META-ANALYSIS

e-ISSN 1643-3750 © Med Sci Monit, 2020; 26: e924009 DOI: 10.12659/MSM.924009

Received: 20 Accepted: 20 Available online: 20 Published: 20	20.03.04 20.05.06 20.06.03 20.07.30	Outcome Centricul Aortic Ba Decompr and Meta	s of V ar (LV) Illoon ession a-Anal	A-ECM) Deco Pumpi Techr ysis	O with mpress ng (IAI liques:	and with ion Using BP) versus A System	out Left Intra- Other LV atic Review
Authors' Contr Study D Data Colle Statistical An Data Interpret Manuscript Prepar Literature S Funds Colle	ibution: ABCE 1,2 esign A CD 3 ction B B 2 alysis C D 1 ation D D 1 ation E D 1 ction G D 1	Pan Pan* Song Zhang* Peng Yan Dawei Liu Xiaoting Wang Xiang Zhou Yun Long			1 Depart Peking P.R. Chi 2 Center Army (I 3 Depart Traditio	ment of Critical Care Medicine Union Medical College and Ch ina of Pulmonary and Critical Car PLA) General Hospital, Beijing, ment of Critical Care Medicine onal Chinese Medicine, Chengo	e, Peking Union Medical College Hospital, inese Academy of Medical Sciences, Beijing e Medicine, Chinese People's Liberation P.R. China e, Hospital of Chengdu University of Ju, Sichuan, P.R. China
Corre	C 2 D 2 A 2 ACE 1	Kun Xiao Weiguo Zhao Lixin Xie Longxiang Su * Pan Pan and Song Zh Longxiang Su, e-mail: s	ang contributed ulongxiang@vip	equally to this 1.163.com, Lixin 1	study Kie, e-mail: xielx30	01@126.com	
 Ma	Background: aterial/Methods: Results:	the China National Key (NCRCG-PLAGH-201700 Left ventricular deco the effect of specific We searched for all analyses were perfor The results showed	Research Progra 03, to Lixin Xie) compression is c methods on published rep ormed using S that the risk c	m (2018ZX0920 the primary r patient outco orts conducte tata 12.0. of death with	nethod for solv method for solv mes and comp ed in patients u ECMO combine	, and the China National G ing VA-ECMO-induced lications is unknown. ndergoing ECMO com d with LVD was 29% lo	LV afterload increase, but bined with LVD. Statistical
	Conclusions	alone (OR=0.71, 95 er LV decompression statistically significa orrhage, stroke/acu (0.66–0.71), 0.82 (0 such as stroke/TIA, combined other LV IABP. ECMO combined wi	% CI: 0.56–0.8 n techniques v ant (OR=1.27, te episodes, la .78–0.89), 0.7 limb ischemia decompressio	19 , 1^2 =59.5%, <i>H</i> was higher the 95% CI: 0.86- power-limb iscl 1 (0.30–1.66) , and hemolysin techniques,	2<0.001). Althou an that with EC -1.87, l ² =44.0% nemia, and hen , and 0.48 (0.1 sis, of ECMO co , and the risk o	ugh the risk of death x MO combined with IA b, P=0.057). In addition nolysis for ECMO com 6-1.39), respectively. mbined with IABP was f bleeding was higher	with ECMO combined oth- BP, the difference was not n, the ORs values of hem- bined with LVD were 0.69 The risk of complications, s lower than that of ECMO for ECMO combined with
Ν	leSH Keywords:	Extracorporeal Me Complications • Ve	mbrane Oxyg entricular Out	genation • In	tra-Aortic Ball	oon Pumping • Mort	ality • Postoperative
	Abbreviations:	AMI – acute myoca LV – left ventricula RCTs – randomized LVEDP – left ventri oxygenation	ardial infarctio r; VADs – left I controlled tr cular end-dia	on; CVP – cen : ventricular a ials; RR – rela stolic pressu	tral venous pr assist devices; ative risk; STE re; VA-ECMO –	essure; IABP – intra-a LVD – left ventricular MI – ST-elevation myo veno-arterial extrace	aortic balloon pumping; r decompression; ocardial infarction; orporeal membrane
	Full-text PDF:	https://www.medso	cimonit.com/a	bstract/index	/idArt/924009		
認行教育		■2 3294	±±±⊇ 2	<u> </u>	2 46		

e924009-1

MEDICAL SCIENCE

MONITOR

Background

Cardiogenic shock is a clinical syndrome resulting from left, right, or biventricular dysfunction that eventually leads to circulatory failure and multiple organ dysfunction [1]. Acute myocardial infarction (AMI), especially ST-elevation myocardial infarction (STEMI), is the most common cause of cardiogenic shock. In addition, the causes of non-acute coronary syndrome can also result in cardiogenic shock [2]. Cardiogenic shock is now considered an acute and lethal disorder in the ICU. The main presentation of cardiogenic shock is hemodynamic instability, and it can even progress to refractory shock, which is associated with a mortality rate of approximately 50% [3].

In cardiogenic shock, ventricular abnormalities mainly manifest as irreversible contraction and diastolic dysfunction, leading to reduced cardiac output, increased ventricular diastolic pressure, and decreased coronary perfusion pressure. Left ventricular (LV) dysfunction and ischemia are the most common complications, elevating left atrial pressure, leading to pulmonary edema, hypoxia, pulmonary blood vessel convulsion, and worsening ischemia [4,5]. Fluids, vasopressors, and inotropes are usually used to assure cardiac output and oxygen delivery. However, the effects of treatment are often not ideal because escalating doses of vasopressors and inotropes are related to higher mortality [6,7]. Thus, mechanical circulatory support may improve the management of refractory cardiogenic shock.

Currently, the most popular and useful method for restoring cardiac function and improving cardiac output is extracorporeal membrane oxygenation (ECMO). Veno-arterial ECMO (VA-ECMO) provides cardiopulmonary support for patients whose heart and lungs are unable to survive. It is also a bridge to myocardial recovery or heart transplantation in cases of refractory cardiogenic shock [8]. Currently, VA-ECMO is widely recognized as a first-line treatment in the clinic. However, from the clinical perspective, ECMO does not improve cardiac function or promote cardiac output as much as expected. In fact, ECMO can only help cardiogenic shock patients achieve LV function but cannot improve LV function during left ventricular (LV) failure. However, VA-ECMO often increases left ventricular afterload and increases the stress on an already dysfunctional left ventricle [9,10]. This phenomenon results in retrograde aortic flow that can increase left ventricular end-diastolic pressure (LVEDP), which leads to severe pulmonary edema and increased wall stress and myocardial oxygen consumption, ultimately impairing myocardial recovery and increasing mortality. As ECMO appears to be the most appropriate way to replace cardiac function, determining how to unload the left ventricle during ECMO administration is essential.

In a recent study, researchers found that left ventricular decompression, such as ECMO combined IABP and ECMO combined other LV decompression techniques (like ventricular assist device, surgical atrial septostomy, or left ventricular drainage), might be useful in decreasing LV afterload [11,12]. The combination of ECMO and left ventricular decompression (LVD) may be a potential treatment for patients on ECMO who have LV dysfunction. However, studies have shown wide variations in clinical results regarding IABP and surgical methods during ECMO [13,14]. The combination of ECMO and LVD has been reviewed, but, to date, no study has been conducted to determine which method is best for reducing LV afterload. Therefore, we performed this systematic review and meta-analysis to assess the methodology of IABP and other left ventricular decompression methods during VA-ECMO and to evaluate the efficacy, feasibility, and safety of the combination of these methodologies.

Material and Methods

Search strategy and selection criteria

We performed a systematic review of published randomized controlled trials (RCTs), quasi-RCTs, and other comparative studies performed in patients undergoing ECMO plus left ventricular decompression. We defined left ventricular decompression as mechanical support including intra-aortic balloon pumping (IABP) and other left ventricular decompression methods, including left ventricular assist devices (VADs) and surgical methods such as surgical atrial septostomy and left ventricular drainage.

We searched the following medical bibliographical databases: PubMed, EMBASE, Web of Knowledge, and the Cochrane Library. We also searched trial registries for ongoing trials. We used text words and MeSH headings containing "VA-extracorporeal membrane oxygenation", "mechanical support", "intra-aortic balloon pumping", "left ventricular assist devices", "atrial septostomy", "left ventricular drainage", "cardiogenic shock", "left ventricular distension", "left ventricular vent", and "left ventricular unloading" in the search. The PubMed search strategy is presented in Figure 1.

Reviews, commentaries, letters, correspondences, conference abstracts, case reports, expert opinions, editorials, and animal experiments were excluded. Articles involving pediatric patients were excluded. Three investigators (PP, PY, and KX) independently performed the search and selection of the articles. Any disagreement was resolved by a third party (DL, XZ, XW, LY, and WZ). The date range for the search was from the date of the first references available to May 31, 2019.

Data extraction and group comparisons

The following data were extracted for each trial: the author, year of publication, study type, study population and number,



Figure 1. Process for the identification of the included studies.

technical parameters, indicators of ECMO, main outcomes, and complications. The primary outcome was hospital mortality, and the secondary outcome was the incidence of complications. We tried to contact the corresponding author(s) if the data were not presented or needed clarification.

When studying left heart decompression, we first divided the studies into 2 groups: the ECMO alone group and ECMO combined with the left ventricular decompression group. The left ventricular decompression group included studies on mechanical assistance (IABP and VAD) and assisted surgery (surgical atrial septostomy and left ventricular drainage). In addition, because there were many studies on IABP and fewer articles on VAD and other assisted surgery, we compared the mortality rate and complications of the ECMO+IABP group with that of the VAD and ECMO-assisted surgery together, defined as the ECMO combined other LV decompression techniques group.

Statistical and meta-analysis

The relative risk (RR) and its confidence interval were calculated by extracting positive and negative numbers from the 2 groups. The meta-analysis results in this study are represented by forest maps. The heterogeneity test between different studies was evaluated by l^2 statistics. When $P \ge 0.1$, there was no obvious heterogeneity, and $l^2 \ge 50\%$, P < 0.1 indicated that heterogeneity was obvious. Random-effects models were used for analysis, regardless of whether there was heterogeneity between the studies. However, if the effect values in the original literature were divided into 2 categories by gender, a fixed-effect model was used to analyze the combined effects. Publication bias was assessed by Begg's test and Egger's test, and the significance level (α) was set to 0.05. If $P \le 0.05$, there was publication bias. Subgroup analysis was used to explore the effects of different study characteristics on outcomes. Statistical analysis and meta-analysis were performed using Stata 12.0 software.

Results

Figure 1 shows the results of the search and selection processes. A total of 584 articles were retrieved after de-duplication. Of them, 525 were eliminated for various reasons based on the title and abstract, leaving 59 studies that were scrutinized by full-text review. There were 23 studies that met our eligibility criteria and were included. We did not identify any more relevant articles in the bibliographies of original articles. These studies are summarized in Table 1 (the ECMO group *vs.* ECMO combined with the left ventricular decompression group) and Table 2 (ECMO+IABP group *vs.* ECMO combined other LV decompression techniques group).

Systematic review

The risk of death with ECMO combined with left ventricular decompression therapy compared with ECMO alone

A total of 23 studies were included in the meta-analysis. The results showed that the risk of death with ECMO combined with left ventricular decompression therapy was 29% lower than that with ECMO alone. This difference was statistically significant (OR=0.71, 95% CI: 0.56–0.89), but I^2 =59.5% (*P*<0.001) indicated that the studies exhibited strong heterogeneity, and further analysis is needed to find the source of heterogeneity (Figure 2).

Author	Year	Region	Design	Males	Females	Mean BMI	Mean age	Sample
Maniuc [24]	2019	Germany	Case control study	54	21	-	61 ± 13	75
Singh [25]	2019	UK	Retrospective study	16	7	28.2±3.3	50 (45–56)	23
Nersesian [26]	2018	Germany	Retrospective study	72	34	-	59 (18–76)	106
Chen [27]	2019	China	Retrospective study	112	40	23.6 (20.8–25.9)	49.5±14.1	152
Solé [28]	2018	Spain	Retrospective study	19	9	-	69.2 (50–89)	28
Schiller [29]	2018	Sweden	Retrospective study	67	27	-	59±15	94
Chen [30]	2018	China	Retrospective study	45	15	23.4 <u>+</u> 4.0	51.4 <u>±</u> 12.7	60
Huang [31]	2018	Taiwan	Retrospective study	40	6	-	57.5±10.1	46
Fiedler [32]	2018	USA	Retrospective study	45	14	31±7.1	59±10.3	59
Matsumoto [33]	2018	Japan	Retrospective study	21	15	21 (19–22)	44 (24–64)	37
Ando [34]	2018	USA	Retrospective study	171	81	27.0 (23.6–32.2)	56.0 (45.0–63.0)	252
Pawale [35]	2017	USA	Retrospective study	38	15	-	54.9±10.8	43
Mourad [36]	2017	France	Retrospective study	35	7	26.5 (25–27.5)	54 (50–60)	42
Shah [37]	2017	USA	Retrospective study	57306	86948	-	68.8±13.3	144254
Centofanti [38]	2017	Italy	Retrospective study	13	11	-	46.0±14.41	24
Abdeen [39]	2016	Germany	Retrospective study	31	9	23±5	51±12	40
Aso [40]	2016	Japan	Retrospective study	774	292	-	-	1066
Pappalardo [19]	2016	Germany	Retrospective study	55	8	-	51 (47–61)	63
Cheng [41]	2016	USA	Retrospective study	50	23	-	53.4 <u>+</u> 12.2	73
Lackermair [42]	2016	Germany	Retrospective study	21	7	-	60.5±17	28
Lin [43]	2016	Taiwan	Retrospective study	399	130	25.1±3.9	56.8±13.4	529
Leidenfrost [44]	2015	USA	Retrospective study	-	-	_	45.6±16	27

 Table 1. Features of the studies included in this systematic review comparing ECMO combined with left ventricular decompression and ECMO alone.

e924009-4

Author	ECMO+ MCS deaths	ECMO+ MCS total	ECMO deaths	ECMO total	Diabetes	Hypertension	CKD
Maniuc [24]	15	50	12	25	-	-	-
Singh [25]	13	18	4	5	1	3	-
Nersesian [26]	20	37	39	69	-	_	_
Chen [27]	66	66	73	86	20	39	-
Solé [28]	5	20	8	8	9	18	_
Schiller [29]	16	46	18	48	-	-	-
Chen [30]	8	38	11	22	10	20	_
Huang [31]	5	12	24	34	17	27	3
Fiedler [32]	3	12	11	37	36	42	–
Matsumoto [33]	2	22	9	15	5	2	_
Ando [34]	30	125	37	127	135	83	–
Pawale [35]	6	21	8	22	-	_	_
Mourad [36]	8	19	11	23	14	12	_
Shah [37]	31011	64338	35962	79916	74680	45208	37283
Centofanti [38]	0	6	4	11	-	_	_
Abdeen [39]	10	17	16	23	-	_	-
Aso [40]	258	533	310	533	14	2	-
Pappalardo [19]	10	21	31	42	-	_	_
Cheng [41]	11	30	31	43	12	-	-
Lackermair [42]	3	9	18	28	-	_	-
Lin [43]	144	302	110	227	171	185	238
Leidenfrost [44]	1	12	7	15	-	-	-

 Table 1 continued.
 Features of the studies included in this systematic review comparing ECMO combined with left ventricular decompression and ECMO alone.

Subgroup analysis for the comparison of the risk of death with ECMO combined with left ventricular decompression therapy to that with ECMO alone

Subgroup analysis was performed based on whether the sample size was greater than 50. The results showed that, in studies with a sample size smaller than 50, the risk of death with ECMO combined with left ventricular decompression therapy was 49% lower than that with ECMO alone. The difference was statistically significant (OR=0.51, 95% CI: 0.33–0.81, I²=0.0%, P=0.859), suggesting low heterogeneity. In studies with a sample size greater than 50, the risk of death with ECMO combined with left ventricular decompression therapy was still less than 22% and was lower than that with ECMO alone, but the difference was not statistically significant (OR=0.78, 95% CI: 0.61–1.01, I²=69.0%, P<0.001). This result indicated high

heterogeneity (see Figure 3A), which may have been because the samples from study 36 and study 39 were much larger than those from the other studies, making the results unstable.

After study 36 and study 39 were excluded, studies with a sample size greater than 50 showed that the risk of death with ECMO combined with left ventricular decompression therapy was still lower than that with ECMO alone (OR=0.79, 95% CI: 0.64–0.99, I²=0.0%, *P*=0.607). The heterogeneity for the entire meta-analysis was small and acceptable (I²=0.0%, *P*=0.732), indicating that the heterogeneity was likely derived from the especially large sample sizes of studies 36 and 39 (see Figure 3B).

e924009-5

Author	Year	Region	Design	Males	Females	Mean BMI	Mean age	Diabetes
Kim [45]	2019	Korea	Case control study	16	51	24 (21–26)	68 (58–77)	11
Chen [27]	2019	China	Retrospective study	112	40	23.6 (20.8–25.9)	49.5±14.1	20
Matsumoto [33]	2018	Japan	Retrospective study	21	15	22 (20–24)	44 (24–64)	5
Nersesian [26]	2018	Germany	Retrospective study	72	34	-	59 (18–76)	-
Schiller [29]	2018	Sweden	Retrospective study	67	27	-	59±15	-
Fiedler [32]	2018	USA	Retrospective study	45	14	28.8±5.9	59±10.3	36
Mourad [36]	2018	France	Retrospective study	35	7	26.5 (25–27.5)	54 [50–60]	14
Bréchot [46]	2017	France	Retrospective study	94	32	26 (23–29)	53 (43–61)	-
Pappalardo [19]	2016	Germany	Retrospective study	55	8	-	51 (47–61)	-
Lin [43]	2016	Taiwan	Retrospective study	399	130	25.1±3.9	56.8±13.4	171
Leidenfrost [44]	2015	USA	Retrospective study	-	-	-	45.6±16	-

Table 2. Features of the studies included in	this systematic review	comparing ECMO combined	with IABP, ECMO-assisted surgery.
--	------------------------	-------------------------	-----------------------------------

Author	Hyperte- nsion	Sample	IABP death	IABP total	VAD death	VAD total	Complications
Kim [45]	12	67	5	44	6	23	Stroke, AF, respiratory complications, kidney damage, lower limb ischaemia, bleeding
Chen [27]	39	158	19	79	10	79	Bleeding, lower limb ischaemia, neurological complications
Matsumoto [33]	2	37	13	15	15	22	Lower limb ischaemia, haemorrhage, stroke
Nersesian [26]	-	37	16	28	5	9	Haemolysis, haemorrhage, stroke
Schiller [29]	-	94	19	46	17	48	-
Fiedler [32]	42	59	3	12	11	47	-
Mourad [36]	12	42	11	23	8	19	Bleeding, haemolysis, stroke
Bréchot [46]	-	126	23	63	31	63	-
Pappalardo [19]	-	63	31	42	10	21	Bleeding
Lin [43]	185	529	144	302	110	227	-
Leidenfrost [44]	_	27	8	27	1	12	-

Comparison of the risk of death with ECMO combined with IABP to that of ECMO combined other LV decompression techniques

To further analyze the effect of different methods of left ventricular decompression on mortality, a total of 11 articles were included in the meta-analysis for the risk of death with ECMO combined with IABP group compared to that of ECMO combined with other LV decompression techniques group (Table 2). The results showed that although the risk of death with ECMO combined other LV decompression techniques group was higher than that in the ECMO+IABP group, the difference was not statistically significant (OR=1.27, 95% CI: 0.86-1.87, I^2 = 44.0%, *P*=0.057), as shown in Figure 4.

e924009-6

Author	Year	Sample	OR (95% CI)	% weight
Maniuc	2019	75	0.46 (0.17, 1.25) 3.94
Singh	2019	23	0.65 (0.06, 7.32) 0.88
Nersesian	2018	106	0.91 (0.41, 2.02) 5.35
Chen	2019	152	0.85 (0.35, 2.07) 4.64
Solé	2018	28	0.33 (0.08, 1.36) 2.96
Schiller	2018	94	0.89 (0.38, 2.06) 4.96
Chen	2018	60	0.80 (0.27, 2.39) 3.45
Huang	2018	46	0.42 (0.11, 1.57) 2.52
Fiedler	2018	59	0.79 (0.18, 3.48) 2.10
Matsumoto	2018	37	0.83 (0.28, 2.50) 3.43
Ando	2018	252	0.77 (0.44, 1.35) 7.86
Pawale	2017	43	0.70 (0.19, 2.53) 2.63
Mourad	2017	42	0.79 (0.23, 2.70) 2.85
Shah	2017	144254	1.14 (1.11, 1.16) 14.51
Centofanti	2017	24	0.36 (0.07, 1.81) 1.78
Abdeen	2016	40	0.63 (0.17, 2.32) 2.59
Aso	2016	1066	 0.67 (0.53, 0.86) 12.55
Pappalardo	2016	63	0.32 (0.11, 0.97) 3.46
Cheng	2016	73	0.41 (0.16, 1.03) 4.35
Lackermair	2016	28	0.28 (0.06, 1.36) 1.92
Lin	2016	529	0.97 (0.69, 1.37) 11.03
Leidenfrost	2015	27 🔶	0.10 (0.01, 1.02) 0.94
Overall (I-squared=	59.5%, p=0.000)	0.71 (0.56, 0.89) 100.0
Note: Weights are fro	om random effec	cts analysis		

Figure 2. Forest plot of comparing the risk of death between ECMO combined with left ventricular decompression (LVD) therapy and ECMO alone.

Subgroup analysis based on different sample sizes (Figure 5A) showed that the risk of death in the ECMO combined other LV decompression techniques group was higher than that in the ECMO+IABP group in studies with a sample size smaller than 50, and the difference was statistically significant (OR=1.99, 95% CI: 1.00–3.98, I²=0.0%, *P*=0.444). In studies with a sample size greater than 50, although the risk of death in the ECMO combined other LV decompression techniques group was higher than that in the ECMO+IABP group, the difference was not statistically significant (OR=1.10, 95% CI: 0.70–1.71, I²=50.6%, *P*=0.059). This result indicates that there was no statistically significant difference in the risk of death between the 2 in the studies with large sample sizes. Therefore, large-sample cohort studies and clinical randomized controlled trials are needed to further validate the therapeutic effects of these 2 methods.

Subgroup analysis based on the different regions (Figure 5B) showed as that in Asia, the risk of death in the ECMO combined other LV decompression techniques group was higher than that in the ECMO+IABP group, but the difference was not statistically significant (OR=1.24, 95% CI: 0.61-2.52, $I^2=63.4\%$, P=0.042), suggesting that the results of the included studies from Asia were heterogeneous, probably due to the significant

differences in sample sizes among these studies; similar results were found for Europe and North America. There was no significant difference in mortality between the 2 groups (Europe: OR=1.17, 95 Cl%: 0.66–2.09, I²=38.5, *P*=0.164; North America: OR=2.18, 95% Cl: 0.53–8.98, I²=44%, *P*=0.057), suggesting that the studies from Europe were less heterogeneous. The heterogeneity of the studies from North America was small, but only 2 articles were included.

Comparison of the risk of complications among ECMO combined with left ventricular decompression therapy vs. ECMO alone and ECMO combined with IABP vs. ECMO combined with other LV decompression techniques

The results showed that the risk of 4 complications of ECMO combined with left ventricular decompression therapy was lower than that of ECMO alone. The ORs for hemorrhage, stroke/acute episodes, lower-limb ischemia, and hemolysis were 0.69 (0.66-0.71), 0.82 (0.78–0.89), 0.71 (0.30–1.66), and 0.48 (0.16–1.39), respectively, as shown in Figure 6A. In addition, the risk of stroke/transient ischemic attack (TIA), limb ischemia, and hemolysis complications in the ECMO combined with IABP group was lower than that of the ECMO combined

Author Year Simple OB (55%, CL) Sivegist Simple ± 30 046 (0.77, 125) 3.94 0.91 (0.1, 220) 3.54 Ninexian 2018 94 0.92 (0.1, 220) 3.54 Shiller 2018 94 0.92 (0.3, 2.00) 4.85 Nonexian 2018 94 0.97 (0.3, 1.84) 2.10 Nonexian 2017 4.12 1.13 (1.11, 1.13) 1.13 (1.11, 1.13) 1.14 (1.11, 1.13) <t< th=""><th></th><th></th><th></th><th></th><th></th></t<>					
Athor Yes Simple 06(95% C0. % weight Mainic 2019 35 06 07 10.1.2.20 5.35 Ocean 2018 16 07 04.1.2.20 5.35 Other 2018 12 0.85 0.85 0.85 0.85 0.85 0.85 0.85 0.85 0.85 0.85 0.85 0.85 0.85 0.85 0.85 0.85 0.97 0.14, 2.84 2.16 0.97 0.14, 2.84 2.16 0.97 0.14, 2.84 2.16 0.97 0.15, 2.84 2.16 0.97 0.15, 2.84 2.16 0.97 0.15, 2.84 2.16 0.97 0.15, 2.84 2.16 0.97 0.15, 2.84 2.16 0.97 0.15, 1.16 1.16 1.11, 11, 11, 11, 11 1.14 1.11, 11, 11, 11 1.15 0.97 0.97 0.97 0.97 0.97 0.97 0.97 0.97 0.97 0.97 0.97 0.97 0.97 0.97 0.97 0.97 0.97					
Sample 2:0 06 (0.17, 125) 3.94 Nenesian 2019 152 0.64 (0.17, 125) 3.94 Chen 2018 10 0.97 (0.1, 2.20) 3.94 Chen 2018 10 0.97 (0.1, 2.20) 3.94 Chen 2018 10 0.97 (0.1, 2.44) 1.14 (1.1, 1.15) Ando 2011 202 0.77 (0.4, 1.35) 7.86 Shift 2016 1.3 0.77 (0.4, 1.35) 7.86 Shift 2016 1.3 0.77 (0.4, 1.35) 7.86 Dery 2016 1.3 0.77 (0.4, 1.35) 1.14 (1.1, 1.16) 1.14 (1.1, 1.16) Massimuth 2016 1.3 0.77 (0.4, 1.37) 1.10 (1.17) 1.25 Single - 20 301 3.10 (1.13, 1.16) 1.15 (1.10) 7.28 Single - 20 301 4.11 (1.1, 1.16) 1.13 (1.17) 1.2 (1.17) Single - 20 301 4.10 (1.17) 1.2 (1.17) 1.2 (1.17) Single - 20 301 4.10 (1.1, 1.17) 1.2 (1.17) 1.2 (1.17) Single - 20 301 (1.13) 3.0 (1.13)		Author	Year	Sample	OR (95% CI) % weight
Maniac 2019 75 046 (0.7, 1.20) 3.35 Oren 2019 132 0.91 (0.1, 2.20) 3.35 Soliller 2018 4.4 0.91 (0.1, 2.20) 3.35 Oren 2018 4.4 0.91 (0.1, 2.20) 3.35 Fielder 2018 3.9 0.97 (0.1, 3.20) 4.4 Open 2018 3.9 0.97 (0.1, 3.440) 2.10 Adds 2018 3.9 0.77 (0.4, 1.33) 7.84 Adds 2018 5.3 0.97 (0.1, 3.1, 0.11) 1.4.51 Adds 2018 5.3 0.97 (0.1, 3.1, 0.11) 1.4.51 Adds 2018 5.3 0.97 (0.1, 3.1, 0.11) 1.4.51 Adds 2018 5.3 0.97 (0.1, 7.2) 2.98 Salabrial (-squared=-0.99) 2.04 0.97 (0.1, 7.2) 2.98 Salabrial (-squared=-0.99) 2.73 0.72 (0.1, 1.91) 7.23 Maximoth 2017 4.9 0.70 (0.1, 2.23) 2.45 Maximoth 2017 4.9 0.71 (0.2, 2.31) 2.45 Maximoth 2		Sample ≥50			
Necession 2018 66 97 011 12.021 533 Olen 2018 94 99 032 253 036 037.001 644 Shiller 2018 99 92 93 94 049.03.2.001 644 Gene 2018 93 97 017.01.2.021 533 945 Fielder 2018 93 97.01.3.2.01 644 97.01.3.2.01 645 Shuh 2017 144.1.3.1 116 116 047.01.3.0.08 12.5 98.01.0.00 Sumple <50 90.01.0.01.01 97.00.0.01 97.00.0.01.00 97.00.0.01 97.0.0.00 97.00.0.01 97.0.0.		Maniuc	2010	75	0.46 (0.17, 1.25) 3.94
Communication 2019 102 005 007 005 007 005 Communication 2018 202 007 001 027 028 029 029 027 028 029 027 028 029 027 028 029 027 028 029 027 028 029 029 027 028 029 <t< td=""><td></td><td>Nersesian</td><td>2019</td><td>106</td><td></td></t<>		Nersesian	2019	106	
Stem 2019 32 0.0 0.00 0.00 0.00 Fedler 2018 9.0 0.00		Chan	2010	100	
Julian 2018 34 34 34 Fried 2018 32 34 34 Fried 2018 32 34 34 Statu 2019 32 34 34 Are 2019 34 34 34 Are 2015 73 34 34 Are 2016 73 34 34 Are 2018 34 34 34 Are 2019 35 34 34 34 Sumple < 20		Citell	2019	152	
Lieft 2018 20 Ando 2018 20 Sub 2017 144254 As 20 Sub 2016 16 As 2016 16 As 2016 16 As 2016 16 As 2016 17 144254 As 2016 16 As 2016 17 144254 As 2016 16 As 2016 17 144254 As 2016 16 Sub 2016 17 1 Sub 2016 17 142 Sub 2017 144 Sub 2018 144 Sub 20		Schlier	2018	94	
rester 2018 29 0.70 (d. 8, 4.8) 210 Sub 2017 14-224 0.70 (d. 8, 4.8) 215 Aco 2016 63 0.70 (d. 8, 4.8) 215 Papplarde 2016 63 0.70 (d. 8, 4.8) 215 Status 2016 53 0.70 (d. 9, 1.37) 11.41 (1.11, 1.6) 14.51 Lin 2016 53 0.70 (d. 9, 1.37) 13.44 0.70 (d. 9, 1.37) 13.44 Sanple <20		Chen	2018	60	
Ands 2018 262		Fiedler	2018	59	0.79 (0.18, 3.48) 2.10
Shah 2017 144254 11.14(11,11,11) 14.51 Ass 2016 16 63 0.73 0.83,0.80 12.55 Pappalario 2016 73 0.73 0.81,0.81,0.81 13.5 Subtral (F-guard=0.0%, p=0.00) Sample <50 0.73 0.65 0.05, 7.20 0.88 Sample <50 Sample <2017 43 0.73 0.83,0.81, 1.80 2.26 Huang 2017 43 0.70 (0.17, 2.32) 2.33 0.73 (0.03, 0.81, 1.80 2.26 Maturnolo 2017 43 0.70 (0.17, 2.32) 2.33 0.73 (0.07, 1.13, 1.35 2.34 Devale 2017 43 0.73 (0.01, 1.80 2.25 0.34 (0.7, 1.32) 2.35 Battorial (Fest analysis 0.51 (0.33, 0.81) 1.78 0.73 (0.02, 1.80 2.39 0.34 (0.7, 1.23) 2.35 Subtral (Fest analysis 0.51 (0.33, 0.81) 1.78 0.73 (0.30, 0.81) 1.78 0.73 (0.30, 0.81) 0.70 (0.17, 1.23) 2.35 Netweight are from random effects analysis 0.71 (0.33, 0.81) 1.78 0.73 (0.7, 1.20) 2.57 0.71 (0.31, 0.81) 0.79		Ando	2018	262	
Ass 2016 1066 Pappalardo 2016 73 Um 2016 73 Sample <50		Shah	2017	144254	1.14 (1.11, 1.16) 14.51
Papalado 2016 63 0.23 (0.1, 0.27) 3.46 Lin 2016 529 0.41 (0.16, 10.20) 4.35 Subhtall (1-squared=60.0%, p=0.01) 0.72 (0.81, 1.37) 11.03 0.72 (0.81, 1.37) 11.03 Singh 2019 23 0.41 (0.16, 10.20) 4.35 0.72 (0.81, 1.37) 10.83 Singh 2019 23 0.65 (0.06, 7.37) 0.88 0.72 (0.81, 1.37) 2.26 Manag 2018 4.6 0.72 (0.81, 1.37) 2.32 0.34 0.72 (0.81, 1.37) 2.32 Manag 2017 4.3 0.70 (0.81, 2.37) 2.43 0.70 (0.81, 2.37) 2.43 Mexical 2017 4.3 0.70 (0.81, 2.37) 2.43 0.70 (0.81, 2.37) 2.43 Advermain 2016 2.3 2.44 0.70 (0.21, 2.07) 2.43 0.43 (0.07, 1.32) 2.43 Statistical (1-squared=0.0%, p=0.659) 0.71 (0.33, 0.81) 1.70 0.22 (0.05, 5.6) 0.41 (0.16, 1.02) 0.41 (0.41, 1.20) 0.40 (0.21, 1.22) 4.00 Statistical (1-squared=0.0%, p=0.670) 0.71 (0.33, 0.81) 10.20 0.71 (0.33, 0.81) 0.		Aso	2016	1066	0.67 (0.53, 0.86) 12.55
Ohing 2016 73 041 (0.16, 1.03) 4.33 Subtrail (I-squared=66.0%, p=0.00) 0.78 (0.61, 1.01) 78.28 Sample -S0 501 0.33 (0.08, 1.36) 2.25 Maturolo 2017 43 0.43 (0.16, 1.01) 78.28 Maturolo 2017 43 0.43 (0.08, 1.36) 2.25 Maturolo 2017 43 0.70 (0.17, 2.23) 2.63 Mound 2017 43 0.70 (0.17, 2.33) 2.33 Abben 2.016 2.8 0.26 (0.06, 7.12) 0.28 (0.06, 1.30) 1.1 Abben 2.016 2.8 0.63 (0.02, 7.18) 1.73 0.28 (0.06, 1.30) 2.97 Sample -S0 0.51 (0.33, 0.81) 2.78 0.43 (0.01, 1.20) 0.94 0.51 (0.33, 0.81) 2.78 Sample -S0 0.97 (0.17, 1.23) 2.95 0.43 (0.01, 1.20) 0.94 0.51 (0.33, 0.81) 100.00 No Author Year Sample 0.97 (0.17, 1.23) 2.93 0.43 (0.01, 1.25) 0.97 (0.18, 1.20) Sample -S0 1 3.5 0.77 (0.01, 1.25) 0.97 (0.01, 1.25) 0.		Pappalardo	2016	63	0.32 (0.11, 0.97) 3.46
Lin <u>2016</u> 529 Suboral (J-squared=60.0%, p=0.00) Singh 2019 23 Suboral (J-squared=60.0%, p=0.00) Harang 2019 44 Harang 2019 44 Harang 2019 44 Harang 2017 44 Addem 2017 44 Addem 2017 44 Addem 2016 429 Ledenfriet 2017 43 Horad Lisquared=0.0%, p=0.639) Hore and first same/size 1 Andro <u>Year Sample</u> 0 (S (06, 7.12) 400 0 (S (07, 7.13) 150 1 (S (06, 7.12) 400 0 (S (07, 7.13) 150 0 (S (07, 7.13) 150 0 (S (07, 7.13) 150 0 (S (07, 7.		Cheng	2016	73	0.41 (0.16, 1.03) 4.35
Subtatal (I-squared=69.0%, p=0.00) Singh 2019 23 Sole 2018 28 Huang 2018 46 0.65 (0.06, 7.32) 0.98 Sole 2018 28 Huang 2018 46 0.33 (0.08, 1.26) 2.26 Matsumoto 2017 37 Pevale 2017 43 Mound 2017 42 Centrofanti 2017 24 Abdeen 2016 49 Subtatal (I-squared=0.0%, p=0.859) Overall (I-squared=0.0%, p=0.67) Sample =50 2 Sinble 2016 73 Supple <50 2 Sinble 2018 25 Overall (I-squared=0.0%, p=0.67) Sample <50 2 Sinble 2018 26 Overall (I-squared=0.0%, p=0.67) Sample <50 2 Sinble 2 Overall (I-squared=0.0%, p=0.67) 3 Sinble 2 Overall (I-squared=0.0%, p=0.67) 3 Sinble 2 Overall		Lin	2016	529	
Sample - 50 Single 2019 23 Sole 2018 46 Sole 0.65 (0.06, 7.32) 0.88 O 30 (0.01, 162) 22 Sole Huang 2018 46 Sole 2017 37 O 20 (0.19, 2.53) 23 O 20 (0.19, 2.53) 24 O 20 (0.19, 2.53) 24 O 20 (0.19, 2.53) 24 O 20 (0.19, 2.53) 24 O 20 (0.19, 2.53) 23 O 20		Subtotal (I-squared:	=69.0% n=0.00)	527	078 (0 61 1 01) 78 28
Sample < 50		Subtotal (i squarea	031070/p 01007		
Sole 2019 23 Sole 2018 26 Haang 2018 26 Matsumoto 2017 33 Pavale 2017 42 Matsumoto 2017 42 Orgo (0.15, 2.53) 2.3 Mourad 2017 42 Mourad 2017 42 Abdeen 2016 40 Jackermain 2016 22 Jackermain 2018 24 Jackermain 2019 25 Jackermain 2018 20 Jackermain 2018 20 <t< td=""><td></td><td>Sample < 50</td><td></td><td></td><td></td></t<>		Sample < 50			
singn cur9 cs Sole 2018 28 Haang 2018 46 Maturnoto 2017 43 Mound 2017 43 Mound 2017 43 Centofanti 2017 24 Adden 2016 40 Centofanti 2017 24 Addenei 2016 40 Leidernair 2016 25 Leidernefet 2015 27 Subtotal (I-squared=0.0%, p=0.559) 20 0000 Not. Kerber Year Sample Sample ≥50 2018 24 04 1 3.5 0.46 (0.17, 12.5) 4.00 3 100.20 5.57 0.46 (0.17, 12.5) 4.00 3 Merssian 2018 24 04 04 4 Chen 2019 75 0.46 (0.17, 12.5) 4.00 3 Merssian 2018 24 04 04 0.05 (0.57, 72) 7 Chen 2018		Circh	2010	22	
Sole 2018 28 0.33 (000, 1.36) 2.22 Matsumoto 2017 37 0.83 (000, 1.36) 2.52 Matsumoto 2017 43 0.70 (01, 9), 2.53 2.53 Mourad 2017 43 0.70 (01, 9), 2.53 2.63 Mourad 2017 42 0.79 (01, 3), 2.79 2.85 Certofonti 2016 40 0.33 (007, 1.81) 1.78 Abdeen 2016 2.8 0.33 (007, 1.23) 2.99 Ladormair 2016 2.8 0.10 (00, 1, 000 0.97 (0.3), 0.81) 2.72 Leiderfret 2.01 (00, 00, 1.36) 2.72 0.10 (00, 1, 1.02) 0.94 Subtotal (I-squared=0.0%, p=0.359) 0.71 (0.33, 0.81) 0.71 (0.33, 0.81) 0.00.0 Not. Author Year Sample 0.46 (0.17, 1.25) 4.00 Sample = 50 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 4 Chem 2019 75 0.46 (0.17, 1.25) 4.00 3 Mercesian 2018 59 0.46 (0.17, 1.25) 4.00 <		Singn	2019	23	0.65 (0.06, 7.32) 0.88
Huang 2018 46 0.42 (0.11, 1.57) 2.52 Maximotic 2017 43 0.70 (0.19, 2.53) 2.63 Mound 2017 24 0.79 (0.12, 2.57) 2.63 Abdeen 2016 40 0.64 (0.07, 1.81) 1.78 Addeen 2016 2.8 0.26 (0.07, 1.81) 1.78 Addeen 2016 2.8 0.26 (0.06, 1.36) 2.92 Leidenfreit 2015 2.7 0.10 (0.01, 1.02) 0.94 Subtocal (1-squared-95%, p=0.000) 0.71 (0.33, 0.81) 2.180 0.71 (0.33, 0.81) 2.180 Orecall (1-squared-95%, p=0.000) Note: Weights are from random effects analysis 0.71 (0.33, 0.81) 100.00 Note: Weights are from random effects analysis 0.71 (0.33, 0.81) 2.180 0.93 (0.37, 2.39) 1 Namic 2.019 75 0.46 (0.17, 1.25) 4.00 3 Neresian 2.019 75 0.46 (0.17, 1.25) 4.00 3 Neresian 2.019 75 0.46 (0.17, 1.25) 4.00 4 Othen 2.019 75 0.46 (0.17, 1.25)		Solé	2018	28	0.33 (0.08, 1.36) 2.26
Matsumotio 2017 37 0.83 0.28 2.90 3.43 Moural 2017 42 0.70 0.128 2.63 Centofanti 2017 42 0.70 0.128 2.63 Abdeen 2016 42 0.30 0.70 0.128 2.59 Lackermair 2016 2.8 0.30 0.07 1.1 1.3 2.59 Lackermair 2016 2.8 0.40 0.63 0.71 0.23 0.28 0.06 0.30 2.29 0.10 0		Huang	2018	46	0.42 (0.11, 1.57) 2.52
Pavale 2017 43 0.72 (019, 253) 2.63 Moriad 2017 24 0.79 (013, 2.70) 2.85 Abdeen 2016 40 0.61 (017, 2.32) 2.59 Ladkermair 2016 2.9 0.28 (0.07, 1.81) 1.7.8 Abdeen 2016 40 0.61 (017, 2.32) 2.9 Leidenfreit 2015 27 0.10 (0.01, 1.02) 0.94 Ostraution 0.10 (0.01, 1.02) 0.94 0.51 (0.33, 0.81) 2.80 Orecall (I-squared-9.9.5%, p=-0.000) 0.71 (0.33, 0.81) 100.00 0.71 (0.33, 0.81) 100.00 Note: Weights are from random effects analysis 0.46 (0.17, 1.25) 4.00 0.91 (0.14, 0.20) 6.26 1 Manue: 2019 75 0.46 (0.17, 1.25) 4.00 0.91 (0.14, 0.20) 6.26 1 Manue: 2019 75 0.46 (0.17, 1.25) 4.00 0.91 (0.14, 0.20) 6.26 4 Chen 2019 152 0.91 (0.14, 0.20) 6.26 0.91 (0.14, 0.20) 6.26 5 Schiller 2018 6.9 <td< td=""><td></td><td>Matsumoto</td><td>2017</td><td>37</td><td>0.83 (0.28, 2.50) 3.43</td></td<>		Matsumoto	2017	37	0.83 (0.28, 2.50) 3.43
Mourad 2017 42 0.79 (0.23, 2.70) 2.85 Critofanti 2016 40 0.56 (0.07, 1.81) 1.78 Abdeen 2016 40 0.56 (0.07, 1.22) 2.59 Ladermair 2015 22 0.26 (0.07, 1.30) 2.92 Ladermair 2015 22 0.10 (0.01, 1.02) 0.94 Subtotal (1-squared=0.0%, p=0.859) 0.71 (0.33, 0.81) 100.00 0.71 (0.33, 0.81) 100.00 Not. Author Year Sample >50 0.64 (0.17, 1.25) 4.00 Sample >50 0.91 (0.41, 2.02) 6.26 0.91 (0.41, 2.02) 6.26 4 Chen 2019 75 0.64 (0.17, 1.25) 4.00 3 Nersesian 2018 60 0.91 (0.41, 2.02) 6.26 4 Chen 2019 75 0.64 (0.17, 1.25) 4.00 3 Nersesian 2018 60 0.91 (0.41, 2.02) 6.26 4 Chen 2019 75 0.64 (0.17, 1.25) 4.00 3 Nersesian 2018 60 0.97 (0.64, 0.97) <		Pawale	2017	43	0.70 (0.19, 2.53) 2.63
Centróanti 2017 24 0.36 (0.07, 1.81) 1.78 Abdeen 2016 40 0.36 (0.07, 1.20) 2.19 Leidenfreit 2015 27 0.36 (0.07, 1.81) 1.78 Subtotal (1-squared=0.0%, p=0.859) 0.9 0.51 (0.33, 0.81) 2.180 Overall (1-squared=0.0%, p=0.59) 0.71 (0.33, 0.81) 100.00 No. Author Year Sample 50 1 1 3.5 0.48 (0.17, 1.25) 4.00 3 Nersesian 2019 75 0.46 (0.17, 1.25) 4.00 3 Nersesian 2019 75 0.46 (0.17, 1.25) 4.00 4 Chen 2019 75 0.46 (0.17, 1.25) 4.00 3 Nersesian 2018 60 0.97 (0.41, 1.35) 1.267 4 Chen 2018 59 0.77 (0.44, 1.35) 1.267 18 Papalardo 2017 63 0.32 (0.01, 1.30) 1.38 11 Ando 2018 59 0.77 (0.44, 1.35) 1.267 18 Papalardo 2017		Mourad	2017	42	0.79 (0.23, 2.70) 2.85
Abdeen 2016 40 Ladermair 2016 29 Leiderneit 2015 27 Subtotal (I-squared=0.0%, p=0.859) 0.31 (0.33, 0.81) 21.80 Overall (I-squared=0.0%, p=0.000) 0.71 (0.33, 0.81) 100.00 Not: Weights are from random effects analysis 0.71 (0.33, 0.81) 100.00 Sample = 50 0.8 (0.07, 1.25) 4.00 9.8 weight Sample = 50 0.46 (0.17, 1.25) 4.00 1 1 3.5 No. Author Year Sample 0.87 (0.95%, CI) % weight Sample = 50 0.46 (0.17, 1.25) 4.00 0.88 (0.35, 2.07) 5.04 6 Schiller 2018 94 0.89 (0.37, 2.39) 3.36 7 Ohen 2018 5.57 0.49 (0.27, 2.39) 3.36 9 Fieller 2018 5.29 0.79 (0.43, 3.48) 1.82 11 Ando 2018 2.29 0.79 (0.43, 3.48) 1.82 11 Ando 2018 2.29 0.79 (0.43, 7.39) 3.36 12 Lin		Centofanti	2017	24	0.36 (0.07, 1.81) 1.78
Lackerniari Lackerniari Lotoreriari Subtorial (I-squared=0.0%, p=0.859) Overall (I-squared=0.0%, p=0.000) Net: Weights are from random effects analysis 1 3.5 No. Author Year Sample Sample ≥50 No. Author Year Sample Sample ≥50 No. Author Year Sample OR (95% CI) % weight 1 3.5 No. Author Year Sample OR (95% CI) % weight 0.71 (0.33, 0.81) 100.00 Net: Weights are from random effects analysis 1 3.5 No. Author Year Sample Sample ≥50 No. Author Year Sample OR (95% CI) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 4 Ohen 2019 152 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 4 Ohen 2019 152 0.85 (0.35, 2.07) 5.04 0.99 (0.38, 2.60) 5.57 7 Ohen 2018 60 9 Fiedler 2018 59 1 Manual 2017 63 1 Papalardo 2017 63 1 Papalardo 2017 63 2 Singh 2019 23 Sample <50 2 Singh 2019 23 Sample <50 2 Singh 2019 23 3 Merseisan 2018 16 3 Merseisan 2018 17 2 Singh 2019 23 3 Merseisan 2018 37 2 Singh 2017 43 3 Merseisan 2018 37 3 Merseisan 20		Abdeen	2016	40	
Ladermain 2010 2.2 Ladermain 2015 2.7 Subtoal (I-squared=-0.0%, p=0.859) Overall (I-squared=-0.9%, p=0.000) Nete: Weights are from random effects analysis 1 1 3.5 No. Author Year Sample Sample >50 1 Maniuc 2019 75 3 Nersesian 2019 75 3 Nersesian 2019 152 6 Schiller 2019 95 7 Chen 2018 94 9 Regulardo 2017 63 9 Regulardo 2017 63 9 Regulardo 2017 63 9 Regulardo 2017 63 9 Solé 2018 25 2 Lin 2016 529 2 Subtoal (I-squared=0.0%, p=0.607) 2 Sample <50 1 Maniuc 2019 75 1 Maniuc 2019 75 3 Nersesian 2018 106 0.77 (0.41, 135) 12.67 1 Ando 2018 252 0.77 (0.41, 135) 12.67 1 Lin 2016 529 2 Subtoal (I-squared=0.0%, p=0.607) 2 Sample <50 2 Singh 2019 23 5 Solé 2018 28 8 Huang 2018 46 1 Maniuroto 2018 37 2 Lin 2016 73 2 Lin 2016 2018 28 3 Mourad 2017 42 4 Autoin 1,157 2 Lin 2016 28 4 Autoin 1,157 4 Autoin 1,151 4 Abdeen 2016 1,44 4 Autoin 1,44 4 Autoin 1,45 4 Autoin 1		Lackormair	2016	78	
Levenness 2015 27 Subtotal (1-squared=0.0%, p=0.859) Overall (1-squared=0.0%, p=0.000) Note: Weights are from random effects analysis 1 1 3.5 No. Author Year Sample Sample 250 1 Maniuc 2019 75 Sample 250 1 Maniuc 2019 75 Chen 2019 152 6 Schiller 2018 94 6 Schiller 2018 94 7 Chen 2018 59 9 Fiedler 2018 529 1 Ando 2018 222 1 Ando 2016 73 19 Cheng 2016 73 19 Cheng 2016 73 10 Cheng 2016 73 10 Cheng 2016 73 10 Cheng 2016 73 11 Ando 2018 222 11 Ando 2018 229 12 Lin 2016 529 13 Mourad 2017 43 13 Mourad 2017 42 14 Add 2018 21 15 Centofanti 2017 24 16 Abdeen 2016 217 2 Singh 2019 23 17 Pavale 2017 43 18 Papalardo 2018 229 19 Cheng 2016 73 2 Singh 2019 23 10 Add (0.17, 1.25) 0.669 0.79 (0.8, 3.48) 1.82 0.77 (0.4, 1.35) 1.267 0.33 (0.08, 1.36) 1.98 0.44 (0.16, 1.03) 4.59 0.79 (0.64, 0.59) 80.53 19 Cheng 2016 73 10 Add (0.17, 1.27) 2.25 10 Matsumoto 2018 24 2 Singh 2019 23 10 Cheng 2016 73 10 Cheng 2018 24 10 Cheng 2019 23 10 Cheng 2018 24 10 Cheng 2019 23 10 Cheng 2018 24 10 Cheng 2018 24 10 Cheng 2018 24 10 Cheng 2019 23 10 Cheng 2019 23		Laukerfildi	2010	20	
Subtract (+squared=-0.95%) 0.51 (0.33, 0.81) 21.80 Overall (I-squared=59.5%), p=0.000) 0.71 (0.33, 0.81) 100.00 Note: Weights are from random effects analysis 0.71 (0.33, 0.81) 100.00 Imanic 2019 75 0.40 (0.17, 125) 4.00 Sample ≥50 0.46 (0.17, 125) 4.00 0.91 (0.41, 202) 6.26 4 Chen 2019 75 0.46 (0.17, 125) 4.00 0.81 (0.83, 0.81) 108 0.83 (0.83, 206) 5.57 7 Chen 2018 59 0.83 (0.84) 1.82 1 Andro 2018 59 0.77 (0.41, 135) 1.267 18 Pappalardo 2017 63 0.32 (0.11, 0.97) 3.36 19 Cheng 2016 73 0.41 (0.16, 1.03) 4.59 21 Lin 2016 529 0.97 (0.44, 1.35) 1.267 19 Cheng 2016 73 0.41 (0.16, 1.03) 4.59 21 Lin 2016 529 0.97 (0.64, 0.99) 80.53 Subtotal (1-squared=0.0%) p=0.6677)<		Leidentrest	2015	∠/ ←	0.10 (0.01, 1.02) 0.94
Overall (I-squared=59.5%, p=0.000) Note: Weights are from random effects analysis 0.71 (0.33, 0.81) 100.00 No. Author Year Sample 0R (95% (1) % weight 1 3.5 0.6 (0.17, 1.25) 4.00 % weight 1 Mariu 2019 75 0.46 (0.17, 1.25) 4.00 3 Mersesian 2019 152 0.85 (0.35, 2.07) 5.04 6 Schiller 2018 94 0.89 (0.38, 2.06) 5.57 7 Chen 2018 59 0.77 (0.41, 1.33) 12.67 18 Pappalardo 2016 73 0.32 (0.11, 0.37) 3.36 9 Fiedler 2016 5.29 0.77 (0.40, 0.09) 80.03.3 21 In 2016 5.29 0.79 (0.59, 1.37) 3.38 5 Sold 2018 24 0.46 (0.07, 1.25) 0.69 2 Singh 2019 23 0.73 (0.60, 0.89) 80.33.200 5 Sold 2018 46		Subtotal (I-squared:	=0.0%, p=0.859)		0.51 (0.33, 0.81) 21.80
Overall (L-squared=-59:5%, p=0.000) 0.71 (0.33, 0.81) 100.00 Note: Weights are from random effects analysis 1 3.5 No. Author Year Sample 0R (95% C) 56 weight Sample >50 0.71 (0.33, 0.81) 100.00 1 Maniuc 2019 75 0.46 (0.17, 1.25) 4.00 3 Nersesian 2018 106 0.91 (0.41, 2.02) 6.26 4 Chen 2019 152 0.85 (0.35, 2.07) 5.04 6 Schiller 2018 94 0.89 (0.38, 2.06) 5.57 7 Chen 2018 59 0.77 (0.44, 1.35) 12.67 18 Pappalardo 2017 63 0.41 (0.16, 1.03) 4.59 21 Lin 2016 529 0.97 (0.64, 0.99) 80.53 Subtotal (I-squared=0.0%, p=0.607) Sample <50					
Note: Weights are from random effects analysis 1 3.5 No. Author Year Sample OR (95% C) % weight Sample 250 OR (95% C) % weight 3 Merssian 2019 75 0.46 (0.17, 1.25) 4.00 4 Chen 2019 152 0.85 (0.35, 2.07) 5.04 6 Schiller 2018 94 0.89 (0.27, 2.39) 3.36 7 Chen 2018 59 0.77 (0.44, 1.35) 12.67 18 Pappalardo 2016 73 0.21 (0.11, 0.97) 3.36 11 Ando 2018 52 0.77 (0.44, 1.35) 12.67 18 Pappalardo 2016 73 0.41 (0.16, 1.03) 4.59 21 Lin 2016 529 0.97 (0.64, 0.99) 80.53 Subtotal (I-squared=0.0%, p=0.677) Solé 0.42 (0.11, 1.57) 2.25 12 Payalardo 2016 32 0.79 (0.23, 2.70) 2.63 12 <t< td=""><td></td><td>Overall (I-squared=</td><td>59.5%, p=0.000)</td><td></td><td>0.71 (0.33, 0.81) 100.00</td></t<>		Overall (I-squared=	59.5%, p=0.000)		0.71 (0.33, 0.81) 100.00
Image: constraint of the squared = 0.0%, p=0.677 Year Sample > 50 OR (95% C) % weight 1 Maniuc 2019 75 0.46 (0.17, 1.25) 4.00 3 Nexessian 2018 106 0.91 (0.41, 2.02) 6.26 4 Chen 2018 94 0.89 (0.38, 2.06) 5.57 7 Chen 2018 69 0.89 (0.38, 2.06) 5.57 7 Chen 2018 59 0.77 (0.44, 1.35) 12.67 11 Ando 2018 252 0.77 (0.44, 1.35) 12.67 18 Pappalardo 2016 73 0.32 (0.11, 0.97) 3.36 19 Cheng 2016 529 0.97 (0.69, 1.37) 3.386 10 Matsumoto 2018 37 0.79 (0.13, 2.53) 2.33 12 Pawale 2017 43 0.42 (0.11, 1.57) 2.25 14 Abdeen 2016 28 0.43 (0.028, 2.50) 3.32 12 Pawale 2017 43 0.42 (0.11, 1.57) 2.25 15 Solé		Note: Weights are fr	om random effects	analysis	
Sample ≥50 1 Maniuc 2019 75 3 Nersesian 2018 106 4 Chen 2019 152 6 Schiller 2018 94 7 Chen 2018 60 9 Fiedler 2018 59 9 Fiedler 2018 59 11 Ando 2018 252 11 Ando 2018 252 12 Corr (0.44, 1.35) 12.67 13 Papalardo 2017 63 19 Cheng 2016 73 21 Lin 2016 529 Subtotal (I-squared=0.0%, p=0.67) 5 Solé 2018 28 8 Huang 2018 46 14 Huang 2018 46 14 Huang 2018 46 14 Huang 2018 46 15 Solé 2018 28 16 Abdeen 2017 43 17 Matsumoto 2018 37 10 Matsumoto 2018 37 12 Pawale 2017 43 13 Mourad 2017 42 14 Huang 2016 40 25 Subtotal (I-squared=0.0%, p=0.67) 15 Centofanti 2017 42 16 Abdeen 2016 40 26 Centofanti 2017 42 17 Centofanti 2017 42 18 Huang 2018 46 19 Centofanti 2017 42 10 Matsumoto 2018 37 12 Pawale 2017 43 13 Mourad 2017 42 14 Centofanti 2017 42 15 Centofanti 2017 24 16 Abdeen 2016 40 20 Lackermair 2016 28 27 Centofanti 2017 24 16 Abdeen 2016 40 20 Lackermair 2016 28 27 Centofanti 2017 24 16 Abdeen 2016 40 20 Lackermair 2016 28 27 Centofanti 2017 24 16 Abdeen 2016 40 20 Lackermair 2016 28 27 Centofanti 2017 24 15 Centofanti 2017 24 16 Abdeen 2016 40 20 Lackermair 2015 27 Centofanti 2017 24 17 Centofanti 2017 24 18 Centofanti 2017 24 19 Centofanti 2017 24 19 Centofanti 2017 24 10 Corr (0.23, 2.70) 2.63 10 Corr (0.13, 0.81) 19.47 15 Centofanti 2017 24 16 Abdeen 2016 40 20 Lackermair 2016 28 20 Lackermair 2016 28 20 Lackermair 2015 27 20 Centofanti 2017 24 20 Corr (0.23, 0.81) 19.47 20 Cor	1	No Author			
1 Mariuc 2019 75 0.46 (0.17, 1.25) 4.00 3 Nersesian 2018 106 0.91 (0.41, 2.02) 6.26 4 Chen 2019 152 0.85 (0.35, 2.07) 5.04 6 Schiller 2018 94 0.89 (0.32, 2.06) 5.57 7 Chen 2018 59 0.80 (0.27, 2.39) 3.36 9 Fiedler 2018 59 0.77 (0.44, 1.35) 12.67 18 Pappalardo 2017 63 0.23 (2.011, 0.97) 3.36 19 Cheng 2016 73 0.41 (0.16, 1.03) 4.59 21 Lin 2016 529 0.97 (0.69, 1.37) 33.86 Subtotal (I-squared=0.0%, p=0.607) Sample <50		NO. AULIIOI	Year	Sample	OR (95% CI) % weight
3 Nersesian 2018 106 4 Chen 2019 152 6 Schiller 2018 94 7 Chen 2018 94 9 Fiedler 2018 59 11 Ando 2018 59 11 Ando 2018 59 11 Ando 2018 252 0.77 (0.44, 1.35) 12.67 18 Pappalardo 2016 73 21 Lin 2016 73 21 Lin 2016 73 3 Subtotal (I-squared=0.0%, p=0.607) 33 0.41 (0.16, 1.03) 5 Solé 2018 28 0.57 (0.69, 1.37) 5 Solé 2018 28 0.33 (0.08, 1.36) 1.98 8 Huang 2017 42 0.79 (0.69, 1.37) 2.25 10 Matsumoto 2018 37 0.33 (0.08, 1.36) 1.98 12 Pawale 2017 42 0.79 (0.28, 2.70) 2.63 12 <td></td> <td>Sample ≥50</td> <td>Year</td> <td>Sample</td> <td>OR (95% CI) % weight</td>		Sample ≥50	Year	Sample	OR (95% CI) % weight
4 Chen 2019 152 6 Schiller 2018 94 7 Chen 2018 60 9 Fiedler 2018 59 11 Ando 2018 252 12 Ando 2018 252 13 Ando 2018 252 14 Cheng 2016 73 15 Cheng 2016 73 16 Cheng 2016 529 Subtotal (I-squared=0.0%, p=0.607) 0.37 (0.44, 1.33) 12.67 16 Singh 2019 23 0.41 (0.16, 1.03) 4.59 21 Lin 2016 529 0.77 (0.44, 1.35) 12.67 16 Adaguate 2017 43 0.43 (0.11, 0.77) 33.66 17 District (I-squared=0.0%, p=0.607) 0.33 (0.08, 1.36) 1.98 18 Huang 2018 26 0.43 (0.01, 1.57) 2.25 10 Matsumoto 2018 37 0.33 (0.08, 1.36) 1.98 19 Pawale <t< td=""><td></td><td>Sample ≥50 1 Maniuc</td><td>Year 2019</td><td>Sample</td><td>OR (95% Cl) % weight 0.46 (0.17, 1.25) 4.00</td></t<>		Sample ≥50 1 Maniuc	Year 2019	Sample	OR (95% Cl) % weight 0.46 (0.17, 1.25) 4.00
4 Citelin 2019 152 0.03 (0.57, 0.57) 0.44 (0.55, 0.57) 6 Schiller 2018 60 0.89 (0.38, 0.26) 5.57 7 Chen 2018 59 0.89 (0.38, 0.26) 5.57 1 Ando 2018 59 0.79 (0.18, 3.48) 1.82 11 Ando 2018 252 0.79 (0.18, 3.48) 1.82 11 Ando 2018 252 0.79 (0.18, 3.48) 1.82 12 Lin 2016 73 0.41 (0.16, 1.03) 4.59 21 Lin 2016 529 0.97 (0.69, 1.37) 33.86 Subtotal (I-squared=0.0%, p=0.607) Sample <50		Sample ≥50 1 Maniuc 3 Nersesian	Year 2019 2018	Sample 75	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41 2.02) 6.26
6 Schliler 2018 94 0.89 (0.38, L.00) 5.57 7 Chen 2018 60 0.80 (0.27, 2.39) 3.36 9 Fiedler 2018 59 0.79 (0.18, 4.80) 1.82 11 Ando 2018 252 0.77 (0.44, 1.35) 12.67 18 Pappalardo 2016 73 0.32 (0.11, 0.97) 3.36 19 Cheng 2016 529 0.97 (0.69, 1.37) 33.86 Subtotal (I-squared=0.0%, p=0.607) Sole 0.79 (0.64, 0.99) 80.53 Sample <50		Sample ≥50 1 Maniuc 3 Nersesian	Year 2019 2018	Sample 75 106	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.95 (0.35, 2.07) 5.04
7 Chen 2018 60 0.88 (0.27, 2.39) 3.36 9 Fiedler 2018 59 0.79 (0.18, 3.48) 1.82 11 Ando 2018 252 0.77 (0.44, 1.35) 12.67 18 Pappalardo 2016 73 0.32 (0.11, 0.97) 3.36 19 Cheng 2016 73 0.97 (0.69, 1.37) 33.86 21 Lin 2016 529 0.97 (0.69, 1.37) 33.86 Subtotal (I-squared=0.0%, p=0.607) Sample <50		Sample ≥50 1 Maniuc 3 Nersesian 4 Chen	Year 2019 2018 2019	Sample 75 106 152	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.90 (0.27, 2.07) 5.04
9 Fiedler 2018 59 11 Ando 2018 252 18 Pappalardo 2017 63 19 Cheng 2016 73 21 Lin 2016 529 Subtotal (I-squared=0.0%, p=0.607) 0.37 (0.44, 1.35) 1.67 Sample <50		Sample ≥50 1 Maniuc 3 Nersesian 4 Chen 6 Schiller	Year 2019 2018 2019 2019 2018	Sample 75 106 152 94	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.89 (0.38, 2.06) 5.57
11 Ando 2018 252 18 Pappalardo 2017 63 19 Cheng 2016 73 21 Lin 2016 529 Subtotal (I-squared=0.0%, p=0.607) 33.86 25 Solé 2018 28 8 Huang 2018 46 10 Matsumoto 2018 37 12 Pawale 2017 43 13 Mourad 2017 43 14 Abdeen 2018 46 10 Matsumoto 2018 37 12 Pawale 2017 43 13 Mourad 2017 42 16 Abdeen 2016 28 22 Leidenfrest 2015 27 Overall (I-squared=0.0%, p=0.732) Note: Weights are from random effects analysis 0.73 (0.60, 0.88) 100.00		Sample ≥50 1 Maniuc 3 Nersesian 4 Chen 6 Schiller 7 Chen	Year 2019 2018 2019 2018 2018 2018	Sample 75 106 152 94 60	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.89 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36
18 Pappalardo 2017 63 19 Cheng 2016 73 21 Lin 2016 529 Subtotal (I-squared=0.0%, p=0.607) 0.41 (0.16, 1.03) 4.59 2 Singh 2019 23 5 Solé 2018 28 8 Huang 2018 46 10 Matsumoto 2018 37 12 Pawale 2017 43 13 Mourad 2017 43 14 Abdeen 2016 28 15 Centofanti 2017 24 16 Abdeen 2016 28 2 Leidenfrest 2015 27 Subtotal (I-squared=0.0%, p=0.732) Not: Weights are from random effects analysis 0.73 (0.60, 0.88) 100.00		Sample ≥50 1 Maniuc 3 Nersesian 4 Chen 6 Schiller 7 Chen 9 Fiedler	Year 2019 2018 2019 2018 2018 2018 2018	Sample 75 106 152 94 60 59	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.89 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82
19 Cheng 2016 73 21 Lin 2016 529 Subtotal (I-squared=0.0%, p=0.607) 0.41 (0.16, 1.03) 4.59 2 Singh 2019 23 5 Solé 2018 28 8 Huang 2018 46 10 Matsumoto 2018 37 12 Pawale 2017 43 13 Mourad 2017 42 14 Octof (0.07, 1.81) 1.51 0.63 (0.07, 1.81) 1.51 0.63 (0.07, 1.81) 1.51 0.63 (0.07, 1.81) 1.51 0.64 (0.09, p=0.859) 0.28 (0.06, 1.36) 0.14 (0.14, 1.02) 0.74 0.25 (0.06, 7.32) 0.33 0.28 (0.06, 1.36) 1.64 0.29 (0.23, 2.70) 2.63 0.28 (0.06, 1.36) 1.64 0.29 (0.23, 0.72) 0.23 0.28 (0.06, 1.36) 1.64 0.29 (0.23, 0.81) 19.47 0.29 (0.23, 0.81) 19.47 0.23 (0.60, 0.88) 100.00	1	Sample ≥50 1 Maniuc 3 Nersesian 4 Chen 6 Schiller 7 Chen 9 Fiedler 1 Ando	Year 2019 2018 2019 2018 2018 2018 2018	Sample 75 106 152 94 60 59 252	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.89 (0.38, 2.06) 5.57 0.89 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82 0.77 (0.44, 1.35) 12.67
10 Cutury 2010 7.3 21 Lin 2016 529 Subtotal (I-squared=0.0%, p=0.607) 0.97 (0.69, 1.37) 33.86 2 Singh 2019 23 5 Solé 2018 28 8 Huang 2017 43 10 Matsumoto 2018 37 12 Pawale 2017 43 13 Mourad 2017 42 14 Abdeen 2016 28 15 Centofanti 2017 43 16 Abdeen 2016 28 16 Abdeen 2016 28 17 Subtotal (I-squared=0.0%, p=0.859) 0.38 (0.07, 1.81) 1.51 16 Abdeen 2016 28 0.28 (0.06, 1.36) 1.64 21 Leidenfrest 2015 27 0.73 (0.60, 0.88) 100.00 Verall (I-squared=0.0%, p=0.732) Note: Weights are from random effects analysis 0.73 (0.60, 0.88) 100.00	1	Sample ≥50 1 Maniuc 3 Nersesian 4 Chen 6 Schiller 7 Chen 9 Fiedler 11 Ando 8 Pappalardo	Year 2019 2018 2019 2018 2018 2018 2018 2018	Sample 75 106 152 94 60 59 252 63	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.89 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82 0.77 (0.44, 1.35) 12.67 0.32 (0.11, 0.97) 3.36
21 Lin 2016 529 Subtotal (I-squared=0.0%, p=0.607) 33.86 Sample <50	1	Sample ≥50 Sample ≥50 Maniuc Nersesian 4 Chen 6 Schiller 7 Chen 9 Fiedler 11 Ando 18 Pappalardo 19	Year 2019 2018 2019 2018 2018 2018 2018 2017 2017	Sample 75 106 152 94 60 59 252 63 72	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.89 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82 0.77 (0.44, 1.05) 12.67 0.32 (0.11, 0.97) 3.36 0.41 (0.16, 1.03) 4.59
Subtotal (I-squared=0.0%, p=0.60/) 0.79 (0.64, 0.99) 80.53 2 Singh 2019 23 5 Solé 2018 28 8 Huang 2018 37 10 Matsumoto 2018 37 12 Pawale 2017 43 13 Mourad 2017 42 15 Centofanti 2017 24 16 Abdeen 2016 40 20 Lackermair 2016 28 20 Lackermair 2016 20 20 Leidenfrest 2015 27 Subtotal (I-squared=0.0%, p=0.732) 0.73 (0.60, 0.88) 100.00 Note: Weights are from random effects analysis 0.73 (0.60, 0.88) 100.00	1 1 1	Sample ≥50 1 Maniuc 3 Nersesian 4 Chen 6 Schiller 7 Chen 9 Fiedler 11 Ando 18 Pappalardo 19 Cheng 10 Lin	Year 2019 2018 2019 2018 2018 2018 2018 2018 2017 2016	Sample 75 106 152 94 60 59 252 63 73 73	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.89 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82 0.77 (0.44, 1.35) 12.67 0.32 (0.11, 0.97) 3.36 0.41 (0.16, 1.03) 4.59 0.67 (0.127, 1.25) 12.67
Sample <50	1 1 1 2	Sample ≥50 1 Maniuc 3 Nersesian 4 Chen 6 Schiller 7 Chen 9 Fiedler 11 Ando 18 Pappalardo 19 Cheng 21 Lin	Year 2019 2018 2019 2018 2018 2018 2018 2017 2016 2016	Sample 75 106 152 94 60 59 252 63 73 529	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.89 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82 0.77 (0.44, 1.35) 12.67 0.32 (0.11, 0.97) 3.36 0.41 (0.16, 1.03) 4.59 0.97 (0.69, 1.37) 33.86
2 Singh 2019 23 5 Solé 2018 28 8 Huang 2018 46 10 Matsumoto 2018 37 12 Pawale 2017 43 13 Mourad 2017 42 15 Centofanti 2017 2.63 15 Centofanti 2017 2.63 16 Abdeen 2016 40 20 Lackermair 2016 28 21 Leidenfrest 2015 27 Overall (I-squared=0.0%, p=0.732) 0.73 (0.60, 0.88) 100.00 Note: Weights are from random effects analysis 0.73 (0.60, 0.88) 100.00	1 1 1 2	Sample ≥50 1 Maniuc 3 Nersesian 4 Chen 6 Schiller 7 Chen 9 Fiedler 11 Ando 18 Pappalardo 19 Cheng 21 Lin Subtotal (I-squared:	Year 2019 2018 2019 2018 2018 2018 2018 2017 2016 2016 =0.0%, p=0.607)	Sample 75 106 152 94 60 59 252 63 73 529	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.89 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82 0.77 (0.44, 1.35) 12.67 0.32 (0.11, 0.97) 3.36 0.41 (0.16, 1.03) 4.59 0.97 (0.69, 1.37) 33.86 0.79 (0.64, 0.99) 80.53
5 Solé 2018 28 8 Huang 2018 46 10 Matsumoto 2018 37 12 Pawale 2017 43 13 Mourad 2017 42 15 Centofanti 2017 24 16 Abdeen 2016 40 20 Lackermair 2016 28 21 Leidenfrest 2015 27 Subtotal (I-squared=0.0%, p=0.859) Overall (I-squared=0.0%, p=0.732) Note: Weights are from random effects analysis	1 1 1 2	Sample ≥50 1 Maniuc 3 Nersesian 4 Chen 6 Schiller 7 Chen 9 Fiedler 11 Ando 18 Pappalardo 19 Cheng 21 Lin Subtotal (I-squared: Sample <50	Year 2019 2018 2019 2018 2018 2018 2018 2017 2016 2016 2016 =0.0%, p=0.607)	Sample 75 106 152 94 60 59 252 63 73 73 529	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.89 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82 0.77 (0.44, 1.35) 12.67 0.32 (0.11, 0.97) 3.36 0.41 (0.16, 1.03) 4.59 0.97 (0.69, 1.37) 33.86 0.79 (0.64, 0.99) 80.53
8 Huang 2018 46 10 Matsumoto 2018 37 12 Pawale 2017 43 13 Mourad 2017 42 15 Centofanti 2017 42 16 Abdeen 2016 40 20 Lackermair 2016 28 21 Leidenfrest 2015 27 Subtotal (I-squared=0.0%, p=0.732) Note: Weights are from random effects analysis 0.73 (0.60, 0.88) 100.00	1 1 2	Sample ≥50 Sample ≥50 Maniuc Sersesian Chen Schiller Chen Fiedler Sersesian Subtotal (I-squared= Sample <50 Singh	Year 2019 2018 2019 2018 2018 2018 2018 2017 2016 2016 =0.0%, p=0.607) 2019	Sample 75 106 152 94 60 59 252 63 73 529 23	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.88 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82 0.77 (0.44, 1.35) 12.67 0.32 (0.11, 0.97) 3.36 0.41 (0.16, 1.03) 4.59 0.97 (0.69, 1.37) 33.86 0.79 (0.64, 0.99) 80.53 0.65 (0.06, 7.32) 0.69
o rudniy 2018 40 0.42 (0.11, 1.57) 2.25 10 Matsumoto 2018 37 0.83 (0.28, 2.50) 3.32 12 Pawale 2017 43 0.70 (0.19, 2.53) 2.38 13 Mourad 2017 42 0.70 (0.19, 2.53) 2.38 15 Centofanti 2017 24 0.36 (0.07, 1.81) 1.51 16 Abdeen 2016 40 0.63 (0.17, 2.32) 2.33 20 Lackermair 2016 28 0.28 (0.06, 1.36) 1.64 21 Leidenfrest 2015 27 0.51 (0.33, 0.81) 19.47 Overall (I-squared=0.0%, p=0.732) Verall (I-squared=0.0%, p=0.732) 0.73 (0.60, 0.88) 100.00	1 1 2	Sample ≥50 1 Maniuc 3 Nersesian 4 Chen 6 Schiller 7 Chen 9 Fiedler 11 Ando 18 Pappalardo 19 Cheng 21 Lin Subtotal (I-squared: Sample <50 2 Singh 5 Solé	Year 2019 2018 2019 2018 2018 2018 2018 2018 2017 2016 2016 =0.0%, p=0.607) 2019 2018	Sample 75 106 152 94 60 59 252 63 73 529 23 23 28	OR (95% CI) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.89 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82 0.77 (0.44, 1.35) 12.67 0.32 (0.11, 0.97) 3.36 0.41 (0.16, 1.03) 4.59 0.97 (0.69, 1.37) 33.86 0.79 (0.64, 0.99) 80.53
10 Matsumoto 2018 37 12 Pawale 2017 43 13 Mourad 2017 42 15 Centofanti 2017 24 16 Abdeen 2016 40 20 Lackermair 2016 28 21 Leidenfrest 2015 27 Subtotal (I-squared=0.0%, p=0.752) Note: Weights are from random effects analysis 0.73 (0.60, 0.88) 100.00	1 1 2	Sample ≥50 Sample ≥50 Maniuc Nersesian Chen Schiller Chen Fiedler Ando Pappalardo Cheng Lin Subtotal (I-squared= Sample <50	Year 2019 2018 2019 2018 2018 2018 2018 2017 2017 2016 2016 =0.0%, p=0.607) 2019 2018 2019 2019 2018	Sample 75 106 152 94 60 59 252 63 73 529 23 23 28	OR (95% CI) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.89 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82 0.77 (0.44, 1.35) 12.67 0.32 (0.11, 0.97) 3.36 0.41 (0.16, 1.03) 4.59 0.97 (0.64, 0.99) 80.53 0.53 0.55 (0.06, 7.32) 0.69 0.33 (0.08, 1.36) 1.98 0.41 (0.14, 1.77) 2.55
12 Pawale 2017 43 13 Mourad 2017 42 15 Centofanti 2017 24 16 Abdeen 2016 40 20 Lackermair 2015 27 Subtotal (I-squared=0.0%, p=0.732) Verall (I-squared=0.0%, p=0.732) 0.73 (0.60, 0.88) 100.00 Verall (I-squared=0.0%, p=0.732) Verall (I-squared=0.0%, p=0.732) Verall (I-squared=0.0%, p=0.732) 0.73 (0.60, 0.88) 100.00	1 1 2	Sample ≥50 1 Maniuc 3 Nersesian 4 Chen 6 Schiller 7 Chen 9 Fiedler 11 Ando 18 Pappalardo 19 Cheng 21 Lin Subtotal (I-squared= Sample <50 2 Singh 5 Solé 8 Huang	Year 2019 2018 2019 2018 2018 2018 2018 2018 2017 2016 2016 =0.0%, p=0.607) 2019 2018 2018	Sample 75 106 152 94 60 59 252 63 73 529 23 28 46 46	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.89 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82 0.77 (0.44, 1.35) 12.67 0.32 (0.11, 0.97) 3.36 0.41 (0.16, 1.03) 4.59 0.97 (0.69, 1.37) 33.86 0.79 (0.64, 0.99) 80.53 0.65 (0.06, 7.32) 0.69 0.33 (0.08, 1.36) 1.98 0.42 (0.11, 1.57) 2.25
13 Mourad 2017 42 15 Centofanti 2017 24 16 Abdeen 2016 40 20 Lackermair 2016 28 21 Leidenfrest 2015 27 Subtotal (I-squared=0.0%, p=0.732) Note: Weights are from random effects analysis 0.73 (0.60, 0.88) 100.00	1 1 2 1	Sample ≥50 Sample ≥50 Maniuc Nersesian 4 Chen 6 Schiller 7 Chen 9 Fiedler 11 Ando 18 Pappalardo 19 Cheng 21 Lin Subtotal (I-squared= Sample <50	Year 2019 2018 2019 2018 2018 2018 2018 2017 2016 2016 =0.0%, p=0.607) 2019 2018 2018 2019 2018 2019 2018 2019 2018 2019 2018 2019 2018 2018 2019 2018 2018 2019 2018 2019 2018 2019 2018 2019 2018 2019 2018 2019 2018 2019 2018 2019 2018 2019 2018 2019 2018 2019 2018 2019 2018 2019 2018 2018 2019 2018 2019 2018 2018 2017 2016 2019 2018 2017 2016 2017 2016 2019 2018 2019 2018 2019 2018 2019 2018 2019 2018 2018 2019 2018 2018 2019 2018 2018 2019 2018 2018 2019 2018 2018 2018 2019 2018 2018 2018 2019 2018 2018 2018 2019 2018 2018 2018 2018 2019 2018 2	Sample 75 106 152 94 60 59 252 63 73 529 23 28 28 46 37	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.89 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82 0.77 (0.44, 1.35) 12.67 0.32 (0.11, 0.97) 3.36 0.41 (0.16, 1.03) 4.59 0.97 (0.69, 1.37) 33.86 0.79 (0.64, 0.99) 80.53 0.53 0.65 (0.06, 7.32) 0.69 0.33 (0.08, 1.36) 1.98 0.42 (0.11, 1.57) 2.25 0.83 (0.28, 2.50) 3.32
15 Centofanti 2017 24 16 Abdeen 2016 40 20 Lackermair 2016 28 21 Leidenfrest 2015 27 Subtotal (I-squared=0.0%, p=0.859) 0.33 (0.02, 1.81) 1.51 0.4 0.10 (0.01, 1.02) 0.74 0.51 (0.33, 0.81) 19.47 0.73 (0.60, 0.88) 100.00	1 1 2 1 1 2	Sample ≥50 Sample ≥50 Maniuc Nersesian Chen Schiller Chen Fiedler Ando Pappalardo Cheng Lin Subtotal (I-squared: Sample <50	Year 2019 2018 2019 2018 2018 2018 2018 2018 2017 2016 2016 =0.0%, p=0.607) 2019 2018 2018 2018 2018 2018 2019	Sample 75 106 152 94 60 59 252 63 73 529 23 28 46 37 28 46 37 43	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.89 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82 0.77 (0.44, 1.35) 12.67 0.32 (0.11, 0.97) 3.36 0.41 (0.16, 1.03) 4.59 0.97 (0.69, 1.37) 33.86 0.79 (0.64, 0.99) 80.53 0.65 (0.06, 7.32) 0.69 0.33 (0.08, 1.36) 1.98 0.42 (0.11, 1.57) 2.25 0.43 (0.28, 2.50) 3.32 0.70 (0.19, 2.53) 2.38
15 Centorianti 2017 24 16 Abdeen 2016 40 20 Lackermair 2016 28 20 Lackermair 2016 28 21 Leidenfrest 2015 27 Subtotal (I-squared=0.0%, p=0.859) 0.51 (0.33, 0.81) 19.47 Overall (I-squared=0.0%, p=0.732) 0.73 (0.60, 0.88) 100.00	1 1 2 1 1	Sample ≥50 Sample ≥50 Maniuc Sample ≥50 Kersesian Chen Chen Chen Fiedler Chen Sedder Chen Sedder Chen Chen Chen Subtotal (I-squared Sample <50 Sample <50 Singh Solé Huang Matsumoto Pawale Sole Sole Sole Sole Sole Sole Sole So	Year 2019 2018 2019 2018 2018 2018 2018 2018 2017 2016 2016 2016 2016 2016 2016 2017 2018 2018 2018 2018 2019 2018 2018 2017 2016 2017 2016 2016 2016 2017 2016 2017 2016 2017 2016 2017 2018 2017 2018 2017 2018 2017 2018 2017 2018 2017 2018 2018 2018 2018 2018 2018 2018 2018 2018 2018 2018 2018 2018 2018 2018 2018 2017 2018 2017 2018 2017 2018 2017 2018 2017 2018 2017 2017 2018 2017	Sample 75 106 152 94 60 59 252 63 73 529 23 28 46 37 23 28 46 37 43	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.88 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82 0.77 (0.44, 1.35) 12.67 0.32 (0.11, 0.97) 3.36 0.41 (0.16, 1.03) 4.59 0.97 (0.69, 1.37) 33.86 0.79 (0.64, 0.99) 80.53 0.79 (0.64, 0.99) 80.53 0.65 (0.06, 7.32) 0.69 0.33 (0.08, 1.36) 1.98 0.42 (0.11, 1.57) 2.25 0.83 (0.28, 2.50) 3.32 0.70 (0.19, 2.53) 2.38 0.70 (0.19, 2.53) 2.38
16 Abdeen 2016 40 0.63 (0.17, 2.32) 2.33 20 Lackermair 2016 28 0.28 (0.06, 1.36) 1.64 22 Leidenfrest 2015 27 0.10 (0.01, 1.02) 0.74 Subtotal (I-squared=0.0%, p=0.859) 0.73 (0.60, 0.88) 19.47 Overall (I-squared=0.0%, p=0.732) 0.73 (0.60, 0.88) 100.00	1 1 2 1 1 1 1	Sample ≥50 Sample ≥50 Maniuc Sample ≥50 Kersesian Chen Schiller Schille	Year 2019 2018 2019 2018 2018 2018 2018 2017 2016 2016 =0.0%, p=0.607) 2019 2018 2018 2018 2019 2018 2019 2018 2017 2018 2019 2018 2019 2018 2019 2018 2019 2018 2019 2018 2019 2018 2019 2018 2019 2018 2019 2018 2019 2018 2019 2018 2019 2018 2019 2018 2019 2018 2018 2019 2018 2018 2019 2018 2018 2017 2016 2016 2016 2016 2016 2017 2016 2016 2017 2016 2018 2017 2016 2018 2017 2016 2016 2016 2017 2016 2018 2017 2016 2017 2016 2017 2016 2017 2016 2017 2018 2017 2016 2017 2016 2017 2016 2017 2018 2017 2016 2017 2016 2017 2018 2017 2016 2017 2018 2017 2016 2017 2018 2017 2016 2017 2018 2017 2016 2017 2018 2017 2018 2017 2018 2017 2018 2017 2018 2017 2018 2017 2018 2018 2017 2018 2018 2018 2017 2018 2018 2017 2018 2018 2017 2018 2017 2	Sample 75 106 152 94 60 59 252 63 73 529 23 28 46 37 43 42 24	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.89 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82 0.77 (0.44, 1.35) 12.67 0.32 (0.11, 0.97) 3.36 0.41 (0.16, 1.03) 4.59 0.97 (0.69, 1.37) 33.86 0.79 (0.64, 0.99) 80.53 0.53 0.65 (0.06, 7.32) 0.69 0.33 (0.08, 1.36) 1.98 0.42 (0.11, 1.57) 2.25 0.83 (0.28, 2.50) 3.32 0.70 (0.19, 2.53) 2.38 0.79 (0.27, 2.10) 2.63
20 Lackermair 2016 28 22 Leidenfrest 2015 27 Subtotal (I-squared=0.0%, p=0.859) 0.28 (0.06, 1.36) 1.64 0.10 (0.01, 1.02) 0.74 0.51 (0.33, 0.81) 19.47 0.73 (0.60, 0.88) 100.00	1 1 2 2 1 1 1 1 1	Sample ≥50 1 Maniuc 3 Nersesian 4 Chen 6 Schiller 7 Chen 9 Fiedler 11 Ando 18 Pappalardo 19 Cheng 21 Lin Subtotal (I-squared= 5 Sample <50 2 Singh 5 Solé 8 Huang 10 Matsumoto 12 Pawale 13 Mourad 15 Centofanti	Year 2019 2018 2019 2018 2018 2018 2018 2017 2016 2016 =0.0%, p=0.607) 2019 2018 2018 2018 2018 2018 2018 2017 2017 2017	Sample 75 106 152 94 60 59 252 63 73 529 23 28 46 37 43 42 24	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.89 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82 0.77 (0.44, 1.35) 12.67 0.32 (0.11, 0.97) 3.36 0.41 (0.16, 1.03) 4.59 0.97 (0.69, 1.37) 33.86 0.79 (0.64, 0.99) 80.53 0.53 0.65 (0.06, 7.32) 0.69 0.33 (0.08, 1.36) 1.98 0.42 (0.11, 1.57) 2.25 0.83 (0.28, 2.50) 3.32 0.70 (0.19, 2.53) 2.38 0.79 (0.23, 2.70) 2.63 0.36 (0.07, 1.81) 1.51
22 Leidenfrest 2015 27 0.10 (0.01, 1.02) 0.74 Subtotal (I-squared=0.0%, p=0.859) 0.51 (0.33, 0.81) 19.47 Overall (I-squared=0.0%, p=0.732) 0.73 (0.60, 0.88) 100.00 Note: Weights are from random effects analysis 0.73 (0.60, 0.88) 100.00	1 1 2 2 1 1 1 1 1 1 1 1	Sample ≥50 Sample ≥50 Maniuc Sample ≥50 Kersesian Chen Schiller Chen Siedler Chen Siedler Chen Semple Chen Chen Subtotal (I-squared: Sample <50 Singh Solé Huang Matsumoto Sample Semple Semple Semple Chen Subtat Chen Subtat Sample Sample Solé Solé Solé Solé Solé Solé Solé Solé	Year 2019 2018 2019 2018 2018 2018 2018 2017 2016 2016 =0.0%, p=0.607) 2019 2018 2018 2018 2018 2018 2018 2019 2019 2016 2017 2016 2019 2016 2017 2016 2017 2018 2017 2016 2019 2018 2017 2016 2016 2016 2017 2016 2016 2017 2016 2016 2017 2017 2016 2017 2016 2017 2016 2017 2017 2016 2017 2017 2016 2017 2017 2016 2017 2017 2016 2017 2017 2016 2017 2017 2016 2017 2017 2016 2017 2017 2016 2017 2017 2017 2017 2017 2017 2017 2017 2017 2017 2017 2017 2017 2018 2017 2018 2017 2018 2017 2018 2017 2018 2017 2018 2017 2018 2017 2016	Sample 75 106 152 94 60 59 252 63 73 529 23 28 46 37 43 42 24 40	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.89 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82 0.77 (0.44, 1.35) 12.67 0.32 (0.11, 0.97) 3.36 0.41 (0.16, 1.03) 4.59 0.97 (0.69, 1.37) 33.86 0.79 (0.64, 0.99) 80.53 0.79 (0.64, 0.99) 80.53 0.65 (0.06, 7.32) 0.69 0.33 (0.08, 1.36) 1.98 0.42 (0.11, 1.57) 2.25 0.83 (0.28, 2.50) 3.32 0.70 (0.19, 2.53) 2.38 0.79 (0.23, 2.70) 2.63 0.36 (0.07, 1.81) 1.51 0.63 (0.17, 2.32) 2.33
Subtotal (I-squared=0.0%, p=0.859) 0.51 (0.33, 0.81) 19.47 Overall (I-squared=0.0%, p=0.732) 0.73 (0.60, 0.88) 100.00 Note: Weights are from random effects analysis 0.73 (0.60, 0.88) 100.00	1 1 2 1 1 1 1 1 1 1 1 1 1 2	Sample ≥50 Sample ≥50 Maniuc Sample ≥50 Kersesian Chen Sersesian Chen Chen Chen Chen Chen Chen Chen Che	Year 2019 2018 2019 2018 2018 2018 2018 2017 2016 2016 =0.0%, p=0.607) 2019 2018 2018 2019 2018 2019 2018 2017 2018 2017 2017 2017 2017 2016 2017 2017 2017 2016 2016 2017 2017 2017 2017 2016 2017 2018 2019 2018 2018 2019 2018 2018 2019 2018 2018 2018 2018 2018 2018 2018 2018 2018 2018 2017 2016 2016 2016 2016 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2017 2017 2016 2017 2016 2017 2017 2016 2017 2017 2017 2017 2017 2016 2017 2017 2017 2017 2017 2017 2017 2017 2016 2017 2016 2017 2017 2017 2016 2017 2017 2017 2016 2017 2016 2017 2016 2016 2017 2016 2	Sample 75 106 152 94 60 59 252 63 73 529 23 28 46 37 43 42 24 40 28	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.89 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82 0.77 (0.44, 1.35) 12.67 0.32 (0.11, 0.97) 3.36 0.41 (0.16, 1.03) 4.59 0.97 (0.69, 1.37) 33.86 0.79 (0.64, 0.99) 80.53 0.79 (0.64, 0.99) 80.53 0.42 (0.11, 1.57) 2.25 0.83 (0.28, 2.50) 3.32 0.70 (0.19, 2.53) 2.38 0.79 (0.23, 2.70) 2.63 0.36 (0.07, 1.81) 1.51 0.63 (0.17, 2.32) 2.33 0.28 (0.06, 1.36) 1.64
Overall (I-squared=0.0%, p=0.732) Note: Weights are from random effects analysis	1 1 2 2 1 1 1 1 1 1 1 1 2 2	Sample ≥50 Sample ≥50 Maniuc Nersesian Kersesian Kerses	Year 2019 2018 2019 2018 2018 2018 2018 2018 2017 2016 2016 =0.0%, p=0.607) 2019 2018 2018 2019 2018 2019 2018 2017 2017 2016 2017 2017 2016 2017 2017 2016 2017 2017 2016 2019 2018 2017 2017 2016 2017 2017 2017 2016 2017 2016 2017 2017 2017 2017 2016 2017 2017 2016 2017 2017 2016 2017 2017 2016 2017 2016 2015 2015	Sample 75 106 152 94 60 59 252 63 73 529 23 28 46 37 43 42 24 40 28 27	0R (95% CI) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.89 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82 0.77 (0.44, 1.35) 12.67 0.32 (0.11, 0.97) 3.36 0.41 (0.16, 1.03) 4.59 0.97 (0.69, 1.37) 33.86 0.79 (0.64, 0.99) 80.53 0.41 (0.16, 1.03) 1.98 0.42 (0.11, 1.57) 2.25 0.83 (0.28, 2.50) 3.32 0.70 (0.19, 2.53) 2.38 0.79 (0.23, 2.70) 2.63 0.36 (0.07, 1.81) 1.51 0.63 (0.17, 2.32) 2.33 0.70 (0.19, 2.53) 2.38 0.79 (0.23, 2.70) 2.63 0.36 (0.07, 1.81) 1.51 0.63 (0.17, 2.32) 2.33 0.74 (0.11, 1.57) 2.25
Verani (1-squared==0.0%, p=-0.752) 0.73 (0.60, 0.88) 100.00 Note: Weights are from random effects analysis	1 1 2 2 1 1 1 1 1 1 1 2 2 2	Sample ≥50 Sample ≥50 Maniuc Sample ≥50 Kersesian Kerse	Year 2019 2018 2019 2018 2018 2018 2018 2018 2017 2016 2016 2019 2018 2019 2018 2018 2017 2017 2018 2019 2018 2017 2017 2017 2018 2017 2017 2016 2019 2018 2017 2016 2019 2018 2017 2016 2017 2016 2017 2016 2017 2018 2017 2016 2017 2018 2017 2016 2017 2016 2017 2016 2017 2018 2017 2018 2017 2016 2017 2016 2017 2018 2017 2016 2017 2017 2018 2017 2018 2017 2017 2017 2017 2017 2017 2017 2017 2017 2017 2017 2017 2017 2016 2017 2017 2017 2017 2016 2017 2017 2017 2017 2016 2015 =0.0%, p=0.659)	Sample 75 106 152 94 60 59 252 63 73 529 23 28 46 37 43 42 24 40 28 27 ←	0R (95% CI) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.89 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82 0.77 (0.44, 1.35) 12.67 0.32 (0.11, 0.97) 3.36 0.41 (0.16, 1.03) 4.59 0.97 (0.69, 1.37) 33.86 0.79 (0.64, 0.99) 80.53 0.53 0.65 (0.06, 7.32) 0.69 0.33 (0.08, 1.36) 1.98 0.42 (0.11, 1.57) 2.25 0.83 (0.28, 2.50) 3.32 0.70 (0.19, 2.53) 2.38 0.79 (0.23, 2.70) 2.63 0.36 (0.07, 1.81) 1.51 0.63 (0.17, 2.32) 2.33 0.28 (0.06, 1.64 0.10 (0.01, 1.02) 0.74 0.51 (0.33, 0.81) 19.47
	1 1 2 2 1 1 1 1 1 1 1 1 2 2 2	Sample ≥50 1 Maniuc 3 Nersesian 4 Chen 6 Schiller 7 Chen 9 Fiedler 11 Ando 18 Pappalardo 19 Cheng 11 Lin Subtotal (I-squared: 5 Solé 8 Huang 10 Matsumoto 12 Pawale 13 Mourad 15 Centofanti 16 Abdeen 10 Lackermair 22 Leidenfrest Subtotal (I-squared: 10 Subtotal (I-squared: 11 Subtotal (I-squared: 12 Subtotal (I-squared: 13 Subtotal (I-squared: 14 Subtotal (I-squared: 15 Subtotal (I-squared: 16 Abdeen 17 Lackermair 18 Subtotal (I-squared: 18 Subtotal (I-squared:	Year 2019 2018 2019 2018 2018 2018 2018 2017 2016 2016 2016 2017 2018 2018 2017 2018 2018 2017 2016 2017 2018 2017 2016 2016 2016 2016 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2017 2016 2017 2016 2017 2018 2018 2017 2016 2017 2016 2017 2016 2017 2017 2017 2017 2017 2017 2017 2016 2017 2017 2017 2017 2017 2017 2017 2017 2017 2017 2017 2017 2016 2017 2016 2015 =0.0%, p=0.859)	Sample 75 106 152 94 60 59 252 63 73 529 23 28 46 37 43 42 24 40 28 27 ←	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.89 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82 0.77 (0.44, 1.35) 12.67 0.32 (0.11, 0.97) 3.36 0.41 (0.16, 1.03) 4.59 0.97 (0.69, 1.37) 33.86 0.79 (0.64, 0.99) 80.53 0.79 (0.64, 0.99) 80.53 0.42 (0.11, 1.57) 2.25 0.83 (0.28, 2.50) 3.32 0.70 (0.19, 2.53) 2.38 0.79 (0.23, 2.70) 2.63 0.36 (0.07, 1.81) 1.51 0.63 (0.07, 1.81) 1.51 0.64 (0.10 (0.01, 1.02) 0.74 0.51 (0.33, 0.81) 1.947
	1 1 2 1 1 1 1 1 1 1 1 1 2 2 2	Sample ≥50 Sample ≥50 Maniuc Sample ≥50 Maniuc Nersesian Chen Sider Fiedler Chen Fiedler Chen Fiedler Ando Repapalardo Cheng	Year 2019 2018 2019 2018 2018 2018 2018 2017 2016 2016 2016 2016 2019 2018 2018 2018 2018 2018 2018 2018 2019 2018 2019 2016 2016 2016 2015 =0.0%, p=0.859) -0.0%, p=0.732) om random effects	Sample 75 106 152 94 60 59 252 63 73 529 23 28 46 37 43 42 24 40 28 27 40 28 27 40 28 24 40 28 27 40 28 24 40 28 24 40 28 24 40 24 24 40 25 25 25 25 25 25 25 25 25 25	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.88 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82 0.77 (0.44, 1.35) 12.67 0.32 (0.11, 0.97) 3.36 0.41 (0.16, 1.03) 4.59 0.97 (0.69, 1.37) 33.86 0.79 (0.64, 0.99) 80.53 0.79 (0.64, 0.99) 80.53 0.79 (0.64, 0.99) 80.53 0.42 (0.11, 1.57) 2.25 0.83 (0.28, 2.50) 3.32 0.70 (0.19, 2.53) 2.38 0.79 (0.54, 0.53) 1.51 0.63 (0.07, 1.81) 1.51 0.63 (0.17, 2.32) 2.33 0.28 (0.06, 1.36) 1.64 0.10 (0.01, 1.02) 0.74 0.51 (0.33, 0.81) 19.47 0.73 (0.60, 0.88) 100.00
	1 1 2 2 1 1 1 1 1 1 1 1 2 2 2	Sample ≥50 Sample ≥50 Maniuc Sample ≥50 Maniuc Nersesian Chen Sider Chen Sider Chen Sider Chen Sider Chen Subtotal Chen Subtota	Year 2019 2018 2019 2018 2018 2018 2017 2016 2016 2016 2017 2018 2018 2017 2016 2018 2017 2018 2018 2017 2016 2017 2017 2016 2017 2017 2016 2017 2017 2016 2017 2017 2016 2017 2018 2019 2018 2019 2018 2019 2018 2019 2018 2018 2017 2016 2016 2016 2016 2016 2016 2016 2016 2016 2016 2017 2016 2016 2017 2016 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2017 2017 2017 2017 2017 2017 2017 2016 2017 2017 2017 2017 2017 2016 2017 2017 2016 2017 2017 2017 2016 2017 2016 2017 2017 2016 2017 2016 2017 2017 2016 2016 2017 2016 2016 2017 2016 2016 2017 2016 2016 2016 2017 2016	Sample	0R (95% Cl) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.89 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82 0.77 (0.44, 1.35) 12.67 0.32 (0.11, 0.97) 3.36 0.41 (0.16, 1.03) 4.59 0.97 (0.69, 1.37) 33.86 0.79 (0.64, 0.99) 80.53 0.79 (0.64, 0.99) 80.53 0.41 (0.11, 1.57) 2.25 0.83 (0.28, 2.50) 3.32 0.70 (0.19, 2.53) 2.38 0.79 (0.23, 2.70) 2.63 0.36 (0.07, 1.81) 1.51 0.63 (0.17, 2.32) 2.33 0.28 (0.06, 1.36) 1.64 0.10 (0.01, 1.02) 0.74 0.51 (0.33, 0.81) 19.47 0.73 (0.60, 0.88) 100.00
	1 1 2 2 1 1 1 1 1 1 2 2 2	Sample ≥50 Sample ≥50 Maniuc Sample ≥50 Kersesian Chen Schiller Chen Sideler Chen Sideler Chen Sideler Chen Subtotal Chen Subtotal (I-squared= Subtotal (I-squared= Note: Weights are fin	Year 2019 2018 2019 2018 2018 2018 2018 2017 2016 2016 2019 2018 2017 2016 2017 2017 2017 2017 2017 2016 2017 2017 2016 2017 2017 2017 2016 2015 =0.0%, p=0.859) *0.0%, p=0.732) om random effects	Sample 75 106 152 94 60 59 252 63 73 529 23 28 46 37 43 42 24 40 28 27 40 23 28 46 37 43 42 24 40 28 46 37 43 42 24 40 27 46 59 59 59 59 59 59 59 59 52 52 63 73 529 529 529 529 529 529 529 529	OR (95% CI) % weight 0.46 (0.17, 1.25) 4.00 0.91 (0.41, 2.02) 6.26 0.85 (0.35, 2.07) 5.04 0.89 (0.38, 2.06) 5.57 0.80 (0.27, 2.39) 3.36 0.79 (0.18, 3.48) 1.82 0.77 (0.44, 1.35) 12.67 0.32 (0.11, 0.97) 3.36 0.41 (0.16, 1.03) 4.59 0.97 (0.69, 1.37) 33.86 0.79 (0.64, 0.99) 80.53 0.97 (0.64, 0.99) 80.53 0.97 (0.64, 0.99) 80.53 0.79 (0.64, 0.99) 80.53 0.79 (0.23, 2.70) 2.63 0.36 (0.07, 1.31) 1.51 0.63 (0.17, 2.32) 2.33 0.70 (0.19, 2.53) 2.38 0.79 (0.23, 2.70) 2.63 0.36 (0.07, 1.31) 1.51 0.63 (0.17, 2.32) 2.33 0.28 (0.06, 1.36) 1.64 0.10 (0.01, 1.02) 0.74 0.51 (0.33, 0.81) 19.47 0.73 (0.60, 0.88) 100.00

Figure 3. Forest plot comparing the risk of death between ECMO combined with left ventricular decompression (LVD) therapy and ECMO alone (A represents all the included studies; B represents the studies excluding ref. [14] and [17]).

e924009-8



Figure 4. Forest plot comparing the risk of death between ECMO combined with ECMO-assisted surgery and ECMO combined with IABP.

other LV decompression techniques group, and the risk of bleeding in the ECMO combined with IABP group was higher than that in the ECMO combined other LV decompression techniques group, as shown in Figure 6B.

Publication bias and sensitivity analysis

Figures 7 and 8 show the Egger's test and sensitivity analysis results for risk of death with ECMO combined with left ventricular decompression therapy compared to that with ECMO alone and the risk of death with ECMO combined other LV decompression techniques compared to that with ECMO combined with IABP. Figure 7A shows that there was no publication bias (P=0.175), and the funnel plot shows that the studies were evenly distributed on the bottom sides of the funnel. Sensitivity analysis showed that after the elimination of studies 36 and 39, the results were more stable, as shown in Figure 8A. The results of Begg's test and Egger's test, shown in Figure 7B, indicated that there was no publication bias, and the P values were 0.484 and 0.241, respectively. The funnel plots showed that the studies were evenly distributed on both sides of the funnel. Sensitivity analysis showed that the results were stable, as shown in Figure 8B.

Discussion

As we often see, central venous pressure (CVP) decreases significantly during ECMO in patients with severe LV dysfunction. However, the left atrial pressure remains high as the left ventricle contracts, and diastolic function is seriously impaired, resulting in excessive LV preload and LVEDP [15]. Elevating ECMO flow is not a good strategy for decreasing preload because a high blood flow rate can injure blood cells and the increase in retrograde perfusion flow further increases the LV afterload [9,16]. At this time, ECMO combined with decompression therapy such as IABP or ECMO combined other LV decompression techniques can effectively reduce LV afterload and balance the left and right heart filling. In this study, we performed a meta-analysis and found that the risk of death with ECMO combined with left ventricular decompression therapy was lower than that with ECMO alone. Through subgroup analysis, we found that a difference in sample sizes was the source of study heterogeneity. By dividing the studies into those with a sample size greater than 50 cases and those with a sample size smaller than 50 cases and excluding studies 36 and 39, we confirmed this conclusion.

The intra-aortic balloon pump (IABP), a counter-pulsation pump placed in the descending aorta, is the most commonly used assist device worldwide. The principle of IABP is inflation of the balloon in diastole and active deflation in systole, which

No.	Author	Year	Sample		OR (95% CI)	% weight
	Sample ≥50					
1	Kim	2019	67 —		0.36 (0.10, 1.36)	6.48
2	Chen	2019	158	↓↓ ■ − − −	2.19 (0.94, 5.06)	11.30
5	Schiller	2018	94	i	1.28 (0.56, 2.95)	11.46
6	Fiedler	2018	59		1.09 (0.25, 4.75)	5.40
8	Bréchot	2017	126	_	0.59 (0.29, 1.21)	13.27
9	Pappalardo	2016	63	- <u>-</u>	3.10 (1.03, 9.29)	8.22
10	lin	2016	529	_ _	0.97 (0.69, 1.37)	20.26
10	Subtotal (I-sou	lared=50.60	% n=0.059)		1 10 (0 70 1 71)	76.40
	Subtotal (i Squ	urcu—50.07	0, p=0.037)	Ť	1.10 (0.70, 1.71)	70.10
	Sample <50					
3	Matsumoto	2018	37		3.03 (0.53, 7.25)	6.46
4	Neresian	2018	37	p ;	1.07 (0.24, 4.84)	5.24
7	Mourad	2017	42	+	1.26 (0.37, 4.29)	7.09
11	Leidenforts	2017	27	<u> ;</u>	4.63 (0.51, 12.11)	4.82
	Subtotal (I-squ	iared=0.0%	, p=0.444)	\leftarrow	1.99 (1.00, 3.98)	23.60
	Querell (Les	ad (4.00/	- 0.0CZ)	-	1 77 /0 0/ 1 07	100.00
	overali (i-squa	red=44.0%	, p=0.057)	\rightarrow	1.27 (0.86, 1.87)	100.00
Note	e: Weights are from	m random ef	fects analysis			
			•			
			.1	1 3.5		
			.1	1 3.5		
_	Author	Year	.1 r Sample	1 3.5	OR (95% CI)	% weight
_	Author Asia	Year	.1 r Sample	1 3.5	OR (95% CI)	% weight
_	Author Asia Kim	Year 201	.1 Sample	1 3.5	OR (95% CI) 0.36 (0.10, 1.36)	% weight 6.48
_	Author Asia Kim Chen	Year 201 201	.1 Sample 9 67 9 158		OR (95% Cl) 0.36 (0.10, 1.36) 2.19 (0.94, 5.06)	% weight 6.48 11.30
	Author Asia Kim Chen Matsumoto	Year 201 201 201	.1 7 Sample 9 67		OR (95% Cl) 0.36 (0.10, 1.36) 2.19 (0.94, 5.06) 3.03 (0.69, 1.37)	% weight 6.48 11.30 6.46
_	Author Asia Kim Chen Matsumoto Lin Subtotal (I-smu	Yeai 201 201 201 201 1ared=50.6°	.1 7 Sample 9 67 9 158 8 37 6 529 6 p=0.059)		OR (95% Cl) 0.36 (0.10, 1.36) 2.19 (0.94, 5.06) 3.03 (0.69, 1.37) 0.97 (0.69, 1.37)	% weight 6.48 11.30 6.46 20.26
	Author Asia Kim Chen Matsumoto Lin Subtotal (I-squ	Year 201 201 201 201 201 ared=50.69	.1 r Sample 9 67		OR (95% Cl) 0.36 (0.10, 1.36) 2.19 (0.94, 5.06) 3.03 (0.69, 1.37) 0.97 (0.69, 1.37) 1.24 (0.61, 2.52)	% weight 6.48 11.30 6.46 20.26 44.50
	Author Asia Kim Chen Matsumoto Lin Subtotal (I-squ Europe	Year 201 201 201 201 ared=50.69	.1 r Sample 9 67		OR (95% Cl) 0.36 (0.10, 1.36) 2.19 (0.94, 5.06) 3.03 (0.69, 1.37) 0.97 (0.69, 1.37) 1.24 (0.61, 2.52)	% weight 6.48 11.30 6.46 20.26 44.50
	Author Asia Kim Chen Matsumoto Lin Subtotal (I-squ Europe Neresian Schiller	Year 201 201 201 201 ared=50.69 201	.1 Sample 9 67 9 158 8 37 6 529 %, p=0.059) 8 37 8 37		OR (95% Cl) 0.36 (0.10, 1.36) 2.19 (0.94, 5.06) 3.03 (0.69, 1.37) 0.97 (0.69, 1.37) 1.24 (0.61, 2.52) 1.07 (0.34, 4.84)	% weight 6.48 11.30 6.46 20.26 44.50 5.24
	Author Asia Kim Chen Matsumoto Lin Subtotal (I-squ Europe Neresian Schiller Mayuzad	Year 201 201 201 201 ared=50.69 201 201	.1 r Sample 9 67 9 158 8 37 6 529 %, p=0.059) 8 37 8 94 7 42		OR (95% Cl) 0.36 (0.10, 1.36) 2.19 (0.94, 5.06) 3.03 (0.69, 1.37) 0.97 (0.69, 1.37) 1.24 (0.61, 2.52) 1.07 (0.34, 4.84) 1.28 (0.56, 2.95) 1.26 (0.37, 4.95)	% weight 6.48 11.30 6.46 20.26 44.50 5.24 11.46 7.00
	Author Asia Kim Chen Matsumoto Lin Subtotal (I-squ Europe Neresian Schiller Mourad Pećchat	Year 201 201 201 201 ared=50.69 201 201 201 201	.1 7 Sample 9 67		OR (95% Cl) 0.36 (0.10, 1.36) 2.19 (0.94, 5.06) 3.03 (0.69, 1.37) 0.97 (0.69, 1.37) 1.24 (0.61, 2.52) 1.07 (0.34, 4.84) 1.28 (0.56, 2.95) 1.26 (0.37, 4.29)	% weight 6.48 11.30 6.46 20.26 44.50 5.24 11.46 7.09 13.27
	Author Asia Kim Chen Matsumoto Lin Subtotal (I-squ Europe Neresian Schiller Mourad Bréchot Danpalardo	Year 201 201 201 201 aared=50.69 201 201 201 201 201	.1 7 Sample 9 67 9 158 8 37 6 529 %, p=0.059) 8 37 8 94 7 42 7 126 6 23		OR (95% Cl) 0.36 (0.10, 1.36) 2.19 (0.94, 5.06) 3.03 (0.69, 1.37) 0.97 (0.69, 1.37) 1.24 (0.61, 2.52) 1.07 (0.34, 4.84) 1.28 (0.56, 2.95) 1.26 (0.37, 4.29) 0.59 (0.29, 1.21)	% weight 6.48 11.30 6.46 20.26 44.50 5.24 11.46 7.09 13.27 9.33
	Author Asia Kim Chen Matsumoto Lin Subtotal (I-squ Europe Neresian Schiller Mourad Bréchot Pappalardo Subtotal (I-squ	Year 201 201 201 201 1ared=50.69 201 201 201 201 201 201 201 201	.1 x Sample 9 67 9 158 8 37 6 529 %, p=0.059) 8 37 8 94 7 42 7 126 6 63 %, p=0.164)		OR (95% Cl) 0.36 (0.10, 1.36) 2.19 (0.94, 5.06) 3.03 (0.69, 1.37) 0.97 (0.69, 1.37) 1.24 (0.61, 2.52) 1.07 (0.34, 4.84) 1.28 (0.56, 2.95) 1.26 (0.37, 4.29) 0.59 (0.29, 1.21) 3.10 (1.03, 9.29) 1.17 (0.66, 2.09)	% weight 6.48 11.30 6.46 20.26 44.50 5.24 11.46 7.09 13.27 8.22 45.28
	Author Asia Kim Chen Matsumoto Lin Subtotal (I-squ Europe Neresian Schiller Mourad Bréchot Pappalardo Subtotal (I-squ	Year 201 201 201 101 201 201 201 201 201 201	.1 2 Sample 9 67 9 158 8 37 6 529 %, p=0.059) 8 37 8 94 7 42 7 126 6 63 %, p=0.164)		OR (95% Cl) 0.36 (0.10, 1.36) 2.19 (0.94, 5.06) 3.03 (0.69, 1.37) 0.97 (0.69, 1.37) 1.24 (0.61, 2.52) 1.07 (0.34, 4.84) 1.28 (0.56, 2.95) 1.26 (0.37, 4.29) 0.59 (0.29, 1.21) 3.10 (1.03, 9.29) 1.17 (0.66, 2.09)	% weight 6.48 11.30 6.46 20.26 44.50 5.24 11.46 7.09 13.27 8.22 45.28
	Author Asia Kim Chen Matsumoto Lin Subtotal (I-squ Europe Neresian Schiller Mourad Bréchot Pappalardo Subtotal (I-squ North America Eiodler	Year 201 201 201 201 ared=50.69 201 201 201 201 201 201 201 201 201 201	.1 Sample 9 67 9 158 8 37 6 529 %, p=0.059) 8 37 8 94 7 42 7 126 6 63 %, p=0.164) 8 50		OR (95% Cl) 0.36 (0.10, 1.36) 2.19 (0.94, 5.06) 3.03 (0.69, 1.37) 0.97 (0.69, 1.37) 1.24 (0.61, 2.52) 1.07 (0.34, 4.84) 1.28 (0.56, 2.95) 1.26 (0.37, 4.29) 0.59 (0.29, 1.21) 3.10 (1.03, 9.29) 1.17 (0.66, 2.09) 1.09 (0.25, 4.75)	% weight 6.48 11.30 6.46 20.26 44.50 5.24 11.46 7.09 13.27 8.22 45.28
	Author Asia Kim Chen Matsumoto Lin Subtotal (I-squ Europe Neresian Schiller Mourad Bréchot Pappalardo Subtotal (I-squ North America Fiedler Leidonforrt	Year 201 201 201 201 201 201 201 201 201 201	.1 5 Sample 9 67 9 158 8 37 6 529 %, p=0.059) 8 37 8 94 7 42 7 126 6 63 %, p=0.164) 8 59 5 27		OR (95% Cl) 0.36 (0.10, 1.36) 2.19 (0.94, 5.06) 3.03 (0.69, 1.37) 0.97 (0.69, 1.37) 1.24 (0.61, 2.52) 1.07 (0.34, 4.84) 1.28 (0.56, 2.95) 1.26 (0.37, 4.29) 0.59 (0.29, 1.21) 3.10 (1.03, 9.29) 1.17 (0.66, 2.09) 1.09 (0.25, 4.75) 4.63 (0.51, 1.2, 11)	% weight 6.48 11.30 6.46 20.26 44.50 5.24 11.46 7.09 13.27 8.22 45.28 5.40 4.82
	Author Asia Kim Chen Matsumoto Lin Subtotal (I-squ Europe Neresian Schiller Mourad Bréchot Pappalardo Subtotal (I-squ North America Fiedler Leidenforst	Year 201 201 201 201 ared=50.69 201 201 201 ared=38.59 201 red=41.99 201	.1 r Sample 9 67 9 158 8 37 6 529 %, p=0.059) 8 37 8 94 7 42 7 126 6 63 %, p=0.164) 8 59 5 27 p=0.190)		OR (95% Cl) 0.36 (0.10, 1.36) 2.19 (0.94, 5.06) 3.03 (0.69, 1.37) 0.97 (0.69, 1.37) 1.24 (0.61, 2.52) 1.07 (0.34, 4.84) 1.28 (0.56, 2.95) 1.26 (0.37, 4.29) 0.59 (0.29, 1.21) 3.10 (1.03, 9.29) 1.17 (0.66, 2.09) 1.09 (0.25, 4.75) 4.63 (0.51, 12.11) 2.18 (0.53, 9.98)	% weight 6.48 11.30 6.46 20.26 44.50 5.24 11.46 7.09 13.27 8.22 45.28 5.40 4.82 10.22
	Author Asia Kim Chen Matsumoto Lin Subtotal (I-squ Europe Neresian Schiller Mourad Bréchot Pappalardo Subtotal (I-squ North America Fiedler Leidenforst Overall (I-squa	Year 201 201 201 201 ared=50.69 201 201 201 ared=38.59 201 201 red=41.8%	.1 7 Sample 9 67 9 158 8 37 6 529 %, p=0.059) 8 37 8 94 7 42 7 126 6 63 %, p=0.164) 8 59 5 27 , p=0.190)		OR (95% Cl) 0.36 (0.10, 1.36) 2.19 (0.94, 5.06) 3.03 (0.69, 1.37) 0.97 (0.69, 1.37) 1.24 (0.61, 2.52) 1.07 (0.34, 4.84) 1.28 (0.56, 2.95) 1.26 (0.37, 4.29) 0.59 (0.29, 1.21) 3.10 (1.03, 9.29) 1.17 (0.66, 2.09) 1.09 (0.25, 4.75) 4.63 (0.51, 12.11) 2.18 (0.53, 9.98)	% weight 6.48 11.30 6.46 20.26 44.50 5.24 11.46 7.09 13.27 8.22 45.28 5.40 4.82 10.22
	Author Asia Kim Chen Matsumoto Lin Subtotal (I-squ Europe Neresian Schiller Mourad Bréchot Pappalardo Subtotal (I-squ Rorth America Fiedler Leidenforst Overall (I-squa	Year 201 201 201 201 201 201 201 201 201 201	.1 7 Sample 9 67 9 158 8 37 6 529 5, p=0.059) 8 37 8 94 7 42 7 126 6 63 6, p=0.164) 8 59 5 27 , p=0.190) , p=0.057)		OR (95% Cl) 0.36 (0.10, 1.36) 2.19 (0.94, 5.06) 3.03 (0.69, 1.37) 0.97 (0.69, 1.37) 1.24 (0.61, 2.52) 1.07 (0.34, 4.84) 1.28 (0.56, 2.95) 1.26 (0.37, 4.29) 0.59 (0.29, 1.21) 3.10 (1.03, 9.29) 1.17 (0.66, 2.09) 1.09 (0.25, 4.75) 4.63 (0.51, 12.11) 2.18 (0.53, 9.98) 1.27 (0.86, 1.87)	% weight 6.48 11.30 6.46 20.26 44.50 5.24 11.46 7.09 13.27 8.22 45.28 5.40 4.82 10.22 100.00

Figure 5. Forest plot comparing the risk of death between ECMO-assisted surgery and ECMO combined with IABP (A represents grouping by sample size; B represents grouping by region).

induces higher diastolic perfusion pressure in the coronary arteries and unloads the diseased heart by reducing left ventricular afterload during systole [17]. According to its mechanistic features, IABP can neutralize some of the adverse effects of VA-ECMO; IABP can reduce the increased afterload of retrograde flow and increase myocardial oxygen supply by lowering myocardial oxygen consumption [13]. Furthermore, in some studies, IABP was found to increase coronary perfusion [17]. The counteracting effect of IABP helps ECMO better reduce the work of the heart and help the heart recover. Our statistical results show that ECMO combined with LVD is more beneficial than using ECMO alone and helps to lower patient

e924009-10



Figure 6. Comparison of the risk of complication between ECMO combined with left ventricular decompression (LVD) therapy and ECMO alone (A) and ECMO-assisted surgery and ECMO combined with IABP (B).

mortality. Similar to our results, another team illustrated that ECMO and IABP have synergistic effects, play complementary roles in the treatment of acute cardiac failure, and can improve treatment outcomes [11], and IABP combined with VA-ECMO can also improve the success rate of weaning from VA-ECMO. However, the advantages of ECMO combined with IABP are largely based on theory and small-sample studies. When we conducted a meta-analysis, the heterogeneity of the results was mainly due to the number of samples and regional differences. Thus, in the future, we plan to carry out large-scale, multi-regional, and multi-center RCT studies to assess changes in hemodynamics and microcirculation with ECMO+IABP.

ECMO combined other LV decompression techniques is increasingly used in patients with left ventricular venting. In the ICU, we prefer a simple and rapid method of decreasing LV afterload. The most common method of LV decompression during ECMO is Impella. As a left ventricular assist device, Impella is a microaxial pump that unloads the left ventricle and reduces left ventricular wall stress [18]. The left ventricular wall tension can be reduced by 80%, and myocardial oxygen demand is reduced by 40%; thus, it is an ideal treatment for correcting refractory heart failure and heart transplantation problems. In recent years, many experiments have proven that Impella combined with ECMO, termed ECMPELLA, can better replace cardiac function [19,20]. Besides Impella, other methods, such as intraoperative left atrial decompression, can be performed by placing a left ventricular drainage tube to improve heart function. In our meta-analysis, our results showed that patients with ECMO combined other LV decompression techniques exhibited lower mortality than those undergoing ECMO alone. Subgroup analysis indicated that, as a method for left ventricular assist, IABP seems to have more advantages than ECMO combined other LV decompression techniques. Although there was no significant difference between the ECMO+IABP group and the ECMO combined other LV decompression techniques group, subgroup analysis showed that the risk of death with ECMO combined other LV decompression techniques as higher than that with ECMO+IABP in studies with a sample size smaller than 50. In addition, high costs and risk of complications should be considered with the use of Impella [19]. Nevertheless, the results are based on retrospective data, and randomized controlled trials should be performed in the future.

When using ECMO and related assist devices, complications, which are decisive factors in the prognosis of patients, are the focus of attention. Many experiments have shown that the cause of death in refractory cardiac shock patients is not heart failure, but is instead incurable complications due to the use of mechanical support [21,22]. To our surprise, the incidence of complications in patients undergoing ECMO combined with assist devices was lower than that in patients undergoing ECMO alone. Similarly, another analysis also showed that VA-ECMO plus IABP is related to decreased in-hospital deaths of patients with extracorporeal cardiopulmonary resuscitation, postcardiotomy



Figure 7. Funnel plot for ECMO combined with left ventricular decompression (LVD) therapy and ECMO alone (A) and ECMO-assisted surgery and ECMO combined with IABP (B).



Figure 8. Sensitivity analysis for ECMO combined with left ventricular decompression (LVD) therapy and ECMO alone (A) and ECMO-assisted surgery and ECMO combined with IABP (B).

cardiogenic shock, and ischemic heart disease [23]. This does not mean that the use of an assist device increases complications. When we use various mechanical devices, we will be more vigilant and fully prepared to prevent or reduce the occurrence of bleeding, ischemia, and hemolysis. In other words, when regular treatments cannot support a patient's life and mechanical devices are needed to replace heart function, complications are by no means an excuse for refusing to use the device.

The present study has several limitations. First, this was a meta-analysis that incorporated a series of related studies, including retrospective studies and prospective studies, from different regions and with different sample sizes, which may have been the source of heterogeneity and may have affected the final conclusions. Second, we compared ECMO+IABP and ECMO combined other LV decompression techniques. Due to the limited literature, we did not discuss the different methods of left ventricular decompression in more detail. It is possible that other methods, such as different surgical methods,

affect the dominant effect of ECMO-assisted surgery and other interventions. Future research should specifically distinguish the different effects of different left ventricular decompression methods in addition to IABP in patients with cardiogenic shock.

Conclusions

ECMO is useful in cardiogenic shock and is associated with lower mortality. Left ventricular decompression is more important for VA-ECMO than for ECMO alone and helps to improve patient outcomes without increasing the risk of ECMO-related complications. Our statistical analysis did not find better outcomes for ECMO combined other LV decompression techniques than for ECMO+IABP. A prospective multi-center study would help determine the potential of this technique to improve the outcomes of critically ill patients. In particular, the hemodynamic effects of different left heart decompression methods should be clearly defined.

Conflict of interest

None.

References:

- Mebazaa A, Combes A, van Diepen S et al: Management of cardiogenic shock complicating myocardial infarction. Intensive Care Med, 2018; 44(6): 760–73
- Harjola VP, Lassus J, Sionis A et al: Clinical picture and risk prediction of short-term mortality in cardiogenic shock. Eur J Heart Fail, 2015; 17(5): 501–9
- Mandawat A, Rao SV: Percutaneous mechanical circulatory support devices in cardiogenic shock. Circ Cardiovasc Interv, 2017; 10(5): e004337
- Hajjar LA, Teboul JL: Mechanical circulatory support devices for cardiogenic shock: State of the art. Crit Care, 2019; 23(1): 76
- Bellumkonda L, Gul B, Masri SC: Evolving concepts in diagnosis and management of cardiogenic shock. Am J Cardiol, 2018; 122(6): 1104–10
- Hamzaoui O, Jozwiak M, Geffriaud T et al: Norepinephrine exerts an inotropic effect during the early phase of human septic shock. Br J Anaesth, 2018; 120(3): 517–24
- 7. Toscani L, Aya HD, Antonakaki D et al: What is the impact of the fluid challenge technique on diagnosis of fluid responsiveness? A systematic review and meta-analysis. Crit Care, 2017; 21(1): 207
- Keebler ME, Haddad EV, Choi CW et al: Venoarterial extracorporeal membrane oxygenation in cardiogenic shock. JACC Heart Fail, 2018; 6(6): 503–16
- 9. Gokalp O, Donmez K, Iner H et al: Should ECMO be used in cardiogenic shock? Crit Care, 2019; 23(1): 174
- Truby LK, Takeda K, Mauro C et al: Incidence and implications of left ventricular distention during venoarterial extracorporeal membrane oxygenation support. ASAIO J, 2017; 63(3): 257–65
- 11. Ma P, Zhang Z, Song T et al: Combining ECMO with IABP for the treatment of critically III adult heart failure patients. Heart Lung Circ, 2014; 23(4): 363–68
- Shinar Z: Is the "Unprotected Heart" a clinical myth? Use of IABP, Impella, and ECMO in the acute cardiac patient. Resuscitation, 2019; 140: 205–6
- 13. Nuding S, Werdan K: IABP plus ECMO is one and one more than two? J Thorac Dis, 2017; 9(4): 961–64
- 14. Li Y, Yan S, Cai L, Zhang Q: Does VA-ECMO plus Impella work in refractory cardiogenic shock? JACC Heart Fail, 2019; 7(4): 364
- 15. Aiyagari RM, Rocchini AP, Remenapp RT, Graziano JN: Decompression of the left atrium during extracorporeal membrane oxygenation using a transseptal cannula incorporated into the circuit. Crit Care Med, 2006; 34(10): 2603–6
- Muller G, Flecher E, Lebreton G et al: The ENCOURAGE mortality risk score and analysis of long-term outcomes after VA-ECMO for acute myocardial infarction with cardiogenic shock. Intensive Care Med, 2016; 42(3): 370–78
- 17. Kapelios CJ, Terrovitis JV, Nanas JN: Current and future applications of the intra-aortic balloon pump. Curr Opin Cardiol, 2014; 29(3): 258–65
- Schrage B, Burkhoff D, Rubsamen N et al: Unloading of the left ventricle during venoarterial extracorporeal membrane oxygenation therapy in cardiogenic shock. JACC Heart Fail, 2018; 6(12): 1035–43
- Pappalardo F, Schulte C, Pieri M et al: Concomitant implantation of Impella((R)) on top of veno-arterial extracorporeal membrane oxygenation may improve survival of patients with cardiogenic shock. Eur J Heart Fail, 2017; 19(3): 404–12
- Moller-Helgestad OK, Hyldebrandt JA, Banke A et al: Impella CP or VA-ECMO in profound cardiogenic shock: Left ventricular unloading and organ perfusion in a large animal model. EuroIntervention, 2019; 14(15): e1585–92
- Le Guennec L, Cholet C, Huang F et al: Ischemic and hemorrhagic brain injury during venoarterial-extracorporeal membrane oxygenation. Ann Intensive Care, 2018; 8(1): 129
- 22. Vaquer S, de Haro C, Peruga P et al: Systematic review and meta-analysis of complications and mortality of veno-venous extracorporeal membrane oxygenation for refractory acute respiratory distress syndrome. Ann Intensive Care, 2017; 7(1): 51

- 23. Li Y, Yan S, Gao S et al: Effect of an intra-aortic balloon pump with venoarterial extracorporeal membrane oxygenation on mortality of patients with cardiogenic shock: A systematic review and meta-analysisdagger. Eur J Cardiothorac Surg, 2019; 55(3): 395–404
- 24. Maniuc O, Salinger T, Anders F et al: Impella CP use in patients with nonischaemic cardiogenic shock. ESC Heart Fail, 2019; 6(4): 863-66
- Avtaar Singh SS, Das De S, Nappi F et al: Mechanical circulatory support for refractory cardiogenic shock post-acute myocardial infarction-a decade of lessons. J Thorac Dis, 2019; 11(2): 542–48
- Nersesian G, Hennig F, Muller M et al: Temporary mechanical circulatory support for refractory heart failure: The German Heart Center Berlin experience. Ann Cardiothorac Surg, 2019; 8(1): 76–83
- Chen K, Hou J, Tang H, Hu S: Concurrent initiation of intra-aortic balloon pumping with extracorporeal membrane oxygenation reduced in-hospital mortality in postcardiotomy cardiogenic shock. Ann Intensive Care, 2019; 9(1): 16
- Ariza-Sole A, Sanchez-Salado JC, Sbraga F et al: The role of perioperative cardiorespiratory support in post infarction ventricular septal rupture-related cardiogenic shock. Eur Heart J Acute Cardiovasc Care, 2020; 9(2): 128–37
- Schiller P, Hellgren L, Vikholm P: Survival after refractory cardiogenic shock is comparable in patients with Impella and veno-arterial extracorporeal membrane oxygenation when adjusted for SAVE score. Eur Heart J Acute Cardiovasc Care, 2019; 8(4): 329–37
- Chen K, Hou J, Tang H, Hu S: Concurrent implantation of intra-aortic balloon pump and extracorporeal membrane oxygenation improved survival of patients with postcardiotomy cardiogenic shock. Artif Organs, 2019; 43(2): 142–49
- Huang CC, Hsu JC, Wu YW et al: Implementation of extracorporeal membrane oxygenation before primary percutaneous coronary intervention may improve the survival of patients with ST-segment elevation myocardial infarction and refractory cardiogenic shock. Int J Cardiol, 2018; 269: 45–50
- 32. Fiedler AG, Dalia A, Axtell AL et al: Impella placement guided by echocardiography can be used as a strategy to unload the left ventricle during peripheral venoarterial extracorporeal membrane oxygenation. J Cardiothorac Vasc Anesth, 2018; 32(6): 2585–91
- 33. Matsumoto M, Asaumi Y, Nakamura Y et al: Clinical determinants of successful weaning from extracorporeal membrane oxygenation in patients with fulminant myocarditis. ESC Heart Fail, 2018; 5(4): 675–84
- Ando M, Garan AR, Takayama H et al: A continuous-flow external ventricular assist device for cardiogenic shock: Evolution over 10 years. J Thorac Cardiovasc Surg, 2018; 156(1): 157–165.e151
- Pawale A, Schwartz Y, Itagaki S et al: Selective implantation of durable left ventricular assist devices as primary therapy for refractory cardiogenic shock. J Thorac Cardiovasc Surg, 2018; 155(3): 1059–68
- Mourad M, Gaudard P, De La Arena P et al: Circulatory support with extracorporeal membrane oxygenation and/or impella for cardiogenic shock during myocardial infarction. ASAIO J, 2018; 64(6): 708–14
- 37. Shah M, Patnaik S, Patel B et al: Trends in mechanical circulatory support use and hospital mortality among patients with acute myocardial infarction and non-infarction related cardiogenic shock in the United States. Clin Res Cardiol, 2018; 107(4): 287–303
- Centofanti P, Attisani M, La Torre M et al: Left ventricular unloading during peripheral extracorporeal membrane oxygenator support: A bridge to life in profound cardiogenic shock. J Extra Corpor Technol, 2017; 49(3): 201–5
- 39. Abdeen MS, Albert A, Maxhera B et al: Implanting permanent left ventricular assist devices in patients on veno-arterial extracorporeal membrane oxygenation support: Do we really need a cardiopulmonary bypass machine? Eur J Cardiothorac Surg, 2016; 50(3): 542–47
- 40. Aso S, Matsui H, Fushimi K, Yasunaga H: The effect of intraaortic balloon pumping under venoarterial extracorporeal membrane oxygenation on mortality of cardiogenic patients: An analysis using a Nationwide Inpatient Database. Crit Care Med, 2016; 44(11): 1974–79

e924009-13

- 41. Cheng R, Ramzy D, Azarbal B et al: Device strategies for patients in INTERMACS profiles 1 and 2 cardiogenic shock: Double bridge with extracorporeal membrane oxygenation and initial implant of more durable devices. Artif Organs, 2017; 41(3): 224–32
- Lackermair K, Sattler S, Huber BC et al: Retrospective analysis of circulatory support with the Impella CP(R) device in patients with therapy refractory cardiogenic shock. Int J Cardiol, 2016; 219: 200–3
- 43. Lin LY, Liao CW, Wang CH et al: Effects of additional intra-aortic balloon counter-pulsation therapy to cardiogenic shock patients supported by extracorporeal membranous oxygenation. Sci Rep, 2016; 6: 23838
- 44. Leidenfrost J, Prasad S, Itoh A et al: Right ventricular assist device with membrane oxygenator support for right ventricular failure following implantable left ventricular assist device placement. Eur J Cardiothorac Surg, 2016; 49(1): 73–77
- 45. Kim Y, Cho YH, Yang JH et al: Outcomes of coronary artery bypass grafting after extracorporeal life support in patients with cardiac arrest or cardiogenic shock. Korean J Thorac Cardiovasc Surg, 2019; 52(2): 70–77
- 46. Brechot N, Demondion P, Santi F et al: Intra-aortic balloon pump protects against hydrostatic pulmonary oedema during peripheral venoarterial-extracorporeal membrane oxygenation. Eur Heart J Acute Cardiovasc Care, 2018; 7(1): 62–69