RESEARCH ARTICLE

# The Role of Hemosiderin Excision in Seizure Outcome in Cerebral Cavernous Malformation Surgery: A Systematic Review and Meta-Analysis

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# Abstract

# **Background and Purpose**

Whether the excision of hemosiderin surrounding cerebral cavernous malformations (CCMs) is necessary to achieve a seizure-free result has been the subject of debate. Here, we report a systematic review of related literature up to Jan 1, 2015 including 594 patients to assess the effect of hemosiderin excision on seizure outcome in patients with CCMs by meta-analysis.

# Methods

Ten studies comparing extended hemosiderin excision with only lesion resection were identified by searching the English-language literature. Meta-analyses, subgroup analyses and sensitivity analysis were conducted to determine the association between hemosiderin excision and seizure outcome after surgery.

### Results

Seizure outcome was significantly improved in the patients who underwent an extended excision of the surrounding hemosiderin (OR, 0.62; 95% CI: 0.42–0.91; P = 0.01). In subgroup analysis, studies from Asia (OR, 0.42; 95% CI: 0.25–0.71; P = 0.001), male-majority (female ratio < 50%) studies (OR, 0.56; 95% CI: 0.33–0.96; P = 0.04), low occurrence rate of multiple CCMs (OR, 0.37; 95% CI: 0.20–0.71; P = 0.003), cohort studies (OR, 0.44; 95% CI: 0.28–0.68; P = 0.78), longer duration of seizure symptoms (> 1 year) before surgery (OR, 0.43; 95% CI: 0.22–0.84; P = 0.01), lesion diameter > 2 cm (OR, 0.41; 95% CI: 0.19–0.87; P = 0.02) and short-term (< 3 years) follow-up (OR, 0.48; 95% CI: 0.29–0.80; P = 0.005) tended to correlate with a significantly favorable outcome.



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## Conclusion

Patients who underwent extended surrounding hemosiderin excision could exhibit significantly improved seizure outcomes compared to patients without hemosiderin excision. However, further well-designed prospective multiple-center RCT studies are still needed.

## Introduction

Seizures are the most common frequent clinical symptom caused by cerebral cavernous malformations (CCMs), presenting in 23%-79% of CCM patients [1-3]. Among these patients, approximately 40% of individuals progress to medically refractory epilepsy, which can dramatically decrease quality of life due to various disabilities [4]. Although the remaining 60% of patients with CCM may benefit from antiepileptic drugs (AEDs), they usually suffer the unfavorable side effects of AEDs [5, 6]. Currently, it is widely accepted that the surgical resection of CCMs is the best treatment strategy for patients with medically refractory epilepsy [7–10]. CCMs are often surrounded by hemosiderin, which has been suggested to produce seizures [11–13]. However, whether the excision of hemosiderin surrounding CCMs is necessary to achieve a seizure-free result has been under debate [14].

Some articles analyzing various predictors of seizure freedom in the surgical treatment of CCMs have been published, but none have specifically focused on hemosiderin excision alone. Among these clinical reports, some supported the idea that extended resection of hemosiderin might improve short-term or long-term seizure outcomes [15-18], but others showed no significant differences between the excision of the hemosiderin along with the lesion and resection of the cavernoma only [19-21]. Given these contradictory reports and the theoretical potential for additional morbidity with extended cortical resection, it is important to systematically evaluate the role of hemosiderin in CCM surgery for clinical treatment [14].

Here, we report a systematic review of related literature up to Jan 1, 2015. Our purposes are as follows: (1) to assess the effect of hemosiderin excision on seizure outcome in patients with CCMs by meta-analysis; (2) to identify the factors influencing our result using subgroup analysis; and (3) to provide some evidence for clinical decision-making.

### Methods

This meta-analysis was performed in accordance with the PRISMA 2009 checklist. (data in <u>S1</u> <u>Checklist</u>)

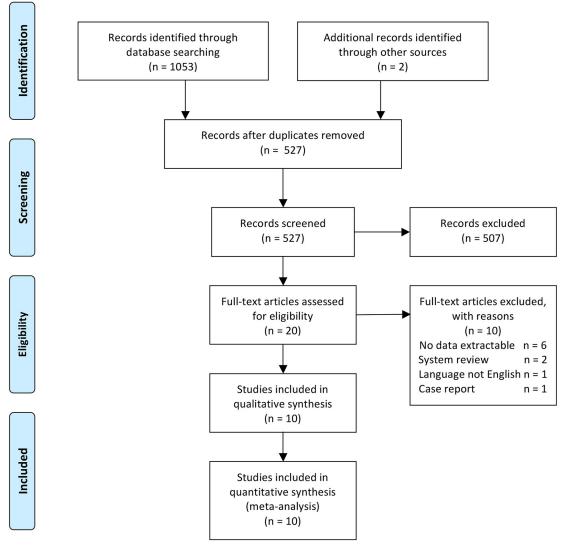
## 1. Search strategy and study identification

Appropriate studies relevant to the effect of hemosiderin excision on seizure outcome in patients with CCM surgery were identified by searching online databases: PubMed, Web of Science and EBSCO. The following key words were used and connected by Boolean logic operators: "cavernous hemangioma", "cavernous angioma", "angiocavernoma", "hemangioma", "cavernous", "hemosiderin ring", "hemosiderin", "epilepsy", "seizure", "surgery". Searches were restricted to the English-language literature but were not limited with regard to the publication year. Three authors (Di Ruan, Xiao-Bo Yu and Sudeep Shrestha) were independently responsible for checking and selecting articles, with disagreements settled by the senior authors (Lin Wang and Gao Chen). Reference lists in the identified publications were also examined to find additional studies.

# 2. Inclusion and exclusion criteria

Fig 1 details the selection criteria we used. The inclusion criteria were as follows: (1) series of at least 10 patients undergoing CCM surgery; (2) cohort or case-control studies comparing the extended hemosiderin excision with lesion resection only; (3) CCM patients with epilepsy or seizure symptoms before surgery; (4) seizure outcomes measured or calculated according to Engel Class; (5) explicitly reported numbers of patients who underwent or did not undergo hemosiderin excision; (6) duration of follow-up of at least 12 months; and (7) study quality





#### Fig 1. Flow chart of literature selection.

score >4 on the Newcastle-Ottawa Scale (NOS) [22]. The exclusion criteria were as follows: (1) study did not provide sufficient extractable data on the patient number and follow-up outcome; (2) study was a system review or case report; (3) study did not compare the seizure outcomes of the excision group and control group; (4) study was not written in English; and (5) study with only the abstract available, or unpublished study. The quality of case-control or cohort studies was assessed by the NOS.

# 3. Data extraction

Data were extracted independently by three authors (Di Ruan, Xiao-Bo Yu and Sudeep Shrestha) using a uniform standardized and digitized data extraction form in Excel 2010 and checked by these three authors until agreement was reached. The primary surgical outcome was the patient seizure status (seizure freedom (Engel ClassI) versus persistent seizures (Engel ClassII-IV)) after some period of follow-up. Although we are aware that the Engel classification has its disadvantages, we had to use it because almost all the related studies used this classification [23]. If a study did not report sufficient information for the calculation of the Engel Class, attempts were made to contact the authors of the articles, who were asked to provided either the Engel Class data or the raw data necessary for calculation. Data on other related factors data, such as age, sex, area, seizure duration before surgery, multiple CCM occurrence, lesion location, lesion size, follow-up time, study quality and study design type, were also extracted.

# 4. Statistical analysis

Meta-analyses and subgroup analysis were performed using Review Manager 5.3. Dichotomous variables were presented as odds ratios (OR; with hemosiderin excision (hemosiderin (-)) versus without hemosiderin excision (hemosiderin (+)). Heterogeneity was evaluated by the I<sup>2</sup> value. A fixed effect model was used if the I<sup>2</sup> value was less than 50%; otherwise, a random effect model was adopted. We set significance at P = 0.05. In addition to visual inspection of funnel plots using RevMan 5.3, the STATA 13.0 software was also used to perform the Begg's test [24] and Egger's test [25] methods to detect potential publication bias. Moreover, sensitivity analysis was performed using STATA 13.0.

# Results

# 1. Literature search findings and included publication characteristics

The search process and results are illustrated in the flowchart (Fig 1). We found a total of 1055 papers, with 527 remaining after duplicates were removed. Of this group, 507 were excluded based on reviewing the title and abstract. For the remaining 20 articles, the full text was accessed, and 10 articles met the inclusion criteria. Ten of the 20 papers were excluded because they lacked extractable data (n = 6), were system reviews (n = 2), were not written in English (n = 1), or were a case report (n = 1). Finally, 10 articles were included in the meta-analysis. [15, 17–21, 26–29]

# 2. Baseline characteristics of included studies

Ten articles containing 13 studies were obtained, including 4 case-control and 9 cohort studies. All studies had at least moderate-level quality using the Newcastle-Ottawa Scale evaluation system. The baseline characteristics of the studies are summarized in <u>Table 1</u>. The 13 included studies reported the outcomes of 594 patients with more than 632 CCMs ranging from 0.4 cm to 5.3 cm in diameter. In total, 234 of 316 patients in the hemosiderin (-) group and 189 of 278 in the hemosiderin (+) group were Engel ClassI.

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Study	Country	Patient number	Female n (%)	Mean age (yrs)	Mean size of the lesion (cm)	Temporal lobe n (%)	Multiple CCMs n (%)	Mean duration before surgery (mo)	Mean follow-up duration (mo)	Chg Engel Class 1	Chg Engel Class 2–4	Khg Engel Class 1	Khg Engel Class 2-4	Study design	Quality score
Huang C, 2013	China	27	8 (29.6)	NA	NA	16 (59.3)	14 (51.9)	NA	24.8	ი	ო	4	ო	8	7
Baumann CR, 2006	N	31	15 (48.4)	36.3	1.8	20 (64.5)	1 (3.2)	144	12	11	ო	÷	9	cohort	9
Baumann CR, 2006	S	29	NA	NA	NA	NA	NA	NA	24	ω	Ð	7	ი	cohort	9
Baumann CR, 2006	N	27	NA	NA	NA	NA	NA	NA	36	11	ო	7	9	cohort	9
von der Brelie C, 2013	Germany	=	4 (36.4)	15.3	NA	5 (45.5)	3 (27.2)	57.8	132.5	Q	ო	÷	÷	cohort	£
Kwon CS, 2013	NSA	56	29 (51.8)	37.5	1.6	27 (48.2)	9 (16.1)	12*	87.9	23	ω	23	N	8	6
Zevgaridis D, 1996	Switzerland	66	NA	NA	NA	NA	NA	NA	39	24	4	33	Ð	cohort	9
Yeon JY, 2009	Korea	54	NA	NA	NA	NA	AN	NA	> 12	26	2	19	4	cohort	9
Cappabianca P, 1997	Italy	35	21 (60.0)	28.8	NA	10 (28.6)	NA	NA	> 24	4	0	25	9	8	7
Hammen T, 2007	Germany	30	13 (42.3)	39.4	NA	21 (70.0)	4 (13.3)	130.8	> 48	4	4	12	4	8	9
Wang X, 2013	China	132	64 (48.5)	39.3	2.9	51 (38.6)	7 (5.3)	NA	12	64	22	25	21	cohort	7
Wang X, 2013	China	60	NA	NA	NA	NA	NA	NA	60	25	17	Ð	13	cohort	7
Jin Y, 2014	China	36	15 (41.7)	37.8	1.9	26 (72.2)	0 (0:0)	5.95	18*	19	N	0	9	cohort	თ
CCMs, cerebral cavernous malformations; mo, month; group. *The data was presented in the median form.	ll cavernous m presented in t	alformation he median t	s; mo, mont form.	th; yrs, ye	ars; NA, n	yrs, years; NA, not available; SI, Switzerland and Italy; cc, case-control; Chg, Cut hemosiderin group; Khg, Keep hemosiderin	SI, Switzerla	nd and Italy;	cc, case-con	itrol; Chg,	Cut hemc	isiderin gr	oup; Khg,	, Keep hem	osiderin



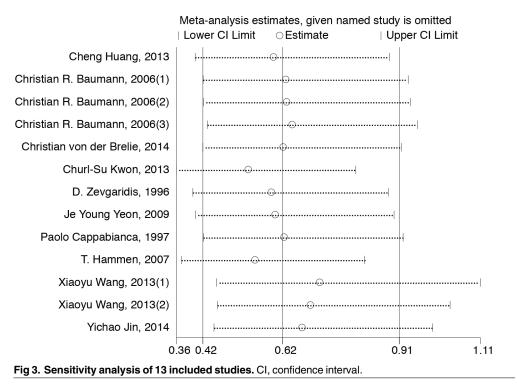
	hemosider	rin (-)	hemosider	in (+)		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Cheng Huang 2013	3	12	3	15	3.0%	1.33 [0.22, 8.22]	
Christian R. Baumann 2006 (1)	3	14	6	17	6.3%	0.50 [0.10, 2.52]	
Christian R. Baumann 2006 (2)	5	13	9	16	7.4%	0.49 [0.11, 2.16]	
Christian R. Baumann 2006 (3)	3	14	6	13	7.3%	0.32 [0.06, 1.71]	
Christian von der Brelie 2014	3	9	1	2	1.6%	0.50 [0.02, 11.09]	
Churl-Su Kwon 2013	8	31	2	25	2.4%	4.00 [0.77, 20.91]	
D. Zevgaridis 1996	4	28	5	38	5.4%	1.10 [0.27, 4.53]	
Je Young Yeon 2009	5	31	4	23	5.7%	0.91 [0.22, 3.86]	
Paolo Cappabianca 1997	0	4	6	31	2.3%	0.44 [0.02, 9.17]	· · · · · · · · · · · · · · · · · · ·
T. Hammen 2007	7	11	7	19	2.8%	3.00 [0.64, 14.02]	
Xiaoyu Wang 2013 (1)	22	86	21	46	30.3%	0.41 [0.19, 0.87]	
Xiaoyu Wang 2013 (2)	17	42	13	18	16.1%	0.26 [0.08, 0.87]	
Yichao Jin 2014	2	21	6	15	9.4%	0.16 [0.03, 0.94]	
Total (95% CI)		316		278	100.0%	0.62 [0.42, 0.91]	•
Total events	82		89				
Heterogeneity: Chi <sup>2</sup> = 16.73, df	= 12 (P = 0.	16); $I^2 =$	28%				0.001 0.1 1 10 1000
Test for overall effect: Z = 2.45	(P = 0.01)						Eavours hemosiderin (-) Favours hemosiderin (+)

Fig 2. Forest plot of seizure outcomes comparing hemosiderin (-) group and hemosiderin (+) group. hemosiderin (-), with hemosiderin excision; hemosiderin (+), without hemosiderin excision; CI, confidence interval.

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#### 3. Meta-analysis and sensitivity analysis

Thirteen studies with a total of 594 patients reported the seizure outcomes after CCM surgeries (234 of 316 obtained Engel ClassI in the hemosiderin (-) group versus 189 of 278 in the hemosiderin (+) group). The seizure outcome was statistically significantly improved in the patients who underwent extended excision of the surrounding hemosiderin (OR, 0.62; 95% CI: 0.42– 0.91; P = 0.01;  $I^2 = 28\%$ ; Fig 2). Sensitivity analysis showed that the results of the association between hemosiderin excision and seizure outcome were robust, which demonstrated that no significant heterogeneity existed across the studies. (Fig 3)



doi:10.1371/journal.pone.0136619.g003

### 4. Subgroup analysis

Although no heterogeneity was found between studies, we still performed subgroup analysis based on our clinical and statistical practice. Thus, age, sex, area, seizure duration before surgery, multiple CCM occurrence, lesion location, lesion size, follow-up time, study quality and study design type were considered as confounding factors in our studies. Among all these factors, there was no significant difference in age, lesion location and study quality level between the two groups according to our classification criteria. (Fig 4)

The studies from Asian countries reported a significantly higher rate of favorable outcomes in the hemosiderin (-) group (OR, 0.42; 95% CI: 0.25–0.71; P = 0.001;  $I^2 = 9\%$ ). The malemajority studies tended to report a favorable outcome in the hemosiderin (-) group (OR, 0.56; 95% CI: 0.33–0.96; P = 0.04;  $I^2 = 38\%$ ). The advantage of hemosiderin excision was obvious in the group with a low occurrence rate of multiple CCMs (OR, 0.37; 95% CI: 0.20–0.71; P = 0.003;  $I^2 = 0\%$ ) but not obvious in the higher occurrence rate group (OR, 2.28; 95% CI: 0.91–5.70; P = 0.08;  $I^2 = 0\%$ ). For different study types, cohort studies were inclined to report favorable outcomes in the hemosiderin (-) group (OR, 0.44; 95% CI: 0.28–0.68; P = 0.78;  $I^2 = 0\%$ ). (Fig 5)

Regarding the seizure duration before surgery, lesion size and follow-up time, patients with seizure duration before surgery > 1 year (OR, 0.43; 95% CI: 0.22–0.84; P = 0.01;  $I^2 = 0\%$ ), lesion diameter > 2 cm (OR, 0.41; 95% CI: 0.19–0.87; P = 0.02) and short-term (< 3 years) follow-up (OR, 0.48; 95% CI: 0.29–0.80; P = 0.005;  $I^2 = 0\%$ ) appeared to have a more favorable outcome tendency in the hemosiderin (-) group. However, the benefit of hemosiderin excision was not significantly different from that gained by patients with seizure duration before surgery < 1 year (P = 0.43;  $I^2 = 0\%$ ), lesion diameter < 2 cm (P = 0.60;  $I^2 = 0\%$ ) and long-term (> 3 years) follow-up (P = 0.26;  $I^2 = 22.1\%$ ), respectively. (Fig 6)

### 5. Publication bias

No publication bias was found in a funnel plot, with plots visually symmetrically distributed along the vertical axis (Fig 7). Begg's test and Egger's test also showed no significant publication bias (Begg's test, z = 0.48, P = 0.631; Egger's test, t = 0.95, P = 0.367).

### Discussion

Here, we present the first meta-analysis of hemosiderin excision on seizure outcome in cerebral cavernous malformations surgery. The results of this paper show that seizure outcome was statistically significantly improved in patients who underwent an extended excision of the surrounding hemosiderin. However, there were many confounding factors that could influence the results. Thus, subgroup analyses were conducted to analyze the outcome more thoroughly. Among all the factors analyzed, studies from Asia, male majority (female ratio < 50%), low multiple CCM occurrence (< 20%) and cohort studies tended to correlate with a more favorable outcome in the hemosiderin excision group.

Regional differences existed among studies. However, we could easily observe that there was only one American article [27] concentrating on this topic. Thus, more non-Asian studies should be introduced to draw a more accurate conclusion. Regarding gender, the male-majority studies tended to report a favorable outcome in the hemosiderin (-) group, while the female-majority studies did not report an obvious result. However, this finding must be interpreted carefully because the sample size of the female group is smaller than that of the male group. For the lesion itself, low occurrence of multiple CCMs was prone to exhibit significant improvement, which might indicate that hemosiderin excision could be facilitated in patients with single CCMs. When focusing on study design type, we observed that cohort studies



Study or Subgroup	hemosider Events	rin (-) Total	hemoside Events		Weight	Odds Ratio M-H, Random, 95% Cl	Odds Ratio M-H, Random, 95% Cl
<b>average age&lt;18y</b> Christian von der Brelie 2014	3	9	1	2	6.7%	0.50 [0.02, 11.09]	
Subtotal (95% CI)	2	9	1	2	6.7%	0.50 [0.02, 11.09]	
Total events	3		1				
Heterogeneity: Not applicable Test for overall effect: Z = 0.44 (	(P = 0.66)						
average age>18y							
Christian R. Baumann 2006 (1) Churl-Su Kwon 2013	3 8	14 31	6 2	17 25	15.6% 15.2%	0.50 [0.10, 2.52] 4.00 [0.77, 20.91]	
Paolo Cappabianca 1997	0	4	6	31	6.9%	0.44 [0.02, 9.17]	
T. Hammen 2007	7	11	7	19	16.3%	3.00 [0.64, 14.02]	
Xiaoyu Wang 2013 (1)	22	86	21	46	25.2%	0.41 [0.19, 0.87]	
Yichao Jin 2014 <b>Subtotal (95% CI)</b>	2	21 167	6	15 153	14.1% <b>93.3%</b>	0.16 [0.03, 0.94] 0.76 [0.28, 2.07]	
Total events	42	107	48	155	55.570	0.70 [0.20, 2.07]	
Heterogeneity: $Tau^2 = 0.86$ ; Chi <sup>2</sup>		f = 5 (P =		= 60%			
Test for overall effect: $Z = 0.54$ (	(P = 0.59)						
Total (95% CI)		176		155	100.0%	0.74 [0.30, 1.83]	-
Total events	45	6 _ C /P	49	E 20%			
Heterogeneity: $Tau^2 = 0.71$ ; Chi <sup>2</sup> Test for overall effect: $Z = 0.66$ (		r = 6 (P =	= 0.05); 1- =	= 52%			0.001 0.1 1 10 1000 Favours hemosiderin (-) Favours hemosiderin (+)
Test for subgroup differences: C	$hi^2 = 0.06, c$					Odds Patio	
Study or Subgroup	Events	Total	hemoside Events		Weiaht	Odds Ratio M-H, Random, 95% Cl	Odds Ratio M-H, Random, 95% Cl
temperal percentage<509		iotal	Lycints	Total	acigiit	ii, kundolii, 55% Cl	
Christian von der Brelie 2014	3	9	1	2	5.6%	0.50 [0.02, 11.09]	
Churl-Su Kwon 2013	8	31	2	25	13.3%	4.00 [0.77, 20.91]	+
Paolo Cappabianca 1997 Xiaoyu Wang 2013 (1)	0 22	4 86	6 21	31 46	5.7% 23.6%	0.44 [0.02, 9.17] 0.41 [0.19, 0.87]	
Subtotal (95% CI)	22	130	21	104	48.1%	0.81 [0.22, 3.04]	
Total events	33		30				
Heterogeneity: Tau <sup>2</sup> = 0.88; Chi <sup>2</sup> Test for overall effect: Z = 0.31 (		= 3 (P =	0.10); I <sup>2</sup> =	51%			
temperal percentage>50%							
Cheng Huang 2013 Christian R. Baumann 2006 (1)	3	12	3 6	15	11.9%	1.33 [0.22, 8.22]	
T. Hammen 2007	5	14 11	7	17 19	13.6% 14.3%	0.50 [0.10, 2.52] 3.00 [0.64, 14.02]	·
Yichao Jin 2014	2	21	6	15	12.1%	0.16 [0.03, 0.94]	
Subtotal (95% CI)		58		66	51.9%	0.78 [0.22, 2.72]	
Total events Heterogeneity: Tau <sup>2</sup> = 0.89; Chi <sup>2</sup> Test for overall effect: Z = 0.40 (		= 3 (P =	22 0.08); I <sup>2</sup> =	55%			
Total (95% CI)		188		170	100.0%	0.79 [0.35, 1.77]	•
Total events	48		52				
Heterogeneity: $Tau^2 = 0.58$ ; Chi <sup>2</sup> Test for overall effect: $Z = 0.58$ (		f = 7 (P :	= 0.07); l <sup>2</sup> =	= 47%			0.001 0.1 1 10 1000
Test for subgroup differences: C	$hi^2 = 0.00, c$						Favours hemosiderin (-) Favours hemosiderin (+)
Study or Subgroup	hemosider Events	rin (-) Total	hemoside Events		Weight	Odds Ratio M-H, Random, 95% Cl	Odds Ratio M–H, Random, 95% Cl
high score	Licito	Total	Liento	Total	mengine	in n, nandon, 55/6 er	
Cheng Huang 2013	3	12	3	15	6.0%	1.33 [0.22, 8.22]	
Churl-Su Kwon 2013	8	31	2	25	7.0%	4.00 [0.77, 20.91]	
Paolo Cappabianca 1997 Xiaoyu Wang 2013 (1)	0 22	4 86	6 21	31 46	2.5% 17.5%	0.44 [0.02, 9.17] 0.41 [0.19, 0.87]	
Xiaoyu Wang 2013 (2)	17	42	13	18	10.9%	0.26 [0.08, 0.87]	
Yichao Jin 2014	2	21	6	15	6.2%	0.16 [0.03, 0.94]	
Subtotal (95% CI) Total events	52	196	51	150	50.2%	0.55 [0.23, 1.32]	
Heterogeneity: $Tau^2 = 0.56$ ; $Chi^2$ Test for overall effect: $Z = 1.34$ (	= 10.23, df	f = 5 (P		= 51%			
moderate score							
Christian R. Baumann 2006 (1)	3	14	6	17	7.2%	0.50 [0.10, 2.52]	
Christian R. Baumann 2006 (2)	5	13	9	16	8.2%	0.49 [0.11, 2.16]	
Christian R. Baumann 2006 (3) Christian von der Brelie 2014	3	14 9	6 1	13 2	6.9% 2.4%	0.32 [0.06, 1.71] 0.50 [0.02, 11.09]	
D. Zevgaridis 1996	4	28	5	38	8.8%	1.10 [0.27, 4.53]	<b>_</b>
Je Young Yeon 2009	5	31	4	23	8.6%	0.91 [0.22, 3.86]	
T. Hammen 2007 Subtotal (95% CI)	7	11 120	7	19 128	7.8% <b>49.8%</b>	3.00 [0.64, 14.02] 0.80 [0.43, 1.47]	
Total events	30	120	38	120	- 5.6%	0.00 [0.43, 1.47]	T
Heterogeneity: $Tau^2 = 0.00$ ; $Chi^2$ Test for overall effect: $Z = 0.72$ (	<sup>e</sup> = 5.05, df =	= 6 (P =		0%			
Total (95% CI)		316		278	100.0%	0.64 [0.39, 1.06]	◆
Total events	82		89	2.0%			
Heterogeneity: Tau <sup>2</sup> = 0.23; Chi <sup>2</sup> Test for overall effect: Z = 1.72 (		i = 12 (P	= 0.16); l <sup>2</sup>	= 28%			0.001 0.1 1 10 1000
Test for subgroup differences: C		df = 1 (P	= 0.49), I <sup>2</sup>	= 0%			Favours hemosiderin (–) Favours hemosiderin (+)

Fig 4. Forest plot comparing seizure outcomes between hemosiderin (+) and hemosiderin (-) groups in age, lesion location and study quality subgroup analyses. hemosiderin (-), with hemosiderin excision; hemosiderin (+), without hemosiderin excision; CI, confidence interval.

	Study or Subgroup	hemoside Events	rin (-) Total	hemosideri Events		Weight	Odds Ratio M-H, Fixed, 95% Cl	Odds Ratio M-H, Fixed, 95% Cl	
Varey Versel 2020	Asia			-		3.000			
log reaching (1)  log reachi							1.33 [0.22, 8.22]		
Name Mark 100         1 <th1< th="">         1         1         <t< td=""><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>_<b></b>]</td></t<></th1<>								_ <b></b> ]	
$ \begin{array}{c} had [h = 10] \\ had [h = 10] $	Xiaoyu Wang 2013 (2)						0.26 [0.08, 0.87]		
all devine	Yichao Jin 2014	2		6			0.16 [0.03, 0.94]		
terogenery, 00 <sup>2</sup> + 4.2, 0 <sup>2</sup> + 6.0, 0 <sup>2</sup> + 7.1 <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogenery</b> <b>Errogene</b>		40	192	47	117	64.4%	0.42 [0.25, 0.71]	•	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Heterogeneity: Chi <sup>2</sup> = 4.42, df =	4 (P = 0.35)	); I <sup>2</sup> = 9%	47					
$ \begin{array}{c} \label{eq:set} \begin{tabular}{ c c c c c } \label{eq:set} \\ \label{eq:set} \begin{tabular}{ c c c c c c c c c c c c c c c c c c c$		3	14	6	17	6.3%	0.50 [0.10, 2.52]		
$ \begin{aligned} \begin{array}{c} \label{eq:horizon} \begin{tabular}{l l l l l l l l l l l l l l l l l l l $	Christian R. Baumann 2006 (2)						0.49 [0.11, 2.16]		
$ \begin{aligned} \begin{array}{c} \label{eq:constraint} 1996 \\ \label$							0.32 [0.06, 1.71]		
balo Capebool (2) Since	D. Zevgaridis 1996						1.10 [0.27, 4.53]		
$\begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} $	Paolo Cappabianca 1997					2.3%	0.44 [0.02, 9.17]		
tail events $1 = \frac{2}{10}$ $\frac{1}{10}$ $\frac{1}{10}$ $\frac{2}{10}$ $\frac{2}$		7		7			3.00 [0.64, 14.02]		
$ \begin{array}{c} \text{teters generic Cul - 5.1, df = 6 (0 - 3.3), f = 0.03} \\ Mercina humble for versi field < 2.0 & 2 & 2.46 & 4.00 [0.77, 20.01] \\ \textbf{Mercina humble field < 0 & 10 & 2 & 2 & 2.46 & 4.00 [0.77, 20.01] \\ \textbf{Mercina humble field < 0 & 10 & 2 & 2 & 2.46 & 4.00 [0.77, 20.01] \\ \textbf{Mercina humble field < 0 & 10 & 2 & 2 & 2.46 & 4.00 [0.77, 20.01] \\ \textbf{Mercina humble field < 0 & 10 & 2 & 2 & 2.46 & 4.00 [0.77, 20.01] \\ \textbf{Mercina humble field < 0 & 10 & 2 & 2 & 2.46 & 4.00 [0.77, 20.01] \\ \textbf{Mercina humble field < 0 & 10 & 2 & 2 & 2.46 & 4.00 [0.77, 20.01] \\ \textbf{Mercina humble field < 0 & 10 & 2 & 0 & 0.01 & 2 & 0.00 \\ \textbf{Mercina humble field < 0 & 10 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 \\ \textbf{Mercina humble field < 0 & 10 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 \\ \textbf{Mercina humble field < 0 & 10 & 0.00 & 0.$		25	93	40	136	33.1%	0.76 [0.40, 1.43]	-	
hub-Size Rook 2013       6       31       2       23       2.44       4.06 (0.77, 20.51)         betrogeney Nuc applicable sets overall effect 2.148 (= 0.10)       10       27       10.00%       0.62 (0.62, 0.51)         out of St O       13       0       2.7       10.00%       0.62 (0.62, 0.51)         out of St O       16       27       10.00%       0.62 (0.62, 0.51)         out of St O       16       27       10.00%       0.62 (0.62, 0.51)         out of St O       16       27       10.00%       0.62 (0.62, 0.51)         out of St O       16       27       10.00%       0.62 (0.62, 0.51)         out of St O       16       10       10.00%       0.64 (0.62, 0.57)         out of St O       10       10       10.00%       0.64 (0.62, 0.57)         out of St O       10       10.00%       10.00%       0.64 (0.62, 0.57)         out of St O       10       10.00%       10.00%       0.64 (0.62, 0.57)         out of St O       10       10.00%       10.00%       0.70 (0.64, 0.10%)         out of St O       10.00%       10.00%       10.00%       0.70 (0.64, 0.10%)         out of St O       10.00%       10.00%       10.00%       0.70 (0.64,	leterogeneity: Chi <sup>2</sup> = 5.14, df =	6 (P = 0.53	); I <sup>2</sup> = 0%	40					
$ \frac{1}{100} + 1$	American								
teal events $6 2$ 2 teal events $6 - 2$ 2 term events $1 - 2 + 2 + 2 + 2 + 2 + 2 + 2 + 2 + 2 + 2$	Churl-Su Kwon 2013	8	31	2	25		4.00 [0.77, 20.91]		
$ \begin{array}{c} \label{eq:started} \\ \begin{tabular}{lllllllllllllllllllllllllllllllllll$			21	2	25	2.4%	4.00 [0.77, 20.91]		
bick events $1_{10} = 1, 2, 1, 2, 1, 2, 1, 2, 1, 2, 1, 2, 1, 2, 2, 1, 0, 1, 0, 1, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2,$	leterogeneity: Not applicable	-		2					
$ \begin{array}{c} \text{betrogeneric Cul^{-1}} = 1.57, df = 1.2 \\ constrained to first order of the Cut 2 \\ \text{to for averal fifter, 2 \\ \text{to for averal fi$	Fotal (95% CI)		316		278	100.0%	0.62 [0.42, 0.91]	•	
est for vertices of the constraint of the const	Fotal events Heterogeneity: Chi <sup>2</sup> = 16.73. df		16): 1 <sup>2</sup> =					L	
$ \begin{array}{c} \mbox{trans} tran$	Test for overall effect: Z = 2.45	(P = 0.01)			72 70/				
femse ruite-50%           is 13 10 2.2 2.23           hints: worder Belle 2014         3           hints: worder Belle 2014         3         1 <th 2"2"2"2"2"2"2"2"2"2"2"2"2"2"2"2"2"2<="" colspa="2" td=""><td></td><td>hemoside</td><td>rin (-)</td><td>hemosideri</td><td>n (+)</td><td></td><td>Odds Ratio</td><td></td></th>	<td></td> <td>hemoside</td> <td>rin (-)</td> <td>hemosideri</td> <td>n (+)</td> <td></td> <td>Odds Ratio</td> <td></td>		hemoside	rin (-)	hemosideri	n (+)		Odds Ratio	
heng hang 2013 3 12 3 12 3 15 5.18 1.33 10.22, 8.22] https://doi.org/10.1001/10.2010/10.2010.0.5.23 https://doi.org/10.1001/10.2010/10.2010.0.5.23 https://doi.org/10.1001/10.2010	study or Subgroup female ratio<50%	Events	Total	Évents	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl	
Initials we derived by the summary 2016 (1) 3 14 6 7 1 20 8 0.50 (10.1, 25.21) 3 2.28 (5.010, 21.12) 3 2.28 (5.010, 21.12) 3 2.28 (5.010, 21.12) 3 2.28 (5.010, 21.12) 3 2.28 (5.010, 21.12) 3 2.28 (5.010, 21.12) 3 2.28 (5.010, 21.12) 3 2.28 (5.010, 21.12) 4 2.2	Cheng Huang 2013							<del></del>	
Hammer 2007 $T$ 11 7 19 48 5.00 [0.64, 14.02] where where $Marg 2013$ 2 2 6 7 2 1 2 2 6 7 2 2 5 4.28 5 0.00 [0.64, 14.02] where $Marg 2013$ 2 2 5 4.28 5 0.00 [0.64, 14.02] where $Marg 2013$ 2 2 5 4.28 5 0.00 [0.67, 20.91] able Carbonic Chi = 2.0 $P = 0.35$ ; $P = 355$ , etc. 12 2 2 5 4.28 5 0.00 [0.67, 20.91] able Carbonic Chi = 2.0 $P = 0.35$ ; $P = 355$ , etc. 12 10 $P = 0.05$ ; $P = 755$ etc. 12 0 $P = 0.00$ ; $P = 0.75$ ; $P = 0.75$ ; $P = 355$ etc. 12 0 $P = 0.00$ ; $P = 0.75$ ;	Christian R. Baumann 2006 (1)		14	6	17	10.9%	0.50 [0.10, 2.52]		
$ \begin{array}{c} \mbox{log} 103 (1) 1 2 2 8 6 21 4 6 52.00 0.41 (13, 0.67) \\ \mbox{log} 103 (2) 11 9 22 8 6 11 9 12.85 0.56 (0.33, 0.96) \\ \mbox{log} 12 9 0.003 \\ \mbox{log} 12 $									
$ \frac{1}{100} = \frac{1}{100} \frac{1}{100} \frac{1}{100} \frac{1}{100} \frac{1}{1000} $	F. Hammen 2007 Kiaovu Wang 2013 (1)								
total events $40$ $44$ tetrogeneticy $Ch^{-1} = 3.04, df = 5 = 0.15$ , $l^{-1} = 3.05$ tetrogeneticy $Ch^{-1} = 3.04, df = 5 = 0.15$ , $l^{-1} = 3.05$ tetrogeneticy $Ch^{-1} = 1.53, df = 12 = 0.21$ , $l^{-2} = 3.05$ tetrogeneticy $Ch^{-1} = 1.53, df = 12 = 0.21$ , $l^{-2} = 3.05$ tetrogeneticy $Ch^{-1} = 1.53, df = 12 = 0.07$ , $l^{-1} = 7.05$ tetrogeneticy $Ch^{-1} = 1.53, df = 12 = 0.07$ , $l^{-1} = 7.05$ tetrogeneticy $Ch^{-1} = 1.53, df = 12 = 0.07$ , $l^{-1} = 7.05$ tetrogeneticy $Ch^{-1} = 1.53, df = 12 = 0.07$ , $l^{-1} = 7.05$ tetrogeneticy $Ch^{-1} = 1.53, df = 12 = 0.05$ , $l^{-1} = 7.05$ tetrogeneticy $Ch^{-1} = 1.53, df = 12 = 0.05$ , $l^{-1} = 7.05$ tetrogeneticy $Ch^{-1} = 1.53, df = 12 = 0.05$ , $l^{-1} = 7.05$ tetrogeneticy $Ch^{-1} = 1.53, df = 12 = 0.05$ , $l^{-1} = 7.05$ tetrogeneticy $Ch^{-1} = 1.53, df = 12 = 0.05$ , $l^{-1} = 7.05$ tetrogeneticy $Ch^{-1} = 1.53, df = 12 = 0.05$ , $l^{-1} = 7.05$ tetrogeneticy $Ch^{-1} = 1.53, df = 12 = 0.05$ , $l^{-1} = 7.05$ tetrogeneticy $Ch^{-1} = 1.53, df = 12 = 0.05$ , $l^{-1} = 7.05$ tetrogeneticy $Ch^{-1} = 1.53, df = 12 = 0.05$ , $l^{-1} = 7.05$ tetrogeneticy $Ch^{-1} = 1.53, df = 12 = 0.05$ , $l^{-1} = 7.05$ tetrogeneticy $Ch^{-1} = 1.53, df = 12 = 0.05$ , $l^{-1} = 7.05$ tetrogeneticy $Ch^{-1} = 1.53, df = 12 = 0.05$ , $l^{-1} = 0.05$ tetrogeneticy $Ch^{-1} = 1.53, df = 12 = 0.05$ , $l^{-1} = 0.05$ tetrogeneticy $Tah^{-1} = 0.00, Ch^{-1} = 1.23, df = 2 = 0.05$ , $l^{-1} = 0.05$ tetrogeneticy $Tah^{-1} = 0.00, Ch^{-1} = 1.23, df = 2 = 0.05$ , $l^{-1} = 0.05$ tetrogeneticy $Tah^{-1} = 0.00, Ch^{-1} = 1.23, df = 12 = 0.01, l^{-1} = 0.01$ tetrogeneticy $Tah^{-1} = 0.00, Ch^{-1} = 1.23, df = 12 = 0.01, l^{-1} = 0.01$ tetrogeneticy $Tah^{-1} = 0.00, Ch^{-1} = 1.03, df = 0 = 0.01, l^{-1} = 0.01$ tetrogenetic $Tah^{-1} = 0.00, Ch^{-1} = 1.03, df = 0 = 0.01, l^{-1} = 0.01$ tetrogenetic $Tah^{-1} = 0.00, Ch^{-1} = 1.03, df = 0 = 0.01, l^{-1} = 0.01$ tetrogenetic $Tah^{-1} = 0.00, Ch^{-1} = 1.03, df = 0 = 0.00, l^{-1} = 0.00$ tetrogenetic $Tah^{-1} $	richao Jin 2014		21		15	16.2%			
$ \begin{aligned} & \text{fereogenery: Ch' = 3.0, d = 5 (P = 0.15); l^2 = 38K \\ & \text{for weall effect 2 + 2.10 (P = 0.05); l^2 = 38K \\ & \text{for weall effect 2 + 2.10 (P = 0.05); l^2 = 37K \\ & \text{ablo Capabiance 197 } 0 & 4 & 6 & 31 & 4.06 & 0.44 [0.02, 9.17] \\ & \text{ablo Capabiance 197 } 0 & 4 & 6 & 31 & 4.06 & 0.44 [0.02, 9.17] \\ & \text{ablo Capabiance 197 } 0 & 4 & 6 & 31 & 4.06 & 0.44 [0.02, 9.17] \\ & \text{ablo Capabiance 197 } 0 & 188 & 170 & 100.05K & 0.70 [0.43, 1.14] \\ & \text{ablo Capabiance 197 } 0 & 188 & 170 & 100.05K & 0.70 [0.43, 1.14] \\ & \text{call events} & -12.06 (P = 0.21); v^2 = 37K \\ & \text{cet for overall effects: 2 + 1.27 (P = 0.05); l^2 = 74.55K \\ & \text{tero overall effect 2 + 1.37 (P = 0.05); l^2 = 0.05; l^2 = 74.55K \\ & \text{tero overall effect 2 - 1.43 (P = 0.05); l^2 = 0.05; l^2 = 0.05K \\ & \text{tero overall effect 2 - 1.43 (P = 0.05); l^2 = 0.05K \\ & \text{tero overall effect 2 - 1.43 (P = 0.05); l^2 = 0.05K \\ & \text{tero overall effect 2 - 0.45K; l^2 = 0.06K \\ & \text{teroopenery: } 1 = 0.00; Ch^4 = 1.12, 0, 0, 13 & 12, 25 & 13, 35 & 0.05 (0, 10, 2, 5, 2) \\ & \text{teroopenery: } 1 = 0.00; Ch^4 = 1.12, 0, 0, 12 & 13 & 13 & 10, 22, 8, 20 \\ & \text{teroopenery: } 1 = 0.00; Ch^4 = 1.12, 0, 0, 12 & 13 & 13 & 10, 22, 8, 20 \\ & \text{teroopenery: } 1 = 0.00; Ch^4 = 1.12, 0, 0, 12 & 13 & 13 & 10, 22, 8, 20 \\ & \text{teroopenery: } 1 = 0.00; Ch^4 = 1.12, 0, 0, 12 & 13 & 13 & 10, 22, 8, 20 \\ & \text{teroopenery: } 1 = 0.00; Ch^4 = 1.12, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,$	Subtotal (95% CI)		153		114	91.8%	0.56 [0.33, 0.96]	◆	
hul-Sa Koon 2013 8 31 2 25 4.28 4.00 (0.77, 20.91] about 4050 C D $\frac{1}{3}$ 6 $\frac{1}{3}$ 6 $\frac{1}{3}$ 4 $\frac{1}{3}$ 6 $\frac{1}{3}$ 6 $\frac{1}{3}$ 4 $\frac{1}{3}$ 6 $\frac{1}{3}$ 7 $\frac{1}{3}$	Heterogeneity: Chi <sup>2</sup> = 8.04, df =	5 (P = 0.15	); I <sup>2</sup> = 38						
hul-Sa Koon 2013 8 31 2 25 4.28 4.00 (0.77, 20.91] about 4050 C D $\frac{1}{3}$ 6 $\frac{1}{3}$ 6 $\frac{1}{3}$ 4 $\frac{1}{3}$ 6 $\frac{1}{3}$ 6 $\frac{1}{3}$ 4 $\frac{1}{3}$ 6 $\frac{1}{3}$ 7 $\frac{1}{3}$									
able Capeablance 1997 0 4 6 31 4 00% 0.24, 9.17 total cents a 3 5 8 223 (0.84, 7.95 b able cents a 4 6 5 1 9 - 0.21); $f = 37x$ a 5 6 2.23 (0.84, 7.95 a 1 9 - 0.21); $f = 37x$ a 1 9 - 0.21); $f = 37x$ b remove 1 1 9 - 0.21); $f = 37x$ a 1 9 - 0.21); $f = 37x$ b remove 1 1 1 0 - 0.21); $f = 37x$ b remove 1 1 1 0 - 0.21); $f = 37x$ b remove 1 1 1 0 - 0.21); $f = 37x$ b remove 1 1 1 0 - 0.21); $f = 37x$ b remove 1 1 1 0 - 0.21); $f = 7x$ b remove 1 1 1 0 - 0.21); $f = 7x$ b remove 1 1 1 0 - 0.21); $f = 7x$ b remove 1 1 1 0 - 0.21); $f = 7x$ b remove 1 1 1 0 - 0.21); $f = 7x$ b remove 1 1 1 0 - 0.21); $f = 7x$ b remove 1 1 1 0 - 0.21); $f = 7x$ b remove 1 1 1 0 - 0.21); $f = 7x$ b remove 1 1 1 0 - 0.21); $f = 7x$ b remove 1 1 1 0 - 0.21); $f = 7x$ b remove 1 1 1 0 - 0.21); $f = 7x$ b remove 1 1 1 0 - 0.21); $f = 7x$ b remove 1 1 1 0 - 0.21); $f = 7x$ b remove 1 1 1 0 - 0.21); $f = 7x$ b remove 1 1 1 0 - 0.21); $f = 7x$ b remove 1 1 1 0 - 0.21); $f = 7x$ b remove 1 1 1 0 - 0.21); $f = 7x$ b remove 1 1 0 - 0.21); $f = 0.21$ ; $f = 3x$ b remove 1 1 0 - 0.21); $f = 0.20$ b remove 1 1 0 - 0.21); $f = 0.20$ b remove 1 1 0 - 0.21); $f = 0.20$ b remove 1 1 0 - 0.21); $f = 0.20$ b remove 1 1 0 - 0.21); $f = 0.20$ b remove 1 1 0 - 0.21); $f = 0.20$ b remove 1 1 0 - 0.21); $f = 0.20$ b remove 1 1 0 - 0.21); $f = 0.20$ b remove 1 1 0 - 0.21); $f = 0.20$ b remove 1 1 1 0 - 0.21); $f = 0.20$ b remove 1 1 1 0 - 0.21); $f = 0.20$ b remove 1 1 1 0 - 0.21); $f = 0.20$ b remove 1 1 1 0 - 0.21); $f = 0.20$ b remove 1 1 1 0 - 0.21); $f = 0.20$ c remove 1 1 1 1 0 - 0.21); $f = 0.20$ c remove 1 1 1 1 0 - 0.21); $f = 0.20$ c remove 1 1 1 1 0 - 0.21); $f = 0.20$ c remove 1 1 1 1 0 - 0.21); $f = 0.20$ c remove 1 1 1 1 0 - 0.21); $f = 0.20$ c remove 1 1 1 1 0 - 0.21); $f = 0.20$ c remove 1 1 1 1 0 - 0.21); $f = 0.20$ c remove 1 1 1 1 0 - 0.21); $f = 0.20$ c remove 1 1 1 1 0 - 0.21); $f = 0.20$ c remove 1 1 1 1 0 - 0.21); $f = 0.20$ c remove 1 1 1 1 0 - 0.21); $f = 0.20$ c remove 1 1 1	Churl-Su Kwon 2013	8	31	2		4.2%	4.00 [0.77, 20.91]		
ball events $3$ $3$ $12$ $13$ $12$ $13$ $12$ $13$ $12$ $13$ $13$ $12$ $13$ $13$ $13$ $13$ $13$ $13$ $13$ $13$	aolo Cappabianca 1997	0	4	6	31		0.44 [0.02, 9.17]		
teterogeneity: Ch <sup>2</sup> = 1.58, df = 10 = 0.21; l <sup>2</sup> = 37% estimates to reveal lefter: 2 = 1.26 p = 0.21; l <sup>2</sup> = 37% estimates to reveal lefter: 2 = 1.26 p = 0.05; l <sup>2</sup> = 47% estimates to reveal lefter: 2 = 1.43 p = 0.05; l <sup>2</sup> = 47.5% estimates to reveal lefter: 2 = 1.43 p = 0.05; l <sup>2</sup> = 47.5% estimates to reveal lefter: 2 = 1.43 p = 0.05; l <sup>2</sup> = 47.5% estimates to reveal lefter: 2 = 1.43 p = 0.05; l <sup>2</sup> = 47.5% estimates to reveal lefter: 2 = 1.43 p = 0.05; l <sup>2</sup> = 47.5% estimates to reveal lefter: 2 = 1.43 p = 0.05; l <sup>2</sup> = 47.5% estimates to reveal lefter: 2 = 1.43 p = 0.05; l <sup>2</sup> = 47.5% estimates to reveal lefter: 2 = 0.01; r <sup>2</sup> = 20 estimates to reveal lefter: 2 = 0.01; r <sup>2</sup> = 20 estimates to reveal lefter: 2 = 0.01; r <sup>2</sup> = 20 estimates to reveal lefter: 2 = 0.01; r <sup>2</sup> = 20 estimates to reveal lefter: 2 = 0.00; r <sup>2</sup> = 20 estimates to reveal lefter: 2 = 0.00; r <sup>2</sup> = 20 estimates to reveal lefter: 2 = 0.00; r <sup>2</sup> = 0.			35		56	8.2%	2.25 [0.64, 7.95]		
est for overall effect: $Z = 1.26 (p = 0.21)$ ordal (95% CD) 18 170 100.0% 0.70 (0.43, 1.14) 10 ordal events 10 ordal events 11 ordal events 10 ordal events 11 ordal events 11 ordal events 11 ordal events 12 ordal events 13 ordal events 14 ordal events 10 ordal ev	lotal events Heterogeneity: Chi <sup>2</sup> = 1.58, df =		); $I^2 = 37$						
$ \begin{array}{c} \text{val events} & \text{dec} & \text{size} \\ \text{strongenity} (Th^2 = 1.0.9, df = 7 P = 0.07), t^2 = 478 \\ \text{st for overall effect: 2 = 1.4.3 P = 0.15 \\ \text{st or subroup} & \text{terms Sign for all events} & \text{terms Sign for all events} \\ \text{terms Sign for all effect: 2 = 1.4.3 P = 0.15 \\ \text{terms Sign for all events} & \text{terms Sign for all events} \\ \text{terms Sign for all events} & \text{terms Sign for all events} \\ \text{terms Sign for all events} & \text{terms Sign for all events} \\ \text{terms Sign for all events} & \text{terms Sign for all events} \\ \text{terms Sign for all events} & \text{terms Sign for all events} \\ \text{terms Sign for all events} & \text{terms Sign for all events} \\ \text{terms Sign for all events} & \text{terms Sign for all events} \\ \text{terms Sign for all events} & \text{terms Sign for all events} \\ \text{terms Sign for all events} & \text{terms Sign for all events} \\ \text{terms Sign for all events} & \text{terms Sign for all events} \\ \text{terms Sign for all events} & \text{terms Sign for all events} \\ \text{terms sign for all events} & \text{terms Sign for all events} \\ \text{terms sign for all events} & \text{terms Sign for all events} \\ \text{terms sign for all events} & \text{terms sign for all events} \\ \text{terms sign for all events} & \text{terms sign for all events} \\ \text{terms sign for all events} & \text{terms sign for all events} \\ \text{terms sign for all events} & \text{terms sign for all events} \\ \text{terms sign for all events} & \text{terms sign for all events} \\ \text{terms sign for all events} & \text{terms sign for all events} \\ \text{terms sign for all events} & \text{terms sign for all events} \\ \text{terms sign for all events} & \text{terms sign for all events} \\ \text{terms sign for all events} & \text{terms sign for all events} \\ \text{terms sign for all events} \\$									
tetrogeneticy: Ch <sup>2</sup> = 13.09, df = 7 ( $\theta$ = 0.05); l <sup>2</sup> = 4.7% tetrogeneticy: Ch <sup>2</sup> = 3.02, df = 1 ( $\theta$ = 0.05), l <sup>2</sup> = 74.5% Ddds Ratio Methodizerin (-) Focus hemosiderin (-) focus to the substrain (-) the substrain (-) Methodizerin (-) Focus hemosiderin (-) Methodizerin (-) Focus hemosiderin (-) Focus hemosiderin (-) Focus hemosiderin (-) Methodizerin (-) Focus hemosiderin (-) Methodizerin (-) Focus hemosiderin (-)	Total (95% CI)		188		170	100.0%	0.70 [0.43, 1.14]	•	
est for overall effect: $Z = 1.33 (P = 0.15)$ hemosiderin (-) hemosiderin (-	Total events								
The for example of the form o			7); $I^2 = 4$	7%				0.001 0.1 1 10 1000	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Test for overall effect: $Z = 1.43$ (	(P = 0.15) $(hi^2 = 2.02)$	df = 1 (P	- 0.05) 12 -	74 5%			Favours hemosiderin (-) Favours hemosiderin (+)	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		hemosider	in (-) h	emosiderin	(+)				
hristian R. Baumann 206 (1) $\frac{3}{2}$ 14 $\frac{6}{6}$ 17 14.5% 0.50 (0.10, 2.52) (chao jin 2014 2 21 $\frac{6}{21}$ 135 13.1% 0.16 (0.03, 0.94) bootal (35% Cf) 121 $\frac{3}{21}$ 3 35 1.4% 0.37 (0.20, 0.71) otal events $\frac{1}{2} = 0.00$ , $Ch^2 = 1.07$ , $df = 2 (P = 0.58)$ , $P = 0.6$ set for overall effect: $Z = 3.02$ ( $P = 0.003$ ) multiple CMs occurrence 2-00 heng Huang 2013 3 12 3 15 12.9% 1.33 (0.22, 6.22) hurf-situ kvon 2013 8 31 2 25 14.2% 4.00 [0.77, 2.91] hurf-situ kvon 2013 8 31 2 25 14.2% 4.00 [0.77, 2.91] hurf-situ kvon 2013 8 31 2 25 14.2% 4.00 [0.77, 2.91] hurf-situ kvon 2013 8 4 31 2 25 14.2% 4.00 [0.77, 2.91] bootal events 21 13 tetrogeneity: Tau <sup>2</sup> = 0.00: Ch <sup>2</sup> = 1.2.0, df = 6 (P = 0.04); P = 54% est for overall effect: Z = 1.77 (P = 0.08) tetrogeneity: Tau <sup>2</sup> = 0.00: Ch <sup>2</sup> = 1.3.02, df = 6 (P = 0.04); P = 0.15 (P = 0.01); P = 0.15 (P = 0.0	Study or Subgroup		Total	Events	Total	Weight M	I-H, Random, 95% CI	M-H, Random, 95% Cl	
laoyu Wang 2013 (1) 22 66 21 46 23.7% 0.41 (0.19, 0.87) (hab jin 2014 2 21 6 15 13.1% 0.16 (0.03, 0.94) ubtoal (055% C1) 121 78 51.4% 0.37 (0.20, 0.71) multiple CMs occurrence 20% hereng Huang 2013 3 12 3 15 12.9% 1.33 (0.22, 8.22) hristian Ramma 2007 7 111 7 19 15.2% 3.00 (0.67, 2.091) Harmen 2007 7 111 7 19 15.2% 3.00 (0.67, 2.091) tad events 21 33 tat everogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 1.02, df = 3 (P = 0.05); l <sup>2</sup> = 0% est for overall effect: $2 = 1.27$ ( $d = 0.2$ , $d = 0.06$ ; $l = 5 d\%$ est for overall effect: $2 = 1.02$ , df = 3 (P = 0.06); l <sup>2</sup> = 5 d\% est for overall effect: $2 = 1.02$ , df = 3 (P = 0.06); l <sup>2</sup> = 5 d\% est for overall effect: $2 = 1.02$ , df = 3 (P = 0.06); l <sup>2</sup> = 5 d\% est for overall effect: $2 = 1.02$ , df = 6 (P = 0.06); l <sup>2</sup> = 5 d\% est for overall effect: $2 = 1.04$ ( $P = 0.00$ ); l <sup>2</sup> = 00.11 l <sup>2</sup> = 90.11 d tad events 48 46 est for overall effect: $2 = 1.04$ ( $P = 0.00$ ); l <sup>2</sup> = 00.11 l <sup>2</sup> = 90.11 d hermosiderin (+) hemosiderin (+) hemosiderin (+) hemosiderin (+) hemosiderin (+) for 0.01 l <sup>2</sup> = 2.28 30.04 (0.07, 72.091) favours hemosiderin (-) Forours hemosiderin (+) favours hemosiderin (+) forours h			14	6	17	14.5%	0.50 [0.10. 2 52]		
ichao jin 2014 2 21 6 15 13.1% 0.16 [0.03, 0.94] total events 27 33 total events 27 33 multiple CMs occurrence 20% heng Huang 2013 1 2 3 15 12.9% 1.33 [0.22, 8.22] hurd-su koon 2013 8 31 2 25 14.2% 4.00 [0.74, 10.9] hurd-su koon 2013 8 31 2 25 14.2% 4.00 [0.74, 10.9] total events 2 1 13 teterogeneity: Tau' = 0.00; $Ch' = 1.32$ , $df = 3 p = 0.51$ ; $l^2 = 0\%$ tetrogeneity: Tau' = 0.00; $Ch' = 1.32$ , $df = 3 p = 0.51$ ; $l^2 = 0\%$ tetrogeneity: Tau' = 0.00; $Ch' = 1.32$ , $df = 3 p = 0.51$ ; $l^2 = 0\%$ tetrogeneity: Tau' = 0.00; $Ch' = 1.52$ , $df = 3 p = 0.51$ ; $l^2 = 0\%$ tetrogeneity: Tau' = 0.00; $Ch' = 1.52$ , $df = 10 p = 0.51$ ; $l^2 = 0\%$ tetrogeneity: Tau' = 0.00; $Ch' = 1.52$ , $df = 10 p = 0.51$ ; $l^2 = 0\%$ tetrogeneity: Tau' = 0.00; $Ch' = 1.52$ , $df = 10 p = 0.51$ ; $l^2 = 0\%$ tetrogeneity: Tau' = 0.00; $Ch' = 1.52$ , $df = 10 p = 0.51$ ; $l^2 = 0\%$ tetrogeneity: Tau' = 0.00; $Ch' = 1.52$ , $df = 10 p = 0.51$ ; $l^2 = 0\%$ tetrogeneity: Tau' = 0.00; $Ch' = 1.52$ , $df = 10 p = 0.51$ ; $l^2 = 0\%$ tetrogeneity: Tau' = 0.00; $Ch' = 1.52$ , $df = 10 p = 0.51$ ; $l^2 = 0\%$ tetrogeneity: Tau' = 0.00; $Ch' = 1.52$ , $df = 10 p = 0.51$ ; $l^2 = 0\%$ tetrogeneity: Tau' = 0.00; $Ch' = 1.52$ , $df = 10 p = 0.51$ ; $l^2 = 0\%$ tetrogeneity: Tau' = 0.00; $h' = 1.52$ , $df = 10 p = 0.51$ ; $l^2 = 0\%$ tetrogeneity: $Ch' = 2.03$ , $df = 3 (p = 0.57)$ ; $l^2 = 0\%$ tetrogeneity: $Ch' = 2.03$ , $df = 3 (p = 0.57)$ ; $l^2 = 0\%$ tetrogeneity: $Ch' = 2.03$ , $df = 3 (p = 0.57)$ ; $l^2 = 0\%$ tetrogeneity: $Ch' = 2.03$ , $df = 3 (p = 0.57)$ ; $l^2 = 0\%$ tetrogeneity: $Ch' = 2.03$ , $df = 3 (p = 0.57)$ ; $l^2 = 0\%$ tetrogeneity: $Ch' = 2.03$ , $df = 3 (p = 0.57)$ ; $l^2 = 0\%$ tetrogeneity: $Ch' = 2.03$ , $df = 3 (p = 0.57)$ ; $l^2 = 0\%$ tetrogeneity: $Ch' = 2.03$ , $df = 3 (p = 0.57)$ ; $l^2 = 0\%$ tetrogeneity: $Ch' = 2.57$ , $df = 12 (p = 0.00)$ tetrogeneity: $Ch' = 1.57, df = 12 (p = 0.00)$ tetrogeneity: $Ch' = 1.57, df = 12 (p = 0.00)$ tetrogeneity: $Ch' = 1.57, df = 12 (p = 0.01)$ tetrogeneity: $Ch' = 1.57, df = 12 (p = 0.01)$ t	Xiaoyu Wang 2013 (1)								
otal events 27 33 est for overall effect: $2 - 3.02$ ( $P = 0.05$ ); $I^2 = 0.55$ ; $I^$	Yichao Jin 2014	2		6		13.1%	0.16 [0.03, 0.94]	· · · · · · · · · · · · · · · · · · ·	
$\begin{array}{c} \text{terrogeneity: Tat^2 = 0.00: Ch^2 = 1.07, df = 2 \ \rho = 0.58); l^2 = 0\% \\ \text{set for overall effect Z = -3.02 \ \rho = 0.003) \\ \hline \textbf{multiple CMs occurrence>20\% \\ \text{heng Hung 2013} & 3 & 12 & 3 & 15 & 12.9\% & 1.33 \ [0.22, 8.22] \\ \text{heng Hung 2013} & 7 & 11 & 2 & 21 & 15.\% & 4.00 \ [0.64, 16.02] \\ \text{ubtotal (95% C)} & 63 & 61 & 48.6\% & 2.28 \ [0.91, 5.70] \\ \text{otal events} & 21 & 13 \\ \text{eterogeneity: Tat^2 = 0.05; Ch^2 = 1.28, df = 3 \ \rho = 0.61); l^2 = 0\% \\ \text{est for overall effect: Z = 1.37 \ (\rho = 0.08) \\ \text{teromosilerin (-1) hemosiderin (+1) } \\ \text{hemosiderin (-1) hemosiderin (+1) } \\ \text{hemosiderin (-1) hemosiderin (+1) } \\ \text{hemosiderin (-1) hemosiderin (+1) } \\ \text{turdy or subgroup } \hline \text{tervents Total Weight M-H, Fixed, 95% C) } \\ \text{otal events } \hline 12 & 3 & 12 & 23 & 5 & 3.0\% \ 1.33 \ [0.22, 8.22] \\ \text{otal events } \hline 100 \ \text{Favour hemosiderin (-1) hemosiderin (+1) } \\ \text{hemosiderin (+1) hemosiderin (+1) } \\ \text{hemosiderin (+2) hemosiderin (+1) } \\ \text{turdy or subgroup } \hline \text{tervents Total Weight M-H, Fixed, 95% C) } \\ \text{otal events Total Weight M-H, Fixed, 95% C) } \\ \text{otal events Total Weight M-H, Fixed, 95% C) } \\ \text{otal events Total Weight M-H, Fixed, 95% C) } \\ \text{otal events Total Weight M-H, Fixed, 95% C) } \\ \text{otal events Total Weight M-H, Fixed, 95% C) } \\ \text{otal events Total Weight M-H, Fixed, 95% C) } \\ \text{otal events Total Weight M-H, Fixed, 95% C) } \\ \text{otal events Store 13 B a 12 } 2 & 2.5 & 2.4\% & 4.00 \ [0.7, 2.091] \\ \text{otal events Store 13 B a 12 } 2 & 2.5 & 2.4\% & 4.00 \ [0.7, 2.091] \\ \text{otal events Store 13 B a 13 } 2 & 2.5 & 2.4\% & 4.00 \ [0.7, 2.091] \\ \text{otal events Store 13 B a 13 } 2 & 2.5 & 2.4\% & 4.00 \ [0.7, 2.091] \\ otal events Store 13 B a 16 \ 13 & 7.3\% & 0.50 \ [0.10, 2.52] \\ \text{therefore 13 B a 16 \ 13 & 7.3\% & 0.52 \ [0.05, 0.51] \\ \text{otal events Store 13 B a 16 \ 13 & 7.3\% & 0.52 \ [0.05, 0.57] \\ \text{otal events Store 13 B a 16 \ 13 & 7.3\% & 0.52 \ [0.05, 0.57] \\ \text{otal events B a 13 \ 13 B \ 15 \ 15 \ 0.25 \ [0.05, 0.57] \\ \text{otal events B a 13 \ 10 \ 2.2 \ 5 \ 13 \ 8 \ 5.5\% & 0.$		27	121	22	78	51.4%	0.37 [0.20, 0.71]	◆	
est for overall effect: $2 = 3.02$ ( $P = 0.003$ ) multiple CMs occurrence>20% hereig Huang 2013 3 12 3 15 12.9% 1.33 [0.22, 8.22] hristian von der Brelle 2014 3 9 1 2 6.3% 0.50 [0.02, 11.09] ubtool (95% Cf) 63 7 661 48.6% 2.28 [0.91, 5.70] otal events 21 13 teterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 1.82, df = 3 g = 0.61); $l2 = 0.05$ est for overall effect: $2 = -1.32$ , $df = 3 g = 0.61$ ); $l2 = 0.05$ est for overall effect: $2 = -1.32$ , $df = 3 g = 0.61$ ); $l2 = 0.05$ est for overall effect: $2 = -0.44$ ( $P = 0.66$ ) est for overall effect: $2 = -0.44$ ( $P = 0.66$ ) est for overall effect: $2 = -0.44$ ( $P = 0.66$ ) est for overall effect: $2 = -0.44$ ( $P = 0.66$ ) est for overall effect: $2 = -0.44$ ( $P = 0.66$ ) est for overall effect: $2 = -0.44$ ( $P = 0.66$ ) est for overall effect: $2 = -0.44$ ( $P = 0.66$ ) est for overall effect: $2 = -0.44$ ( $P = 0.66$ ) est for overall effect: $2 = -0.44$ ( $P = 0.66$ ) est for overall effect: $2 = -0.44$ ( $P = 0.66$ ) est for overall effect: $2 = -0.61$ herosiderin (-) Forours hemosiderin (-) encodering (-) herosidering (-) herosidering (-) herosidering (-) est for overall effect: $2 = -0.61$ est for overall effect: $2 = -0.57$ ; $l^2 = 0.05$ est for overall effect: $2 = -0.57$ ; $l^2 = 0.05$ est for overall effect: $2 = -1.54$ ( $0.07$ ; $0.09$ ] is the overall effect: $2 = -1.54$ ( $0.07$ ) est for overall effect: $2 = -1.54$ ( $0.07$ ) est for overall effect: $2 = -1.54$ ( $0.07$ ) est for overall effect: $2 = -1.54$ ( $0.07$ ) est for overall effect: $2 = -1.54$ ( $0.07$ ) est for overall effect: $2 = -1.54$ ( $0.07$ ) est for overall effect: $2 = -1.54$ ( $0.07$ ) est for overall effect: $2 = -1.54$ ( $0.07$ ) est for overall effect: $2 = -1.54$ ( $0.07$ ) est for overall effect: $2 = -1.54$ ( $0.07$ ) est for overall effect: $2 = -1.54$ ( $0.07$ ) est for overall effect: $2 = -1.54$ ( $0.07$ ) est for overall effect: $2 = -1.54$ ( $0.07$ ) est for overall effect: $2 = -1.54$ ( $0.07$ ) est for overall effect: $2 = -1.54$ ( $0.07$ ) est for overall effect: $2 = -$			= 2 (P = 0						
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heng Hung 2013 3 12 3 15 12 9% (1, 31 [0, 22, 8, 22] hurd-Su Kvon 2013 8 31 2 25 14, 2% 4, 00 [0, 27, 20, 91] hurd-Su Kvon 2013 8 31 2 25 14, 2% 4, 00 [0, 27, 20, 91] butotal (95% C1) 6 3 61 48, 6% 2, 28 [0, 94, 1, 102] butotal (95% C1) 6 3 64 - 1, 0 = 0, 00, 1/1 = 0, 00, 0/1 = 0, 0/1 = 0, 0/2, 0/2, 0/2, 0/2, 0/2, 0/2, 0/2, 0	multiple CMs occurence>	20%							
hristian von der Breile 2014 3 9 1 2 6.3% 0.50 [0.02, 11.09] hristian R. Bauman 2066 (1) 3 14 6 17 6.3% 0.50 [0.10, 77, 20, 91] tarter operate 1 effect: $Z = 1.57$ ( $P = 0.08$ ) est for overall effect: $Z = 1.57$ ( $P = 0.08$ ) est for overall effect: $Z = 1.57$ ( $P = 0.08$ ) est for overall effect: $Z = 0.76$ ( $P = 0.01$ ); $P = 0\%$ est for overall effect: $Z = 0.76$ ( $P = 0.01$ ); $P = 0\%$ est for overall effect: $Z = 0.76$ ( $P = 0.01$ ); $P = 0\%$ est for overall effect: $Z = 0.76$ ( $P = 0.01$ ); $P = 0\%$ est for overall effect: $Z = 0.76$ ( $P = 0.0002$ ); $P = 5\%$ est for overall effect: $Z = 0.44$ ( $P = 0.06$ ); $P = 5\%$ est for overall effect: $Z = 0.44$ ( $P = 0.06$ ); $P = 5\%$ tart overall effect: $Z = 0.44$ ( $P = 0.06$ ); $P = 0.01$ ; $P = 0.01$	Cheng Huang 2013	3					1.33 [0.22, 8.22]	·	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Christian von der Brelie 2014						0.50 [0.02, 11.09]		
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $						14.2%	4.00 [0.77, 20.91]		
total events 21 13 enterogeneity: Tul = 0.00; Ch <sup>2</sup> = 1.28, df = 3 (P = 0.61); l <sup>2</sup> = 0%, st for overall effect: 2 = 1.77 (P = 0.08) orall 95% C() 184 139 100.0% 0.82 [0.34, 1.98] tetrogeneity: Ch <sup>2</sup> = 2.03, df = 6 (P = 0.04); l <sup>2</sup> = 54% tetrogeneity: Ch <sup>2</sup> = 2.03, df = 16 (P = 0.04); l <sup>2</sup> = 54% tetrogeneity: Ch <sup>2</sup> = 2.03, df = 16 (P = 0.04); l <sup>2</sup> = 54% tetrogeneity: Ch <sup>2</sup> = 2.03, df = 16 (P = 0.04); l <sup>2</sup> = 90.1% tetrogeneity: Ch <sup>2</sup> = 2.03, df = 16 (P = 0.04); l <sup>2</sup> = 90.1% tetrogeneity: Ch <sup>2</sup> = 2.03, df = 16 (P = 0.04); l <sup>2</sup> = 90.1% tetrogeneity: Ch <sup>2</sup> = 2.03, df = 16 (P = 0.57); l <sup>2</sup> = 0% st for overall effect: Z = 1.04 (P = 0.57); l <sup>2</sup> = 0% st for overall effect: Z = 1.04 (P = 0.57); l <sup>2</sup> = 0% st for overall effect: Z = 1.04 (P = 0.57); l <sup>2</sup> = 0% st for overall effect: Z = 1.04 (P = 0.57); l <sup>2</sup> = 0% st for overall effect: Z = 1.04 (P = 0.57); l <sup>2</sup> = 0% st for overall effect: Z = 1.04 (P = 0.57); l <sup>2</sup> = 0% st for overall effect: Z = 1.04 (P = 0.57); l <sup>2</sup> = 0% st for overall effect: Z = 1.04 (P = 0.57); l <sup>2</sup> = 0% st for overall effect: Z = 1.04 (P = 0.57); l <sup>2</sup> = 0% st for overall effect: Z = 1.05 (P = 0.57); l <sup>2</sup> = 0% st for overall effect: Z = 1.05 (P = 0.57); l <sup>2</sup> = 0% st for overall effect: Z = 1.05 (P = 0.57); l <sup>2</sup> = 0% st for overall effect: Z = 1.50 (P = 0.57); l <sup>2</sup> = 0% st for overall effect: Z = 1.50 (P = 0.57); l <sup>2</sup> = 0% st for overall effect: Z = 1.50 (P = 0.57); l <sup>2</sup> = 0% st for overall effect: Z = 1.50 (P = 0.57); l <sup>2</sup> = 0% st for overall effect: Z = 1.50 (P = 0.57); l <sup>2</sup> = 0% st for overall effect: Z = 1.50 (P = 0.57); l <sup>2</sup> = 0% st for overall effect: Z = 1.50 (P = 0.57); l <sup>2</sup> = 0% st for overall effect: Z = 1.50 (P = 0.57); l <sup>2</sup> = 0% st for overall effect: Z = 1.50 (P = 0.57); l <sup>2</sup> = 0% st for overall effect: Z = 1.50 (P = 0.00)	Subtotal (95% CI)	'	63	'	61	48.6%	2.28 [0.91, 5.70]	-	
ext for overall effect: $Z = 1.77 (P = 0.08)$ total (95% CI) 184 139 100.0% 0.82 [0.34, 1.98] otal (95% CI) 184 46 tetrogenerity: Tut <sup>2</sup> = 0.70; Ch <sup>2</sup> = 13.02, df = 6 (P = 0.04); f = 54% tst for suburous differences: 0.06; df = 1 (P = 0.01); f = 90.1% tst for suburous differences: 0.06; df = 1 (P = 0.01); f = 90.1% tst for suburous differences: 0.06; df = 1 (P = 0.01); f = 90.1% tst for suburous differences: 0.06; df = 1 (P = 0.01); f = 0.1% tst for suburous differences: 0.06; df = 1 (P = 0.01); f = 0.1% tst for suburous differences: 0.06; df = 1 (P = 0.01); f = 0.01% case-control study hurd-su kwon 2013 8 31 2 25 2.4% 4.00 (0.7.7, 2091] dolC 2apablanca: 1997 0 4 6 31 2.3% 0.44 (0.02, 9.17] Hammer 2007 7 1 18 7 19 2.2% 3.00 (0.64, 14.02] and careants 18 18 teterogeneral effect: Z = 1.80 (P = 0.07); f = 0% est for overall effect: Z = 1.80 (P = 0.07); f = 0% est for overall effect: Z = 1.80 (P = 0.07); f = 0% est for overall effect: Z = 1.80 (P = 0.07); f = 0% est for overall effect: Z = 1.80 (P = 0.07); f = 0% est for overall effect: Z = 1.80 (P = 0.07); f = 0% est for overall effect: Z = 1.80 (P = 0.07); f = 0% est for overall effect: Z = 1.80 (P = 0.07); f = 0% est for overall effect: Z = 1.80 (P = 0.07); f = 0% est for overall effect: Z = 1.80 (P = 0.07); f = 0% est for overall effect: Z = 1.80 (P = 0.07); f = 0% est for overall effect: Z = 1.80 (P = 0.07); f = 0% est for overall effect: Z = 1.80 (P = 0.07); f = 0% est for overall effect: Z = 1.50 (P = 0.07); f = 0% est for overall effect: Z = 1.50 (P = 0.07); f = 0% est for overall effect: Z = 1.50 (P = 0.07); f = 0% est for overall effect: Z = 1.50 (P = 0.07); f = 0% est for overall effect: Z = 1.50 (P = 0.07); f = 0% est for overall effect: Z = 1.50 (P = 0.07); f = 0% est for overall effect: Z = 1.50 (P = 0.07); f = 0% est for overall effect: Z = 1.50 (P = 0.07); f = 0% est for overall effect: Z = 1.50 (P = 0.07); f = 0% est for overall effect: Z = 1.50 (P = 0.07); f = 0% est for overal effect: Z = 1.50 (P = 0.07); f	Fotal events	21	D. (F	13				-	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $			- 5 (P = 0	.01); 1' = 0%					
total events $48 = 46$ terrogenetity: Tube 2.07: Ch <sup>-1</sup> = 10.03. df = 6 [P 0.04]; lf = 54% test for overall efferct: Z = 0.44 (P = 0.66) tube 2.00.04 (P = 0.67); lf = 0.00 Case-control tube 2.00.04 (P = 0.00); lf = 90.01% tube 2.00.07, 20.91] tube 2.00.04 (P = 0.01); lf = 90.01% tube 2.00.04 (P = 0.00, P = 0.01); lf = 90.01% tube 2.00.04 (P = 0.01); lf = 2.00, df = 1 (P = 0.01); lf = 2.00, df = 1 (P = 0.01); lf = 0.00, df = 1 (P = 0.01); lf = 0.00, df = 1 (P = 0.01); lf = 0.00, df = 1 (P = 0.01); lf = 0.00, df = 1 (P = 0.01); lf = 0.00, df = 1 (P = 0.01); lf = 0.00, df = 1 (P = 0.01); lf = 0.00, df = 1 (P = 0.01); lf = 0.00, df = 1 (P = 0.01); lf = 0.00, df = 1 (P = 0.01); lf = 0.00, df = 1 (P = 0.01); lf = 0.00, df = 1 (P = 0.01); lf = 0.00, df = 1 (P = 0.01); lf = 0.00, df = 1 (P = 0.01); lf = 0.00, df = 1 (P = 0.01); lf = 0.00, df = 1 (P = 0.01); lf = 0.00, df = 0.	Total (95% CI)		184		139	100.0%	0.82 [0.34, 1.98]	•	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Total events								
bit 07 orderal bit (2, 2 = 0.44, 2 = 0.00), bit of solution of differences: bit of solution bit of bi	reterogeneity: Tau <sup>2</sup> = 0.70; Chi <sup>2</sup>	= 13.02, df	= 6 (P =	0.04); l <sup>2</sup> = 5	4%			0.001 0.1 1 10 1000	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		$hi^2 = 10.08$ .	df = 1 (P	= 0.001). I <sup>2</sup>	= 90.1	%			
case-control study         hang-Sut Kvon 2013       3       12       3       15       3.0%       1.33       [0.22, 8.22]         hund-Sut Kvon 2013       8       31       2       25       2.4%       4.00       [0.02, 7, 2091]         dolo Capabilance 1997       0       4       6       31       2.3%       0.44       [0.02, 9.17]         Hammen 2007       7       11       7       19       2.8%       3.00       [0.03, 5.15]         otal events       18       18         est for overall effect: Z = 1.50 (P = 0.57); I* 2 0%         station R.Bauman 2006 (1)       3       14       6       17       6.3%       0.50 [0.10, 2.52]         Intristan R.Bauman 2006 (2)       5       13       9       16       7.4%       0.49 [0.11, 2.16]         Aristan R.Bauman 2006 (2)       3       14       6       17       6.3%       0.50 [0.02, 1.109]       100         Aristan R.Bauman 2006 (2)       3       14       6       15       6.4%       100       100       100       100       100       100       11       10       100       100       100		hemoside	rin (-)	hemosideri	n (+)				
heng Huang 2013 3 12 3 15 3.0% 1.33 [0.22, 822] hundro 5u Kovo 7013 8 31 2 25 2.4% 4.00 (0.77, 20.91] abo Cappabianca 1997 0 4 6 31 2.3% 0.44 [0.02, 9.17] bub total (95% C) 58 90 10.5% 2.19 [0.05%, 5.15] colar study hristian R. Bauman 2006 (1) 3 14 6 17 6.3% 0.50 [0.10, 2.52] hristian R. Bauman 2006 (2) 5 13 9 16 7.4% 0.49 [0.11, 2.16] hristian R. Bauman 2006 (2) 5 13 9 16 7.4% 0.50 [0.10, 2.74] hristian R. Bauman 2006 (2) 5 13 9 16 7.4% 0.49 [0.11, 2.16] hristian R. Bauman 2006 (2) 5 13 9 16 7.4% 0.50 [0.10, 2.74] hristian R. Bauman 2006 (2) 5 13 9 16 7.4% 0.49 [0.10, 2.16] hristian R. Bauman 2006 (2) 5 13 9 16 7.4% 0.50 [0.10, 2.74] hristian R. Bauman 2006 (2) 5 13 9 16 7.4% 0.50 [0.02, 1.109] bristian R. Bauman 2006 (2) 5 13 9 16 7.4% 0.50 [0.10, 2.74, 53] i Young Yeon 2009 5 31 4 23 5.7% 0.91 [0.22, 3.86] laoyu Wang 2013 (2) 17 42 13 18 16.1% 0.26 [0.08, 0.87] laoyu Wang 2013 (2) 17 42 13 18 16.1% 0.26 [0.08, 0.87] teterogeneity: Ch <sup>2</sup> = 4.81, df = 8 (P = 0.78); <sup>12</sup> = 0% stef or overall effect Z = 4.56 (P = 0.0002) total events 64 71 teterogeneity: Ch <sup>2</sup> = 4.81, df = 8 (P = 0.78); <sup>12</sup> = 0% stef or overall effect Z = 4.56 (P = 0.0002) total events 62 89 betterogeneity: Ch <sup>2</sup> = 6.73, df = 12 (P = 0.10); <sup>12</sup> = 28% betterogeneity: Ch <sup>2</sup> = 16.73, df = 12 (P = 0.01); <sup>12</sup> = 28% betterogeneity: Ch <sup>2</sup> = 16.73, df = 12 (P = 0.01); <sup>12</sup> = 28% betterogeneity: Ch <sup>2</sup> = 16.73, df = 12 (P = 0.01); <sup>12</sup> = 28% betterogeneity: Ch <sup>2</sup> = 16.73, df = 12 (P = 0.01); <sup>12</sup> = 28% betterogeneity: Ch <sup>2</sup> = 16.73, df = 12 (P = 0.01); <sup>12</sup> = 28% betterogeneity: Ch <sup>2</sup> = 16.73, df = 12 (P = 0.01); <sup>12</sup> = 28% betterogeneity: Ch <sup>2</sup> = 16.73, df = 12 (P = 0.01); <sup>12</sup> = 28% betterogeneity: Ch <sup>2</sup> = 16.73, df = 12 (P = 0.01); <sup>12</sup> = 28% betterogeneity: Ch <sup>2</sup> = 16.73, df = 12 (P = 0.01); <sup>12</sup> = 28% betterogeneity: Ch <sup>2</sup> = 16.73, df = 12 (P = 0.01); <sup>12</sup> = 28% betterogeneity: Ch <sup>2</sup> = 16.73, df = 12 (P = 0.01); <sup>12</sup> = 28% betterogeneity: Ch <sup>2</sup> = 16.73, df = 12 (P = 0.01); <sup>13</sup> = 28% betterogeneity: Ch <sup>2</sup> = 16.	Study or Subgroup	Events	Total	Events	Fotal	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		3	12	3	15	3.0≅	1.33 [0.22 8.22]		
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Churl-Su Kwon 2013					2.4%	4.00 [0.77, 20.91]	+	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Paolo Cappabianca 1997	0	4	6	31	2.3%	0.44 [0.02, 9.17]		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	F. Hammen 2007	7		7			3.00 [0.64, 14.02]		
tetrogenetity: Ch <sup>2</sup> = 2.03, df = 3 (P = 0.57); l <sup>2</sup> = 0% est for overall effect: Z = 1.80 (P = 0.07) cohort study hristian R. Bauman 2006 (1) 3 14 6 17 6.3% 0.50 [0.10, 2.52] hristian R. Bauman 2006 (3) 3 14 6 11 7.2% 0.32 [0.06, 1.710] hristian R. Bauman 2006 (3) 3 14 6 11 7.2% 0.32 [0.06, 1.710] Legendris 1992 2014 4 28 5 38 5.4% 1.10 [0.27, 4.53] L'Young Youn 2009 5 31 4 23 5.7% 0.91 [0.27, 4.53] L'Young Youn 2009 5 31 4 23 5.7% 0.91 [0.27, 4.53] haoyu Wang 2013 (1) 22 86 21 46 30.3% 0.41 [0.19, 0.87] haoyu Wang 2013 (2) 17 42 13 18 16.1% 0.26 [0.08, 0.87] haoyu Wang 2013 (2) 258 71 88 89.5% 0.44 [0.28, 0.68] ubtotal (95% Cf) 3 216 278 100.0% 0.62 [0.42, 0.91] eterogenetity: Ch <sup>2</sup> = 6.78, df = 8 (P = 0.78); l <sup>2</sup> = 0% stef or overall effect: Z = 4.5 (P = 0.0002) oral (95% Cf) 3 16 278 100.0% 0.62 [0.42, 0.91] oral events 8 89 heterogenetity: Ch <sup>2</sup> = 16.73, df = 12 (P = 0.10); l <sup>2</sup> = 28% stef or overall effect: Z = 4.5 (P = 0.01)		1.8	58	1.8	90	10.5%	2.19 [0.93, 5.15]	-	
exit for overall effect: Z = 1.80 (P = 0.07) cohort study hristian R. Bauman 2006 (1) 3 14 6 17 6.3% 0.50 [0.10, 2.52] hristian R. Bauman 2006 (2) 5 13 9 16 7.4% 0.49 [0.11, 2.16] hristian R. Bauman 2006 (3) 3 14 6 13 7.3% 0.32 [0.06, 1.71] hristian R. Bauman 2006 (3) 3 14 6 13 7.3% 0.32 [0.06, 1.71] hristian R. Bauman 2006 (3) 3 14 2 3 5.7% 0.91 [0.27, 4.53] Young Yeon 2009 5 31 4 23 5.7% 0.91 [0.27, 4.53] Young Yeon 2009 5 31 4 23 5.7% 0.91 [0.27, 4.53] hory Wang 2013 (1) 22 66 21 46 30.3% 0.41 [0.19, 0.87] hory Wang 2013 (2) 17 42 13 18 16.1% 0.26 [0.08, 0.87] hory Wang 2013 (2) 2 56 128 89.5% 0.44 [0.28, 0.68] otal events 6 4 71 terrogeneity: Chi' = 4.81, df = 6 (7.78); <sup>12</sup> 0.2% est for overall effect: Z = 3.69 (P = 0.002) otal events 6 2 89 tetrogeneity: Chi' = 16.73, df = 12 (P = 0.16); <sup>12</sup> = 28% est for overall effect: Z = -3.69 (P = 0.01) Double terrogeneity: Chi' = 16.73, df = 12 (P = 0.16); <sup>12</sup> = 28%	Heterogeneity: Chi <sup>2</sup> = 2.03, df =	3 (P = 0.57	); I <sup>2</sup> = 0%						
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$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Christian R. Baumann 2006 (1)		1.2	9					
$\begin{array}{c} 2 \operatorname{eva}(\operatorname{ard}(s) 1996 & 4 & 28 & 5 & 38 & 5.4\% & 1.10 \left[0.27, 4.53\right] \\ \operatorname{isony} \operatorname{Wang} 2013 (0) & 22 & 86 & 21 & 46 & 30.3\% & 0.41 \left[0.19, 0.87\right] \\ \operatorname{isony} \operatorname{Wang} 2013 (2) & 17 & 42 & 18 & 16.1\% & 0.26 \left[0.08, 0.87\right] \\ \operatorname{ichao} \operatorname{in} 2014 & 2 & 21 & 6 & 15 & 9.4\% & 0.16 \left[0.03, 0.94\right] \\ \operatorname{wbtatal} (95\% C) & 258 & 188 & 90.5\% & 0.44 \left[0.28, 0.68\right] \\ \operatorname{exterogeneity} : \operatorname{chi}^{2} = 4.81, \operatorname{df} = 5 \left(P = 0.73\right); {}^{12} = 0\% \\ \operatorname{exterogeneity} : \operatorname{chi}^{2} = 4.81, \operatorname{df} = 5 \left(P = 0.73\right); {}^{12} = 0\% \\ \operatorname{exterogeneity} : \operatorname{chi}^{2} = 16.73, \operatorname{df} = 12 \left(P = 0.16\right); {}^{12} = 28\% \\ \operatorname{exterogeneity} : \operatorname{chi}^{2} = 16.73, \operatorname{df} = 12 \left(P = 0.16\right); {}^{12} = 28\% \\ \operatorname{exterogeneity} : \operatorname{chi}^{2} = 16.73, \operatorname{df} = 12 \left(P = 0.01\right) \\ \operatorname{voluments} & \frac{82}{1000000000000000000000000000000000000$	Christian R. Baumann 2006 (1) Christian R. Baumann 2006 (2)	5		6					
laoyu Wang 2013 (1) 22 86 21 46 30.3% 0.41 (0.19, 0.87) ichao jin 2014 2 21 6 15 9.4% 0.16 [0.08, 0.87] ichao jin 2014 2 21 6 15 9.4% 0.16 [0.03, 0.94] ubtotal (95% C) 258 188 99.5% 0.44 [0.28, 0.68] otal events 64 71 est for overall effect: Z = 3.69 (P = 0.0002) otal events 82 89 esterogeneity: Ch <sup>2</sup> = 16.73, lf = 12 (P = 0.16); l <sup>2</sup> = 28% 89 100 use to for overall effect: Z = 2.45 (P = 0.01); l <sup>2</sup> = 28% 100 use to for overall effect: Z = 2.45 (P = 0.01); l <sup>2</sup> = 28% 100 use to for overall effect: Z = 2.45 (P = 0.01); l <sup>2</sup> = 28%	Christian R. Baumann 2006 (1) Christian R. Baumann 2006 (2) Christian R. Baumann 2006 (3) Christian von der Brelie 2014	5	14			1.6%	0.50 [0.02, 11.09]		
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Christian R. Baumann 2006 (1) Christian R. Baumann 2006 (2) Christian R. Baumann 2006 (3) Christian von der Brelie 2014 D. Zevgaridis 1996	5 3 3 4	14 9 28	1 5	2 38	5.4%	1.10 [0.27, 4.53]		
$\begin{array}{c chao   n 2014 \\ botcal (95% C) \\ ctal events \\ ctal $	Christian R. Baumann 2006 (1) Christian R. Baumann 2006 (2) Christian R. Baumann 2006 (3) Christian von der Brelie 2014 O. Zevgaridis 1996 e Young Yeon 2009	5 3 4 5	14 9 28 31	1 5 4	2 38 23	5.4% 5.7%	1.10 [0.27, 4.53] 0.91 [0.22, 3.86]		
ubtotal (95% C) 258 188 89.5% 0.44 [0.28, 0.68] 64 71 teterogeneity: Ch <sup>2</sup> = 4.81, df = 5 (P = 0.78); t <sup>2</sup> = 0% est for overall effect: 2 = 3.69 (P = 0.0002) otal (95% CI) 316 278 100.0% 0.62 [0.42, 0.91] 0.001 0.1 1 10 0.001 0.1 1 10 0.001 0.1 1 10 0.001 0.1 1 10 0.001 0.01 100 Exycurs hemosidering (4)	Christian R. Baumann 2006 (1) Christian R. Baumann 2006 (2) Christian R. Baumann 2006 (3) Christian von der Brelie 2014 2. Zevgaridis 1996 e Young Yeon 2009 (iaoyu Wang 2013 (1)	5 3 4 5 22	14 9 28 31 86	1 5 4 21	2 38 23 46	5.4% 5.7% 30.3%	1.10 [0.27, 4.53] 0.91 [0.22, 3.86] 0.41 [0.19, 0.87]		
$\frac{1000}{1000} \frac{1000}{1000} $	Christian R. Baumann 2006 (1) Christian R. Baumann 2006 (2) Christian R. Baumann 2006 (2) Christian R. Baumann 2006 (2) Christian von der Brelie 2014 J. Zevgaridis 1996 e Young Yeon 2009 Giaoyu Wang 2013 (1) Giaoyu Wang 2013 (2) (chao Jin 2014	5 3 4 5 22 17	14 9 28 31 86 42 21	1 5 4 21 13	2 38 23 46 18 15	5.4% 5.7% 30.3% 16.1% 9.4%	1.10 [0.27, 4.53] 0.91 [0.22, 3.86] 0.41 [0.19, 0.87] 0.26 [0.08, 0.87] 0.16 [0.03, 0.94]		
est for overall effect: Z = 3.69 (P = 0.0002) otal (95% Cl) 316 278 100.0% 0.62 [0.42, 0.91] eterogeneity: Ch <sup>2</sup> = 16.73, dF = 12 (P = 0.16); l <sup>2</sup> = 28% est for overall effect: Z = 2.45 (P = 0.01) 0.001 Envours hemosiderin (L) Exours hemosiderin (L)	Christian R. Baumann 2006 (1) Christian R. Baumann 2006 (2) Christian R. Baumann 2006 (3) Christian von der Brelie 2014 ). Zevgardiß 1996 e Young Yeon 2009 Giaoyu Wang 2013 (1) Giaoyu Wang 2013 (2) (ichao Jin 2014 Libotoat (95% CI)	5 3 4 5 22 17 2	14 9 28 31 86 42 21	1 5 4 21 13 6	2 38 23 46 18 15	5.4% 5.7% 30.3% 16.1% 9.4%	1.10 [0.27, 4.53] 0.91 [0.22, 3.86] 0.41 [0.19, 0.87] 0.26 [0.08, 0.87] 0.16 [0.03, 0.94]		
otal (95% CI) 316 278 100.0% 0.62 [0.42, 0.91] otal events 82 89 deterogeneity: Ch <sup>2</sup> = 16.73, df = 12 (P = 0.16); l <sup>2</sup> = 28% to row rail effect: 2 = 2.45 (P = 0.01) 0.001 i 100 Exorum: hempositerin (-) Exorum: hempo	Christian R. Baumann 2006 (1) Christian R. Baumann 2006 (2) Christian R. Baumann 2006 (3) Christian von der Breile 2014 D. Zevgardist 1996 e Young Yeon 2009 tiaoyu Wang 2013 (1) tiaoyu Wang 2013 (2) richao jin 2014 Jubtotal (95% C1) Otal events	5 3 4 5 22 17 2 64	14 9 28 31 86 42 21 258	1 5 4 21 13 6 71	2 38 23 46 18 15	5.4% 5.7% 30.3% 16.1% 9.4%	1.10 [0.27, 4.53] 0.91 [0.22, 3.86] 0.41 [0.19, 0.87] 0.26 [0.08, 0.87] 0.16 [0.03, 0.94]		
otal events \$2 89 eterogeneity: Chi <sup>2</sup> = 16.73, df = 12 (P = 0.16); l <sup>2</sup> = 28% 0.001 0.1 1 0 Exposure hemosiderin (-1) Expose hemosiderin (-1) 00 Expose hemosiderin (-1) Expose hemosiderin (-1) 00 Expose hemosiderin (-1)	Lhristian R. Baumann 2006 (1) Christian R. Baumann 2006 (2) Lhristian R. Baumann 2006 (2) Lhristian N. Baumann 2006 (2) Lorgaridis 1996 e Young Yeon 2009 (aoyu Wang 2013 (1) (aoyu Wang 2013 (2) (chao Jin 2014 Jubotal (95% C1) Total events deterogeneity: Chi <sup>2</sup> = 4.81, df =	5 3 4 5 22 17 2 64 8 (P = 0.78	14 9 28 31 86 42 21 258 ); $I^2 = 0\%$	1 5 4 21 13 6 71	2 38 23 46 18 15	5.4% 5.7% 30.3% 16.1% 9.4%	1.10 [0.27, 4.53] 0.91 [0.22, 3.86] 0.41 [0.19, 0.87] 0.26 [0.08, 0.87] 0.16 [0.03, 0.94]		
tererogeneity: Chi <sup>2</sup> = 16.73, df = 12 (P = 0.16); l <sup>2</sup> = 28% est for overall effect: Z = 2.45 (P = 0.01) Favours bemosiderin (+)	Lhristian R. Baumann 2006 (1) Lhristian R. Baumann 2006 (3) Lhristian R. Baumann 2006 (3) Lhristian on der Breile 2014 J. Zevgaridis 1996 e Young Yeon 2009 Giaoyu Wang 2013 (1) Giaoyu Wang 2013 (2) Circhao Jin 2014 Lubtotal (95% C1) Total events deterogeneity: Chi <sup>2</sup> = 4.81, df = fest for overall effect: Z = 3.69 i	5 3 4 5 22 17 2 64 8 (P = 0.78	14 9 28 31 86 42 21 258 ); $I^2 = 0\%$	1 5 4 21 13 6 71	2 38 23 46 18 15 <b>188</b>	5.4% 5.7% 30.3% 16.1% 9.4% <b>89.5</b> %	1.10 [0.27, 4.53] 0.91 [0.22, 3.86] 0.41 [0.19, 0.87] 0.26 [0.08, 0.87] 0.16 [0.03, 0.94] 0.44 [0.28, 0.68]		
est for overall effect: $Z = 2.45$ (P = 0.01) Eavours hemosiderin (+)	Christian R. Baumann 2006 (1) Christian R. Baumann 2006 (3) Christian R. Baumann 2006 (3) Christian on der Breile 2014 J. Zevgardis 1.996 e Young Yeon 2009 Gaoyu Wang 2013 (1) Giaoyu Wang 2013 (2) Tichao Jin 2014 Lubtotal (95% C1) O'ral events deterogeneity: Chi <sup>2</sup> = 4.81, df = fest for overall effect: Z = 3.69 i Total (95% C1) Total events	5 3 4 5 22 17 2 64 64 64 (P = 0.78 (P = 0.0002 82	14 9 28 31 86 42 21 258 316	1 5 4 21 13 6 71	2 38 23 46 18 15 <b>188</b>	5.4% 5.7% 30.3% 16.1% 9.4% <b>89.5</b> %	1.10 [0.27, 4.53] 0.91 [0.22, 3.86] 0.41 [0.19, 0.87] 0.26 [0.08, 0.87] 0.16 [0.03, 0.94] 0.44 [0.28, 0.68]	• •	
	Christian R. Baumann 2006 (1) Christian R. Baumann 2006 (3) Christian R. Baumann 2006 (3) Christian von der Breile 2014 J. Zevgardis 1996 Voung Yeon 2009 Gaoyu Wang 2013 (1) Gaoyu Wang 2013 (2) Critao Jin 2014 Universal (95% Ct) Vetal (95% Ct) Ctal (95% Ct) Total events teterogeneity: Chi <sup>2</sup> = 16.73, df	5 = 3 = 3 = 3 = 3 = 3 = 3 = 3 = 3 = 3 =	14 9 28 31 86 42 21 258 316	1 5 4 21 13 6 71	2 38 23 46 18 15 <b>188</b>	5.4% 5.7% 30.3% 16.1% 9.4% <b>89.5</b> %	1.10 [0.27, 4.53] 0.91 [0.22, 3.86] 0.41 [0.19, 0.87] 0.26 [0.08, 0.87] 0.16 [0.03, 0.94] 0.44 [0.28, 0.68]		

Fig 5. Forest plot comparing seizure outcomes between hemosiderin (+) and hemosiderin (-) groups in country, female ratio, occurrence of multiple CCMs and study design subgroup analyses. hemosiderin (-), with hemosiderin excision; hemosiderin (+), without hemosiderin excision; CI, confidence interval.



	hemoside		hemoside		Woight	Odds Ratio	Odds Ratio
Study or Subgroup duration before surgery<	Events 1v	Total	Events	TOTAL	weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Paolo Cappabianca 1997	-, 0	4	6	31	4.7%	0.44 [0.02, 9.17]	
(ichao Jin 2014	2	21	6	15		0.16 [0.03, 0.94]	
Subtotal (95% CI)	2	25	0	46		0.21 [0.04, 1.04]	
Fotal events	2		12				
Heterogeneity: $Chi^2 = 0.32$ , df = Fest for overall effect: Z = 1.92 (I	1 (P = 0.57)	); $I^2 = 0\%$					
duration before surgery>							
Christian R. Baumann 2006 (1)	3	14	6	17		0.50 [0.10, 2.52]	
Christian von der Brelie 2014	3	9	1	2		0.50 [0.02, 11.09]	
(iaoyu Wang 2013 (1)	22	86	21	46		0.41 [0.19, 0.87]	
ubtotal (95% CI)		109		65	76.5%	0.43 [0.22, 0.841	-
otal events	28	7	28				
leterogeneity: Chi <sup>2</sup> = 0.06, df = Test for overall effect: Z = 2.48 (I		); $1^2 = 0\%$	ó				
otal (95% CI)		134		111	100.0%	0.38 [0.21, 0.69]	•
otal events	30		40				
Heterogeneity: $Chi^2 = 1.11$ , df =	4 (P = 0.89)	); $I^2 = 0\%$	6				
est for overall effect: Z = 3.13 (I	P = 0.002)						0.001 0.1 İ İ0 10 Favours hemosiderin (-) Favours hemosiderin (+)
est for subgroup differences: Ch	$hi^2 = 0.63, d$						
	hemosider		hemosider			Odds Ratio	Odds Ratio
itudy or Subgroup	Events	Total	Events	Total	Weight N	I-H, Random, 95% CI	M-H, Random, 95% Cl
size of lesion<2cm							
Christian R. Baumann 2006 (1)	3	14	6	17	22.5%	0.50 [0.10, 2.52]	
Churl-Su Kwon 2013	8	31	2	25	22.1%	4.00 [0.77, 20.91]	+
ichao Jin 2014	2	21	6	15	20.5%	0.16 [0.03, 0.94]	
ubtotal (95% CI)		66		57	65.1%	0.69 [0.11, 4.36]	
Total events leterogeneity: Tau <sup>2</sup> = 1.89; Chi <sup>2</sup> Test for overall effect: Z = 0.39 (P		= 2 (P = C	14 0.03); I <sup>2</sup> = 7	72%			
size of lesion>2cm (iaoyu Wang 2013 (1)	22	86	21	46	34.9%	0.41 [0.19, 0.87]	
Subtotal (95% CI)	22	86	21	40	34.9% 34.9%	0.41 [0.19, 0.87]	<b>.</b>
otal events	22		21			- / -	•
leterogeneity: Not applicable Test for overall effect: Z = 2.32 (P							
Fotal (95% CI)		152		103	100.0%	0.58 [0.19, 1.82]	
<b>Total (95% CI)</b> Total events	35 8 02 df		35		100.0%	0.58 [0.19, 1.82]	
Fotal events Heterogeneity: Tau <sup>2</sup> = 0.82; Chi <sup>2</sup> Fest for overall effect: Z = 0.93 (P	= 8.02, df = P = 0.35)	= 3 (P = 0	$(0.05); I^2 = 6$	53%	100.0%	0.58 [0.19, 1.82]	0.001 0.1 1 10 100 Favours hemosiderin (-) Favours hemosiderin (+)
Fotal events Heterogeneity: Tau <sup>2</sup> = 0.82; Chi <sup>2</sup> Fest for overall effect: Z = 0.93 (P Fest for subgroup differences: Ch	= 8.02, df = P = 0.35)	= 3 (P = 0) f = 1 (P = 0)	$(0.05); I^2 = 6$	53% = 0% in (+)		0.58 [0.19, 1.82] Odds Ratio 4-H, Random, 95% CI	0.001 0.1 1 10 100 Favours hemosiderin (-) Favours hemosiderin (+) Odds Ratio
Fotal events Heterogeneity: Tau <sup>2</sup> = 0.82; Chi <sup>2</sup> Fest for overall effect: Z = 0.93 (P Fest for subgroup differences: Ch	= 8.02, df = <sup>2</sup> = 0.35) ii <sup>2</sup> = 0.27, d hemosider Events	= 3 (P = 0 f = 1 (P = in (-)	0.05); l <sup>2</sup> = 6 = 0.60), l <sup>2</sup> = hemosider	53% = 0% in (+)		Odds Ratio	0.001 0.1 1 10 100 Favours hemosiderin (-) Favours hemosiderin (+) Odds Ratio
Fotal events Heterogeneity: Tau <sup>2</sup> = 0.82; Chi <sup>2</sup> Fest for overall effect: Z = 0.93 (P Fest for subgroup differences: Ch Study or Subgroup	= 8.02, df = <sup>2</sup> = 0.35) ii <sup>2</sup> = 0.27, d hemosider Events	= 3 (P = 0 f = 1 (P = in (-)	0.05); l <sup>2</sup> = 6 = 0.60), l <sup>2</sup> = hemosider	53% = 0% in (+)		Odds Ratio	0.001 0.1 i 10 10 Favours hemosiderin () Favours hemosiderin (+) Odds Ratio M-H, Random, 95% Cl
otal events leterogeneity: Tau <sup>2</sup> = 0.82; Chi <sup>2</sup> iest for overall effect: Z = 0.93 (P est for subgroup differences: Ch tudy or Subgroup follow-up duration<3 y Cheng Huang 2013	= 8.02, df = P = 0.35) $ii^2 = 0.27$ , d hemosideri Events rears 3 3	= 3 (P = 0 f = 1 (P = in (-) I Total	0.05); l <sup>2</sup> = 6 = 0.60), l <sup>2</sup> = hemosider Events	53% = 0% in (+) Total	Weight 1	Odds Ratio 1-H, Random, 95% Cl	0.001 0.1 i 10 10 Favours hemosiderin (-) Favours hemosiderin (+) Odds Ratio M-H, Random, 95% Cl
otal events leterogeneity: Tau <sup>2</sup> = 0.82; Chi <sup>2</sup> jest for overall effect: Z = 0.93 (P eest for subgroup differences: Ch tudy or Subgroup follow-up duration<3 y icheng Huang 2013 ichristian R. Baumann 2006 (1) ichristian R. Baumann 2006 (2)	= 8.02, df = P = 0.35) ii <sup>2</sup> = 0.27, d hemosideri Events rears 3 3 5	= 3 (P = 0 f = 1 (P = in (-) I Total	0.05);   <sup>2</sup> = 6 = 0.60),   <sup>2</sup> = hemosider <u>Events</u> 3	53% = 0% in (+) Total 15	Weight 1 6.0%	Odds Ratio M-H, Random, 95% CI 1.33 [0.22, 8.22]	0.001 0.1 i 10 10 Favours hemosiderin (-) Favours hemosiderin (+) Odds Ratio M-H, Random, 95% Cl
otal events leterogeneity: Tau <sup>2</sup> = 0.82; Chi <sup>2</sup> 'est for overall effect: Z = 0.93 (P 'est for subgroup differences: Ch <b>tudy or Subgroup</b> follow-up duration<3 y Cheng Huang 2013 Christian R. Baumann 2006 (1) Christian R. Baumann 2006 (2) e Young Yeon 2009	= 8.02, df = P = 0.35) i <sup>2</sup> = 0.27, d hemosideri Events rears 3 3 5 5	= 3 (P = 0 f = 1 (P = in (-) I Total 12 14 13 31	0.05); l <sup>2</sup> = 6 = 0.60), l <sup>2</sup> = hemosider <u>Events</u> 3 6 9 4	53% = 0% in (+) Total 15 17 16 23	Weight M 6.0% 7.2% 8.2% 8.6%	Odds Ratio <i>A</i> -H, Random, 95% Cl 1.33 [0.22, 8.22] 0.50 [0.10, 2.52] 0.49 [0.11, 2.16] 0.91 [0.22, 3.86]	0.001 0.1 1 10 10 Favours hemosiderin (-) Favours hemosiderin (+) Odds Ratio M-H, Random, 95% Cl
otal events leterogeneity: Tau <sup>2</sup> = 0.82; Chi <sup>2</sup> iest for overall effect: Z = 0.93 (P iest for subgroup differences: Ch tudy or Subgroup follow-up duration<3 y cheng Huang 2013 christian R. Baumann 2006 (1) christian R. Baumann 2006 (2) a Young Yeon 2009 aolo Cappabianca 1997	= 8.02, df = P = 0.35) i <sup>2</sup> = 0.27, d hemosideri Events 3 5 5 0	f = 3 (P = 0) $f = 1 (P = 0)$ $Total$ $12$ $14$ $13$ $31$ $4$	0.05); l <sup>2</sup> = 6 = 0.60), l <sup>2</sup> = hemosider <u>Events</u> 3 6 9 4 6	53% = 0% in (+) Total 15 17 16 23 31	Weight M 6.0% 7.2% 8.2% 8.6% 2.5%	Odds Ratio A-H, Random, 95% Cl 1.33 [0.22, 8.22] 0.50 [0.10, 2.52] 0.49 [0.11, 2.16] 0.91 [0.22, 3.86] 0.44 [0.02, 9.17]	0.001 0.1 1 10 10 Favours hemosiderin (-) Favours hemosiderin (+) Odds Ratio M-H, Random, 95% Cl
Total events leterogeneity: Tau <sup>2</sup> = 0.82; Chi <sup>2</sup> Test for overall effect: Z = 0.93 (P Test for subgroup differences: Ch litudy or Subgroup follow-up duration<3 y Cheng Huang 2013 Christian R. Baumann 2006 (1) Christian R. Baumann 2006 (2) e Young Yeon 2009 Taolo Cappabianca 1997 (iaoyu Wang 2013 (1)	= 8.02, df =	= 3 (P = C f = 1 (P = in (-) I Total 12 14 13 31 4 86	0.05); I <sup>2</sup> = 6 = 0.60), I <sup>2</sup> = hemosider <u>Events</u> 3 6 9 4 6 21	53% = 0% in (+) Total 15 17 16 23 31 46	Weight M 6.0% 7.2% 8.2% 8.6% 2.5% 17.5%	Odds Ratio 1-H, Random, 95% CI 1.33 [0.22, 8.22] 0.50 [0.10, 2.52] 0.49 [0.11, 2.16] 0.91 [0.22, 3.86] 0.44 [0.02, 9.17] 0.41 [0.19, 0.87]	0.001 0.1 1 10 10 Favours hemosiderin (-) Favours hemosiderin (+) Odds Ratio M-H, Random, 95% Cl
Total events leterogeneity: Tau <sup>2</sup> = 0.82; Chi <sup>2</sup> Test for overall effect: Z = 0.93 (P rest for subgroup differences: Ch <b>itudy or Subgroup</b> <b>follow-up duration&lt;3 y</b> Cheng Huang 2013 Christian R. Baumann 2006 (1) Christian R. Baumann 2006 (2) e Young Yeon 2009 Paolo Cappabianca 1997 Giaoyu Wang 2013 (1) Tichao Jin 2014	= 8.02, df = P = 0.35) i <sup>2</sup> = 0.27, d hemosideri Events 3 5 5 0	= 3 (P = C f = 1 (P = in (-) I Total 12 14 13 31 4 86 21	0.05); l <sup>2</sup> = 6 = 0.60), l <sup>2</sup> = hemosider <u>Events</u> 3 6 9 4 6	53% = 0% in (+) Total 15 17 16 23 31 46 15	Weight 1 6.0% 7.2% 8.2% 8.6% 2.5% 17.5% 6.2%	Odds Ratio A-H, Random, 95% Cl 1.33 [0.22, 8.22] 0.49 [0.10, 2.52] 0.49 [0.11, 2.16] 0.91 [0.22, 3.86] 0.44 [0.02, 9.17] 0.16 [0.03, 0.94] 0.16 [0.03, 0.94]	0.001 0.1 1 10 10 Favours hemosiderin (-) Favours hemosiderin (+) Odds Ratio M-H, Random, 95% Cl
otal events leterogeneity: Tau <sup>2</sup> = 0.82; Chi <sup>2</sup> iest for overall effect: Z = 0.93 (P iest for subgroup differences: Ch <b>tudy or Subgroup</b> <b>follow-up duration&lt;3 y</b> cheng Huang 2013 christian R. Baumann 2006 (1) christian R. Baumann 2006 (2) a Young Yeon 2009 aolo Cappabianca 1997 iaoyu Wang 2013 (1) ichao Jin 2014 <b>ubtotal (95% CI)</b>	= 8.02, df = 2 = 0.35) i <sup>2</sup> = 0.27, d hemosider Events rears 3 5 5 0 22 2	= 3 (P = C f = 1 (P = in (-) I Total 12 14 13 31 4 86	0.05);   <sup>2</sup> = 6 = 0.60),   <sup>2</sup> = hemosider Events 3 6 9 4 6 21 6	53% = 0% in (+) Total 15 17 16 23 31 46	Weight M 6.0% 7.2% 8.2% 8.6% 2.5% 17.5%	Odds Ratio 1-H, Random, 95% CI 1.33 [0.22, 8.22] 0.50 [0.10, 2.52] 0.49 [0.11, 2.16] 0.91 [0.22, 3.86] 0.44 [0.02, 9.17] 0.41 [0.19, 0.87]	0.001 0.1 1 10 10 Favours hemosiderin (-) Favours hemosiderin (+) Odds Ratio M-H, Random, 95% Cl
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Fotal events deterogeneity: Tau <sup>2</sup> = 0.82; Chi <sup>2</sup> Frest for overall effect: Z = 0.93 (P Fest for subgroup differences: Ch itudy or Subgroup follow-up duration<3 y Cheng Huang 2013 Christian R. Baumann 2006 (1) Christian R. Baumann 2006 (2) e Young Yeon 2009 Paolo Cappabianca 1997 (iaoyu Wang 2013 (1) (ichao Jin 2014 Subtotal (95% CI) Fotal events Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> Follow-up duration>3 y Christian R. Baumann 2006 (3) Christian von der Brelie 2014 Churl-Su Kwon 2013 D. Zevgaridis 1996 F. Hammen 2007 (iaoyu Wang 2013 (2) Subtotal (95% CI) Fotal events Heterogeneity: Tau <sup>2</sup> = 0.83; Chi <sup>2</sup>	= 8.02, df = = 0.35) i <sup>2</sup> = 0.27, d hemosider Events ears 40 = 3.64, df = 0 = 0.005) rears 40 = 11.20, df = 0.87) = 0.87) = 22 22 40 = 0.005)	= 3 (P = C) $ f = 1 (P = C) $ $ f = 1 (P = C) $ $ 12 $ $ 14 $ $ 4 $ $ 86 $ $ 21 $ $ 181 $ $ = 6 (P = C) $ $ 14 $ $ 9 $ $ 31 $ $ 28 $ $ 11 $ $ 28 $ $ 11 $ $ 28 $ $ 135 $ $ = 5 (P = 316 $ $ 316$	$\begin{array}{llllllllllllllllllllllllllllllllllll$	33% = 0% in (+) Total 15 16 23 31 6 23 31 16 30% 13 25 38 19 18 115 555% 278	Weight 1 6.0% 7.2% 8.2% 8.6% 2.5% 17.5% 6.2% 56.2% 6.9% 2.4% 7.0% 8.8% 7.8% 10.9% 43.8%	Odds Ratio A-H, Random, 95% Cl 1.33 [0.22, 8.22] 0.50 [0.10, 2.52] 0.49 [0.11, 2.16] 0.91 [0.22, 3.86] 0.44 [0.02, 9.17] 0.16 [0.03, 0.94] 0.48 [0.29, 0.80] 0.32 [0.06, 1.71] 0.50 [0.02, 11.09] 4.00 [0.77, 20.91] 1.10 [0.27, 4.53] 3.00 [0.64, 14.02] 0.26 [0.08, 0.87] 0.92 [0.34, 2.49]	0.001 0.1 1 10 10 Favours hemosiderin (-) Favours hemosiderin (+) Odds Ratio M-H, Random, 95% Cl

Fig 6. Forest plot comparing seizure outcomes between hemosiderin (+) and hemosiderin (-) groups in duration before surgery, lesion size and follow-up duration subgroup analyses. hemosiderin (-), with hemosiderin excision; hemosiderin (+), without hemosiderin excision; CI, confidence interval.

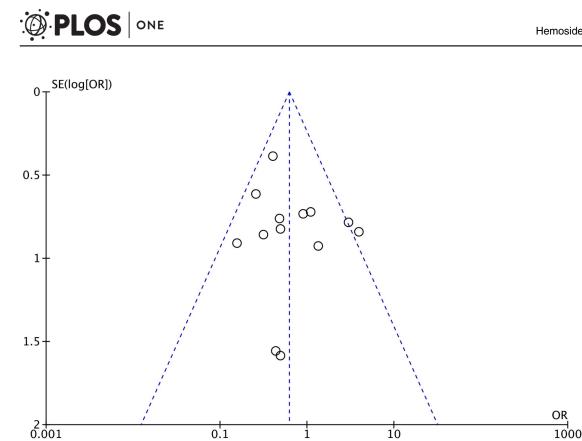


Fig 7. Funnel plot of publication bias. SE, standard error; OR, odds ratio.

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tended to report a more favorable outcome in the hemosiderin excision group, which increased the credibility of our meta-analysis result, as the cohort studies could justify or control for more confounders than case-control studies.

Patients with seizure duration before surgery > 1 year, lesion diameter > 2 cm and shortterm (< 3 years) follow-up appeared to have a more favorable outcome tendency in the hemosiderin (-) group. However, we could not easily draw a conclusion that these kinds of patients could obtain a better prognosis after hemosiderin excision, because the benefit of hemosiderin excision was not significantly different from that gained by patients with seizure duration before surgery < 1 year, lesion diameter < 2 cm and long-term (> 3 years) follow-up, respectively. Thus, larger prospective trials are necessary to determine whether seizure duration before surgery, lesion size and follow-up time are significant confounding factors.

One previous system review [4] focused on the predictors of seizure outcome in the surgical treatment of cavernous malformations where hemosiderin excision was selected as one of the predictors. This review included a total of 763 CCM patients from 1985 to 2011 and stated that extended resection of the hemosiderin ring was not significantly predictive. The difference might be caused by the following reasons. First, the statistical method was different: Englot DJ et al. [4] used regression, while we used meta-analysis, allowing us to concentrate more on specific factors. Second, in our study, half of the articles were published after 2013, and the article sample was more precise because we only chose papers related to hemosiderin excision. Third, the significant improvement in seizure outcome after hemosiderin excision might result from recent advances in neurosurgery, allowing clinical excision to be performed more accurately and less invasively.

Up to now, the detail steps of epilepsy development in CCM has not been comprehended completely. However, chronic silent microhemorrhages were thought to be the main culprit

[1, 28, 30-33]. When deposited in adjacent brain parenchyma, hemosiderin, a degradation product of blood, could produce free radicals and lipid peroxides to cause excitotoxicity of adjacent neurons and proliferation of the glial tissue by interrupting receptor activity, calcium hemostasis and neurotransmitter (glutamate, aspartate and phosphorylethanolamine) levels [11, 13, 30, 34, 35]. This mainstream hypothesis of the epileptogenicity of hemosiderin provided strong support to our results.

The shortcomings of this meta-analysis were as follows. First, the assessment methods of the complete removal of the hemosiderin ring were different between studies. Most of the included studies assessed the complete removal of the hemosiderin ring by post-operative MRI, while four studies [16, 18, 19, 26] used surgical records to determine whether hemosiderin deposits had been resected as postoperative MRI findings were not available. It was generally known that the surgical description of hemosiderin removal might differ from postoperative MRI controls, so we'd better use post-operative MRI, which could reflect hemosiderin ring excision more objectively, as the assessment criteria. Second, hemosiderin excision was only one of the factors related to seizure outcome in most studies, and only three articles [15, 17, 29] directly compare a hemosiderin excision group and a control group. Therefore, the patient baseline characteristics for the hemosiderin (+) group and hemosiderin (-) group were usually unavailable or incomplete, leading to the loss of some evidence in the subgroup analysis. Third, we only included studies using Engel I rather than Engel Ia (e.g., Stavrou I [16]) as the outcome index, which might omit some meaningful evidence. However, the Engel classification is a common clinical method in evaluating seizures. Fourth, as we searched only studies in English, some potential reports not written in English (e.g., Stefan H [36]) might have been missed. Fifth, many factors could influence the seizure state of CCM patients after operation, but we only focused on whether the excision of hemosiderin is necessary to achieve seizure freedom, which is currently uncertain. Sixth, all the data we extracted were from observational studies, as no randomized control trials (RCTs) were yet available; therefore, more convincingly designed studies are urgently needed. In summary, for a better answer to this question, a well-designed prospective multiple-center randomized control trial should be performed.

# Conclusions

This meta-analysis compared hemosiderin excision and hemosiderin reservation groups in CCM surgery and demonstrated that seizure outcome could be significantly improved in patients who undergo extended excision of the surrounding hemosiderin.

# **Supporting Information**

**S1 Checklist. PRISMA 2009 checklist.** (DOC)

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# **Author Contributions**

Conceived and designed the experiments: DR XBY. Performed the experiments: DR XBY SS. Analyzed the data: XBY. Contributed reagents/materials/analysis tools: XBY LW GC. Wrote the paper: DR XBY.

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