quantified with  $I^2$  statistic, and an  $I^2$  of >50% was considered to indicate substantial heterogeneity. The random-effects model or the fixed-effect model was used depending on the heterogeneity of studies included. A random-effects model was used for heterogeneous data. Otherwise, a fixed-effect

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TABLE 2: Outcomes of meta-analysis for risk fact
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Risk factors	No. of studies	Pooled OR (95% CI)	Heterogeneity $I^2$ (%)	P value	Effects model
Admission to ICU	3	2.51 (0.38-4.64)	0	0.944	Fixed
Age	7	1.07 (1.04-1.09)	16.5	0.304	Fixed
Age >65	3	4.77 (4.37-5.16)	0	0.383	Fixed
Age >70	3	15.87 (6.03-41.73)	48	0.14	Fixed
Age >80	2	1.91 (1.78-2.03)	0	0.844	Fixed
Alcohol abuse	4	2.11 (1.67-2.56)	0	0.397	Fixed
Anxiety	2	1.74 (1.04-2.44)	0	0.773	Fixed
Blood loss	5	1 (0.99-1.01)	83.9	< 0.001	Random
Blood transfusion	3	0.62 (0.07-1.17)	74.4	0.02	Random
Cardiovascular comorbidity	10	0.81 (0.34-1.29)	0	0.697	Fixed
CCI	2	1.26 (0.56-1.96)	0	0.355	Fixed
Cervical surgery	6	0.97 (0.45-1.48)	0	0.514	Fixed
Congestive heart failure	3	1.4 (1.21-1.6)	0	0.708	Fixed
Depression	7	2.5 (1.52-3.49)	76	< 0.001	Random
DM	13	1.09 (0.6-1.59)	0	0.978	Fixed
Dural tear	2	3.21 (0.07-6.35)	0	0.864	Fixed
Gender (male)	17	0.81 (0.76-0.86)	44.6	0.025	Fixed
History of surgery	6	1.09 (0.55-1.64)	0	0.617	Fixed
Hypertension	13	1.12 (1.04-1.2)	28.3	0.16	Fixed
Kidney disease	6	1.41 (1.16-1.66)	0	0.92	Fixed
MMSE score	3	0.7 (0.5-0.89)	51.7	0.126	Random
Neurological disorder	4	4.66 (4.22-5.11)	0	0.521	Fixed
Operated levels	2	1.02 (0.81-1.22)	0	0.523	Fixed
Operation time	4	1 (0.99–1)	0	0.725	Fixed
Parkinsonism	5	5.37 (0.63-10.1)	88	< 0.001	Random
Preoperative VAS	2	1.88 (1.11-2.64)	0	0.816	Fixed
Previous cerebral vascular diseases	7	1.82 (0.7-2.94)	0	0.952	Fixed
Previous mild cognitive impairment	5	2.43 (0.99-3.86)	0	0.967	Fixed
Previous opioid use	3	1.86 (1.18-2.54)	0	0.659	Fixed
Psychoses	5	2.77 (2.29-3.25)	0	0.474	Fixed
Pulmonary disease	6	1.81 (1.27-2.35)	0	0.925	Fixed
Postoperative UTI	2	5.68 (2.41-13.39)	0	0.463	Fixed
Superficial surgical site infection	2	0.28 (-3.25-3.81)	0	0.433	Fixed

CCI, Charlson Comorbidity Index; DM, diabetes mellitus; MMSE, mini-mental state examination; VAS, Visual Analogue Scale; UTI, urinary tract infection.

model was used. Begg's and Egger's test were used to estimate publication bias, when 10 or more studies are presented. For any variable presenting with large heterogeneity, sensitive analysis or subgroup analysis was used to investigate the potential origin of heterogeneity.

2.6. Search Results. There were 1360 relevant studies included according to the search strategy. After the titles and abstracts were reviewed, 1256 of them were removed. A full-text review was evaluated in the 104 records maintained, and 64 of them were excluded because they did not meet the inclusion criteria. Finally, 40 studies representing 712820 patients were included in the present meta-analysis (Figure 1).

2.7. Study Characteristics and Quality Assessment. The characteristics of the included studies are summarized in Table 1. 22 studies were conducted in Asian countries, 16 studies in North America, and 2 studies in Europe. 31 studies were retrospective, and 9 were prospective in design. The sample size ranged from 35 to 578457 patients. The reported incidence of delirium ranged from 0.49% to 31.43% for

patients after spinal surgery. To evaluate the quality of each study, the NOS was utilized. In those studies, all of them were of moderate to high quality (range, 6–8) (Table 1).

2.8. Incidence of Postoperative Delirium after Spine Surgery. The final meta-analysis included 40 studies [1, 8-46] from 7 different countries, and the pooled incidence was 8% (Figure 2). There was high heterogeneity (*I*-squared > 50%, P < 0.001). Interestingly, the heterogeneity remained high with each of the subgroups of study type, countries, or operated levels (Figure 2(a)-2(c)). After sensitive analysis, 3 studies [11, 25, 41] showed great influence on the pooled result (Figure 2(d)). The asymmetry Begg's funnel plot suggested the presence of publication bias for incidence of postoperative delirium after spine surgery (P < 0.001) (Figure 2(e)).

2.9. Risk Factors for Postoperative Delirium after Spine Surgery. The ORs and 95% CIs of the risk factors are displayed in Table 2. Among these, 33 factors were examined in 2 or more studies and 18 factors demonstrated statistical significance.

Study ID		OR (95% CI)	% weight
Prospective			
Pan et al. (2019)		0.10 (0.01, 0.66)	1.98
Kim et al. (2018)	<b>→</b>	1.16 (0.22, 6.17)	0.02
Soh et al. (2017)	<b>↓</b>	0.74 (0.20, 2.71)	0.13
Brown et al. (2016)	+	0.69 (0.30, 1.59)	0.50
Seo et al. (2014)	<b>↓</b>	0.78 (0.27, 2.31)	0.20
Subtotal ( $I^2 = 10.2\%, P = 0.348$ )	0	0.29 (0.02, 0.56)	2.83
Retrospective			
Oe et al. (2019)	<b>←</b>	1.74 (0.75, 4.06)	0.08
Elsamadicy et al. (2019)	•	2.98 (0.78, 11.40)	0.01
Kin et al. (2019)	<b> </b>	2.46 (0.58, 10.44)	0.01
Morino et al. (2018)	<b>←</b>	1.93 (1.00, 3.70)	0.11
Jiang et al. (2017)	+	0.90 (0.48, 1.68)	0.58
Elsamadicy et al. (2017)		1.02 (0.40, 2.61)	0.17
Kobayashi et al. (2017)		1.00 (0.37, 2.75)	0.15
Glennie et al. (2015)	· · · · · · · · · · · · · · · · · · ·	10.00 (2.50, 33.33)	0.00
Fineberg et al. (2013)	•	0.82 (0.78, 0.87)	96.04
Lee et al. (2010)	_ <b>_</b>	2.80 (0.81, 9.68)	0.01
Gao et al. (2008)	<b>↓</b> →→	5.19 (2.06, 13.10)	0.01
Kawaguchi et al. (2006)	<b></b>	5.39 (0.91, 31.90)	0.00
Subtotal ( $I^2 = 0.0\%, P = 0.535$ )		0.83 (0.78, 0.87)	97.17
Heterogeneity between groups: $P = 0.000$			
Overall ( $I^2 = 44.6\%, P = 0.025$ )		0.81 (0.76, 0.86)	100.00
	1 33	3.3	
	(a)		
Begg's funnel pl	ot with pseudo 95% confidence lim	iits	
	•		



FIGURE 3: Pooled result of male: (a) subgroup analysis based on the factor of study type; (b) Begg's funnel plot.

After synthesis of 7 studies, it revealed that patients who developed delirium were significantly older (OR 1.07; 95% CI 1.04–1.09). Meanwhile, age older than 65 (OR 4.77; 95% CI 4.37–5.16), 70 (OR 15.87; 95% CI 6.03–41.73), and 80 (OR 1.91; 95% CI 1.78–2.03) years were significantly associated with the risk of developing delirium. Another demographic factor male was considered to be associated with less delirium risk in the pooled analysis (OR 0.81; 95% CI 0.76–0.86).

A history of alcohol abuse (OR 2.11; 95% CI 1.67– 2.56), anxiety (OR 1.74; 95% CI 1.04–2.44), congestive heart failure (OR 1.4; 95% CI 1.21–1.6), depression (OR 2.5; 95% CI 1.52–3.49), hypertension (OR 1.12; 95% CI 1.04–1.2), kidney disease (OR 1.41; 95% CI 1.16–1.66), neurological disorder (OR 4.66; 95% CI 4.22–5.11), opioid use (OR 1.86; 95% CI 1.18–2.54), psychoses (OR 2.77; 95% CI 2.29–3.25), and pulmonary disease (OR 1.81; 95% CI 1.27–2.35) were more likely to develop delirium than controls. Assessment of mental state, as measured by mini-mental state examination (MMSE), demonstrated a significantly lower risk to develop delirium in patients with higher scores (OR 0.7; 95% CI 0.5–0.89). In addition, preoperative pain and postoperative urinary tract infection (UTI) were related to the development of delirium



FIGURE 4: Pooled result of cardiovascular comorbidity: (a) forest plot of cardiovascular comorbidity; (b) Begg's funnel plot.

(OR 1.88; 95% CI 1.11–2.64 and OR 5.68; 95% CI 2.41–13.39, respectively).

#### 3. Discussion

Delirium is thought to be a less transient disorder than previously believed in several studies [8, 11]. In addition, it has been reported that patients with postoperative delirium have a higher mortality rate than in those without it [4]. Due to the fact that delirium is varying and multifactorial, it will be helpful for prevention of delirium through identifying predictable risk factors.

This systematic review and meta-analysis were performed to pool and identify the incidence and risk factors of postoperative delirium after spine surgery. The pooled incidence of delirium in this meta-analysis is 8%. However, the present study showed wide variation and heterogeneity in incidence of delirium. A previous meta-analysis of 6 studies reported incidence of delirium after spine surgery varies from 0.84% to 21.3% [47]. Interestingly, the heterogeneity remained high with each of the subgroups of study type, countries, or operated levels (Figures 2(a)-2(c)). We found that patients with spinal deformity have higher rate of delirium (10%) and lower rate in patients with lumbar spine (1%). Meanwhile, prospective studies have a higher incidence of postoperative delirium than retrospective studies. After sensitive analysis, 3 studies [11, 25, 41] showed great influence on the pooled result (Figure 2(d)). All these 3 studies have relatively a larger sample size (range, 13188 to 578457), low incidence of delirium (range, 0.49 to 5.1%), and retrospective nature of study design, which may contribute to the heterogeneity. The asymmetry Begg's funnel plot suggested the presence of publication bias for incidence of postoperative delirium

Study ID	OR (95% CI)	% weight
Prospective		
Pan et al. (2019)	1.53 (0.38, 6.19)	0.08
Kim et al. (2018)	— 1.12 (0.35, 3.57)	0.26
Soh et al. (2017)	0.39 (0.10, 1.53)	1.33
Brown et al. (2016)	<b>→</b> 4.11 (1.31, 12.79)	0.02
Seo et al. (2014)	1.57 (0.50, 4.91)	0.14
Subtotal ( $I^2 = 0.0\%, P = 0.518$ )	0.68 (0.07, 1.29)	1.83
Retrospective		
Kin et al. (2019)	0.50 (0.12, 2.08)	0.71
Jiang et al. (2017)	1.03 (0.43, 2.49)	0.63
Elsamadicy et al. (2017)	0.44 (0.17, 1.12)	2.97
Kobayashi et al. (2017)	2.75 (0.95, 7.92)	0.06
Fineberg et al. (2013)	1.15 (1.07, 1.24)	93.44
Lee et al. (2010)	1.27 (0.37, 4.31)	0.17
Gao et al. (2008)	2.34 (0.84, 7.58)	0.06
Kawaguchi et al. (2006)	1.63 (0.53, 5.01)	0.13
Subtotal ( $I^2 = 38.8\%, P = 0.120$ )	1.13 (1.04, 1.21)	98.17
Heterogeneity between groups: $P = 0.152$		
Overall ( $I^2 = 28.3\%$ , $P = 0.160$ )	1.12 (1.04, 1.20)	100.00
-12.8 1	12.8	
(a)		

Begg's funnel plot with pseudo 95% confidence limits



FIGURE 5: Pooled result of hypertension: (a) forest plot of hypertension; (b) Begg's funnel plot.

after spine surgery, and lower incidence values could be missing (Figure 2(e)).

One of the most important risk factors was older age, especially in patients over 65. This may be attributed to the fact that elderly patients are more likely influenced by agerelated physical and psychical changes. Aging is also associated with a higher incidence of comorbidity such as hypertension, diabetes mellitus, and pulmonary disease [12, 30]. The highest rate of delirium in our meta-analysis is 31.43% in a multicenter prospective study with patient's age more than 90 [21]. Another significant demographic factor is male as a protective factor. Through subgroup analysis, we found that study design may contribute to the heterogeneity and prospective studies showing relatively a higher risk of developing delirium in females (Figure 3(a)). For publication bias, Begg' funnel plot demonstrated no significant bias (Figure 3(b)).

The present study showed that comorbidities significantly increase the risk of postoperative delirium after spine surgery. A history of alcohol abuse, congestive heart failure, hypertension, neurological disorder, opioid use, psychoses, and pulmonary disease are related to develop delirium. However, diabetes mellitus, history of surgery, and cerebral vascular diseases were not found to be related to developing



FIGURE 6: Pooled result of parkinsonism: (a) forest plot of parkinsonism; (b) result of sensitive analysis.

delirium, which was consistent with the previous metaanalysis [47]. For the cardiovascular comorbidity, the pooled result of 10 studies [8, 11, 15, 23, 26, 30, 31, 34, 43, 45] showed no significance (OR 0.81; 95% CI 0.34–1.29) with low heterogeneity ( $I^2$  0%) (Figure 4(a)). Only one study found cardiovascular comorbidity as a risk factor for delirium [11]. The symmetry Begg's funnel plot suggested no presence of publication bias for cardiovascular comorbidity (Figure 4(b)). Interestingly, however, pooled results showed congestive heart failure as a significant factor. This may be due to the severity of heart diseases.

Regarding the comorbidity of hypertension, the metaanalysis of 13 studies [1, 8, 12, 23, 26, 30, 31, 34, 39, 41, 43, 45, 46] identified it as a significant factor, and subgroup analysis showed heterogeneity comes from study design (Figure 5(a)). For publication bias, Begg's funnel plot suggested no significant bias (Figure 5(b)). Previous study showed that hypertension leading to microembolization phenomena and cerebral ischemia may be responsible for the occurrence of delirium [48].

For neurological or mental diseases, neurological disorder, psychoses, anxiety, and depression were found to be associated with developing delirium. The meta-analysis of 5 studies showed that mild cognitive impairment is not related to the occurrence of delirium (OR 2.43; 95% CI 0.99–3.86;  $I^2$ 0%). Meanwhile, parkinsonism was also not found to be related to postoperative delirium (OR 5.37; 95% CI 0.63– 10.1). However, there is still controversy in the role of parkinsonism for postoperative delirium. Kim et al. [23]

MMSE score				
Study ID		OR (95% CI)	% weight	
Asia				
Pan et al. (2019)		0.71 (0.52, 0.97)	34.57	
Kim et al. (2018)		0.86 (0.66, 1.12)	33.86	
Subtotal ( $I^2 = 0.0\%, P = 0.361$ )		0.78 (0.62, 0.94)	68.43	
America				
Brown et al. (2016)		0.51 (0.32, 0.81)	31.57	
Subtotal ( $I^2 = .\%, P = .$ )		0.51 (0.26, 0.76)	31.57	
Overall ( $I^2 = 51.7\%$ , $P = 0.126$ )		0.70 (0.50, 0.89)	100.00	
Note: weights are from random effects analysis				
-1.12	1 1.1	12		

FIGURE 7: Pooled result of MMSE score. Subgroup analysis based on the factor of country.

Study ID		OR (95% CI)	% weight
Pan et al. (2019)	•	0.99 (0.99, 1.00)	36.66
Kin et al. (2019)	•	1.00 (0.99, 1.01)	23.34
Morino et al. (2018)	•	0.14 (0.02, 0.97)	0.04
Kim et al. (2018)	•	1.00 (1.00, 1.00)	39.96
Jiang et al. (2017)		3.51 (0.15, 10.33)	0.00
Overall ( $I^2 = 83.9\%, P = 0.000$ )		1.00 (0.99, 1.01)	100.00
Note: weights are from random effects analysis			
-10.3	1 10.3		





Meta-analysis estimates, given named study is omitted

FIGURE 8: Pooled result of blood loss: (a) forest plot of blood loss; (b) result of sensitive analysis.



FIGURE 9: Pooled result of blood transfusion: (a) forest plot of blood transfusion; (b) result of sensitive analysis.

found that that parkinsonism is not a risk factor for postoperative delirium after multivariable analysis. Interestingly, Pan et al. [8] found an opposite result, which may be attributed to relatively a smaller sample of patients with parkinsonism in their study. Notably, the result should be explained with caution since the heterogeneity is high ( $I^2$ 88%). After subgroup analysis, there was a high heterogeneity between retrospective studies (Figure 6(a)). Moreover, the result of sensitive analysis showed two studies [24, 25] contributing greatly to the high heterogeneity (Figure 6(b)). Both studies were retrospective design and focus on patients with parkinsonism, which may result in high heterogeneity.

Mental states, as assessed by MMSE, were associated with the development of delirium (OR 0.7; 95% CI 0.5–0.89). Through subgroup analysis, we found that geographical factors may contribute to heterogeneity (Figure 7). This measure of the state of mental health appears to have a clearer association with postoperative delirium compared to Charlson Comorbidity Index (CCI) which assesses the number of specific medical comorbidities. These findings are also seen in other studies where CCI appears less clearly associated with the incidence of delirium in older patients [12, 49].

The finding that preoperative pain and opioid use is associated with increased probability of delirium has been previously reported in patients with or without hip fracture or patients with cancer [49, 50]. In addition, elderly patients are more sensitive to opioid-related adverse events [51]. In patients with spine disease, pain may lead to stress reaction and changes of nerve conduction if not effectively controlled [34]. However, the accumulation of active metabolites in patients receiving opioid may contribute to the psychotic features such as delirium [52]. Hence, it is suggested that a less toxic drug, buprenorphine patch other than morphine, should be considered for patients with osteoarthrosis and other types of lumbago when pain continues despite adequate administrations of nonopioid analgesics [53].

In our study, intraoperative factors do not appear to influence the prevalence of delirium based on normal clinical practice such as blood loss, blood transfusion, cervical surgery, dural tear, operated levels, and operation time. Notably, for intraoperative blood loss, there was high heterogeneity among studies (Figure 8(a)). After sensitive analysis, we found that one study [23] focused on patients with parkinsonism lead to the high heterogeneity. In addition, high heterogeneity was also seen in the meta-analysis of blood transfusion (Figure 9(a)). The sensitive analysis showed that the heterogeneity comes from one study [43], which had more fusion levels  $(2.27 \pm 1.34)$  and blood loss  $(1263 \pm 903)$  than other studies (Figure 9(b)). Postoperatively, patients experiencing complications such as UTI had a higher probability to develop delirium.

There are some limitations in our study. First, no randomized controlled trials were included despite our exhausted search from literatures, which may influence the quality of the result. Second, although subgroup analyses were used, the pooled result of incidence was still reported with high heterogeneity, which should be explained with caution.

#### 4. Conclusions

In summary, the study reveals that pooled incidence of delirium is 8% and age, gender, history of alcohol abuse, anxiety, congestive heart failure, depression, hypertension, kidney disease, neurological disorder, opioid use, psychoses, pulmonary disease, MMSE, preoperative pain, and postoperative UTI were significant factors for delirium after spine surgery. A comprehensive understanding of incidence and risk factors of delirium can improve prevention, diagnosis, and management.

#### **Conflicts of Interest**

The authors declare that they have no conflicts of interest.

#### **Authors' Contributions**

Mingsheng Tan designed the study, and Xinjie Wu wrote this manuscript. Xinjie Wu and Wei Sun searched database, reviewed studies, and collected and analyzed data. All of the authors have read and approved the final manuscript.

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