Table S1 Modified AHRQ Quality Assessment Criteria for Observational Studies.

Criteria	Score	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)
Study question	***2***																		
Clearly focused and appropriate question	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Study population	***8***																		
Description of study population	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Sample size justification	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Comparability of subjects for all observational studies	***22***																		
Specific inclusion/exclusion criteria for all group	5	5	5	5	0	5	5	5	0	0	0	5	0	0	5	5	5	5	5
Criteria applied equally to all groups	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Comparability of groups at baseline with regard to disease status and prognostic factor	3	1	1	3	1	1	1	3	3	3	3	3	1	1	3	3	3	3	3
Study groups comparable to nonparticipants with regard to confounding factors	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Use of concurrent controls	5	-	-	-	-	-	-	-	-	-	-	-	-	-	5	5	5	-	5
Comparability of follow-up among groups at each assessment	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Exposure or intervention	***11***																		
Clear definition of exposure	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Measurement method standard, valid,	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

and reliable																				
Exposure measured equally in all study groups	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Outcome measures	***20***																			
Primary/secondary outcomes clearly defined	5	1	1	5	1	1	5	5	5	1	1	1	1	1	3	4	5	3	3	
Outcomes assessed blind to exposure or intervention	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Method of outcome assessment standard, valid,and reliable	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Length of follow-up adequate for question	5	2	3	5	5	3	5	5	5	5	5	5	5	3	5	5	5	5	5	
Statistical analysis	***19***																			
Statistical tests appropriate	5	4	4	4	4	4	5	4	4	5	5	5	5	4	5	5	5	4	5	
Multiple comparisons taken into consideration	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Modeling and multivariate techniques appropriate	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Power calculation provided	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Assessment of confounding	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Dose-response assessment if appropriate	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
Results	***8***																			
Measure of effect for outcomes and appropriate measure of precision	5	5	5	5	5	5	5	4	5	5	5	5	5	5	5	5	5	5	5	
Adequacy of follow-up for each study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	

group																			
Discussion	***5***																		
Conclusions supported by results with possible biases and limitations taken into consideration	5	4	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Funding or sponsorship	***5***																		
Type and sources of support for study	5	5	5	5	5	5	0	5	5	0	5	5	5	5	5	5	5	5	5
Total	**100**	**52**	**54**	**65**	**54**	**57**	**59**	**59**	**60**	**52**	**57**	**62**	**55**	**52**	**69**	**70**	**71**	**63**	**69**

AHRQ= Agency for Healthcare Review and Quality.

(1): 2000 Kavuru.et al; (2): 2001 Seymour.et al; (3): 2002 Bonfield.et al; (4): 2005 Tazawa.et al; (5): 2006 Venkateshiah.et al ; (6): 2006 Wylam.et al; (7): 2010 Tazawa.et al; (8): 2011 Ohashi.et al; (9): 2012 Khan.et al; (10): 2014 Tazawa.et al; (11): 2014 Papiris.et al; (12): 2016 Hadda.et al; (13): 2017 Ohkouchi.et al; (14): 2019 Weng.et al; (15): 2019 Tazawa.et al; (16): 2020 Trapnell.et al; (17): 2020 zhang.et al; (18): 2020 Tian.et al

Table S2 Side effects with GM-CSF therapy on patients with aPAP.

Study / year	Seymour et al./2001	Bonfield et al./2002	Venkateshiah et al./2006	Hadda et al./2016	Wylam et al./2006	Tazawa et al./2010	Papiris et al./2014	Tazawa et al. /2019	Tian et al. / 2020	Trapnell et al./2020	Zhang et al. /2020
side effect	neutropenia; fevers, chills, nausea/ vomiting	local skin reaction and arthralgias	injection-site edema, erythema, malaise and Shortness of breath	None	None	None	None	congestive heart failure, worsening of autoimmune pulmonary alveolar proteinosis, pneumothorax, influenza type A infection, lacunar infarction, and breast cancer	Leukocytosis/ Increase in aminotransfe-rases/ Increase in bilirubin	Chest pain	Mild skin stiffness at the subcutaneo-us injection site (arm)
No.	(1/4) 5	1	10	0	0	0	0	6	(2/15/8)25	/	2

No.= Number of patients with side effects

Table 3 Subgroup analysis of the effects of GM-CSF therapy on aPAP patients

Subgroup	Response rate [95% CI]	Studies/patients N/n	p value	p value for interaction
Combined with WLL, %				
Yes	0.986(0.950-1.020)	4/48	P< 0.001	P=0.018
No	0.739(0.950-0.860)	11/187	P< 0.001	
Age				
<45	0.800(0.579-0.961)	8/93	P < 0.001	P=0.704
≥45	0.745(0.590-0.878)	7/142	P < 0.001	
Gender,men%				
<60	0.871(0.701-0.985)	7/115	P < 0.001	P=0.210
≥60	0.850(0.621-0.968)	8/120	P < 0.001	
Smoker,%				
<60	0.716(0.554-0.857)	10/196	P < 0.001	P=0.242
≥60	0.932(0.621-1.000)	2/9	P < 0.001	
Initial dose,ug/d				
<250	0.801(0.631-0.934)	5/83	P < 0.001	P=0.750
≥250	0.764(0.556-0.893)	9/119	P < 0.001	
Treatment time，weeks				
≤24	0.651(0.402-0.868)	5/61	P < 0.001	P=0.485
>24	0.739(0.594-0.865)	9/169	P < 0.001	
Route of GM-CSF				
Subcutaneous	0.655(0.445-0.842)	7/87	P < 0.001	P=0.034
Inhaled	0.887(0.779-0.968)	7/129	P < 0.001	
Sample capacity,n				
<15	0.831(0.607-0.983)	9/68	P < 0.001	P=0.559
≥15	0.727(0.574-0.858)	6/167	P < 0.001	
Subgroup	Relapse rate [95% CI]	Studies/patients, N/n	p value	p value for interaction
Combined with WLL, %				
Yes	0.030(-0.030-0.090)	4/33	P=0.302	P<0.001
No	0.290(0.150-0.430)	10/135	P<0.001	
Age				
<45	0.133(0.019-0.301)	8/70	p = 0.005	P=0.451
≥45	0.243(0.051-0.496)	6/98	p = 0.002	
Gender,men%				
<60	0.186(0.016-0.440)	6/84	P= 0.011	P=0.987
≥60	0.187(0.097-0.291)	8/84	P < 0.001	
Smoker,%				
<60	0.200(0.093-0.329)	7/114	P < 0.001	P=0.787
≥60	0.135(0.000-0.390)	4/24	P=0.053	
Initial dose,ug/d				
<250	0.194(0.000-0.589)	4/64	p = 0.087	P=0.901
≥250	0.214(0.094-0.357)	9/86	P < 0.001	

Treatment time，weeks				
≤24	0.081(0.000-0.333)	5/38	p = 0.189	P=0.171
>24	0.291(0.143-0.461)	8/125	P < 0.001	
Route of GM-CSF				
Subcutaneous	0.216（0.017-0.507）	7/66	p = 0.013	P=0.651
Inhaled	0.158（0.076-0.256）	7/102	P < 0.001	
Sample capacity,n				
<15	0.192(0.075-0.336)	10/72	P < 0.001	P=0.778
≥15	0.262(0.056-0.540)	4/96	p = 0.002	

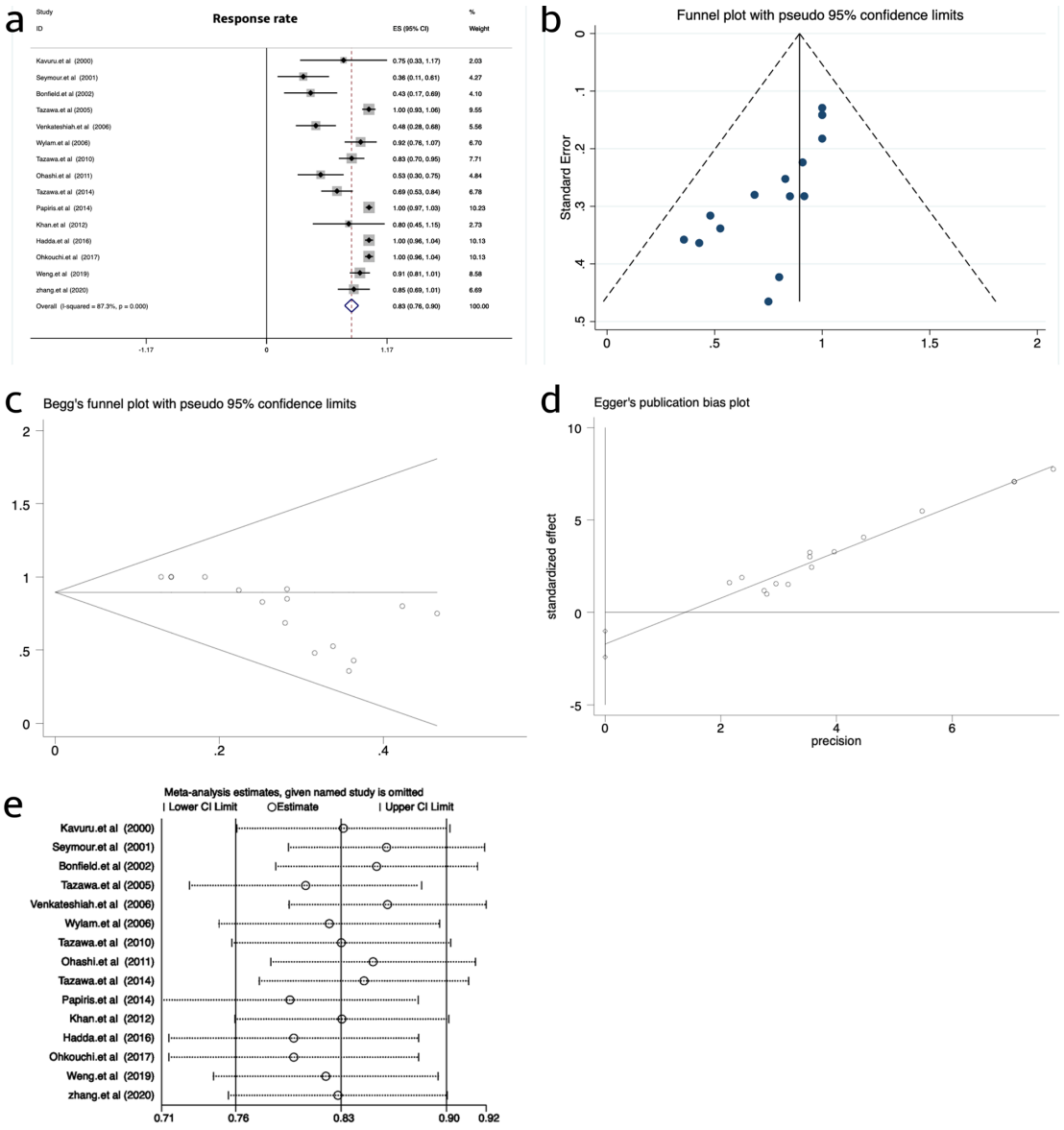

Figure S1: (a) Forest plot showing the pooled effect of response rate. (b). Funnel plot showing no publication bias of response rate. (c). Begg's funnel plot showing no publication bias of response rate. (d). Egger's publication bias plot showing no publication bias of response rate. (e). Sensitive analysis of response rate shows no significant difference.

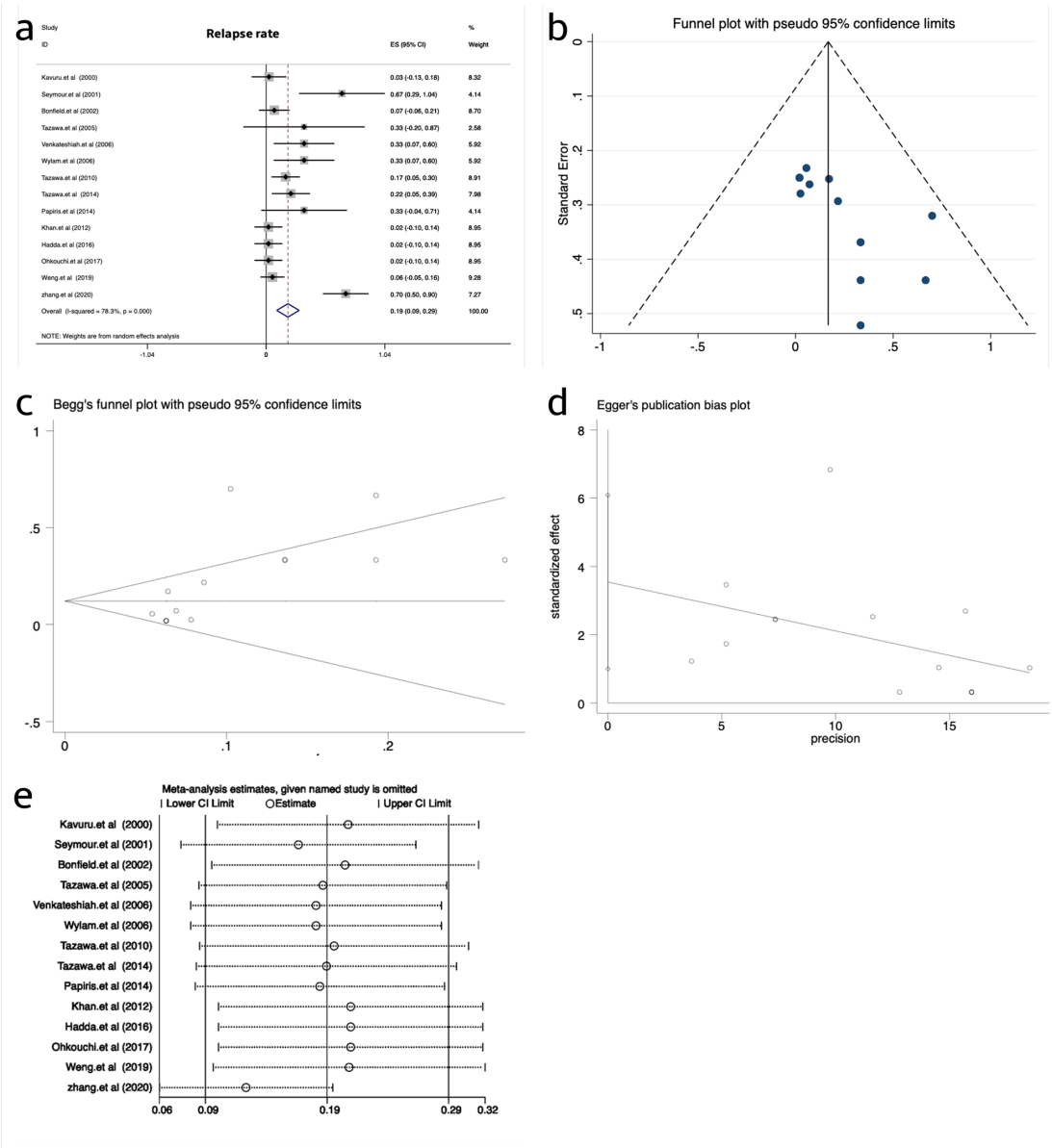

Figure S2: (a). Forest plot showing the pooled effect of relapse rate. (b). Funnel plot showing no publication bias of relapse rate. (c). Begg's funnel plot showing no publication bias of relapse rate. (d). Egger's publication bias plot showing no publication bias of relapse rate. (e). Sensitive analysis of relapse rate shows no significant difference.

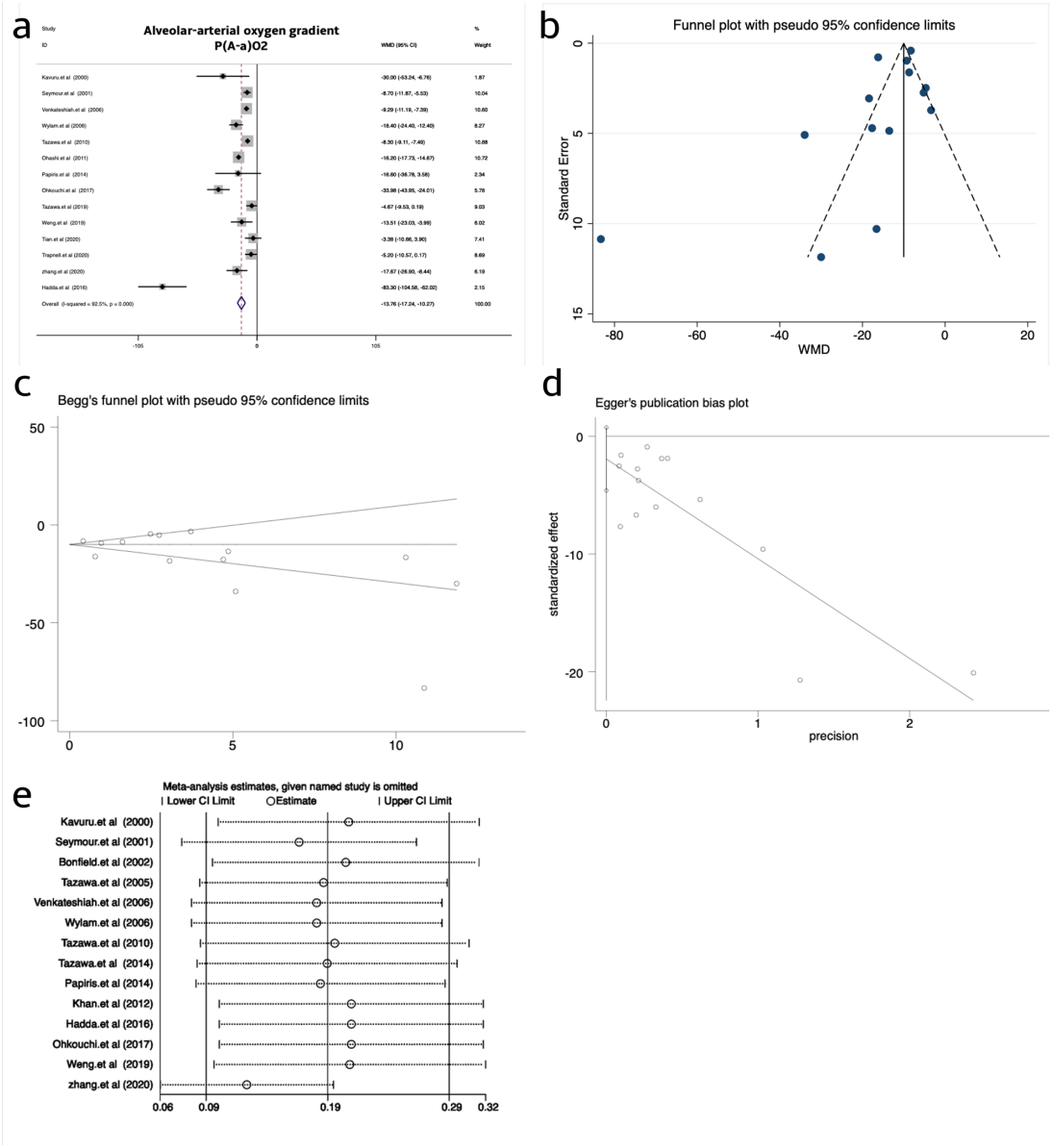

Figure S3: (a). Forest plot showing the pooled effect of $P(A\text{-}a)O_2$. (b). Funnel plot showing no publication bias of $P(A\text{-}a)O_2$. (c). Begg's funnel plot showing no publication bias of $P(A\text{-}a)O_2$. (d). Egger's publication bias plot showing no publication bias of $P(A\text{-}a)O_2$. (e). Sensitive analysis of $P(A\text{-}a)O_2$ shows no significant difference.

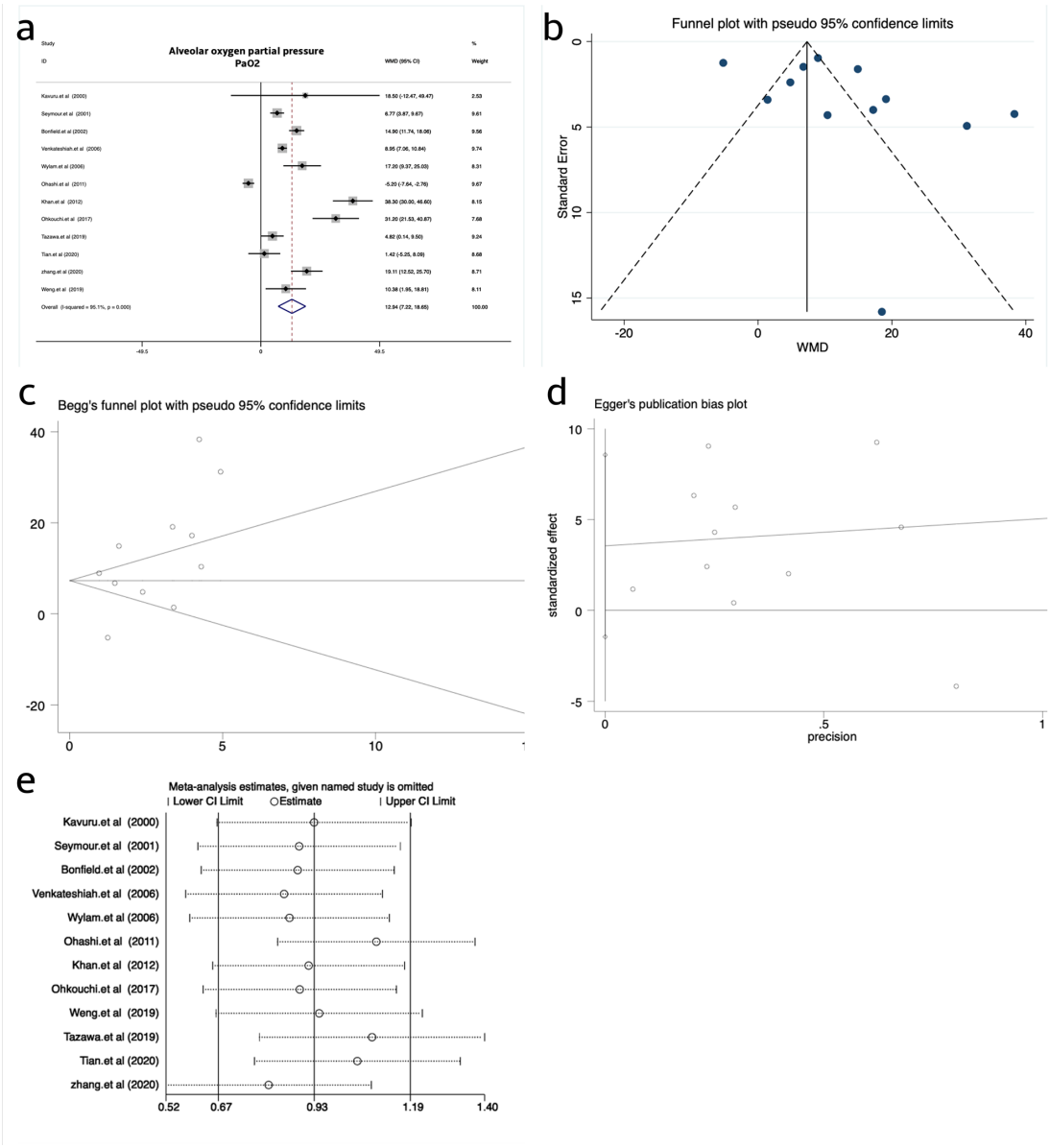

Figure S4: (a). Forest plot showing the pooled effect of PaO_2. (b). Funnel plot showing no publication bias of PaO_2. (c). Begg's funnel plot showing no publication bias of PaO_2. (d). Egger's publication bias plot showing no publication bias of PaO_2. (e). Sensitive analysis of PaO_2 shows no significant difference.

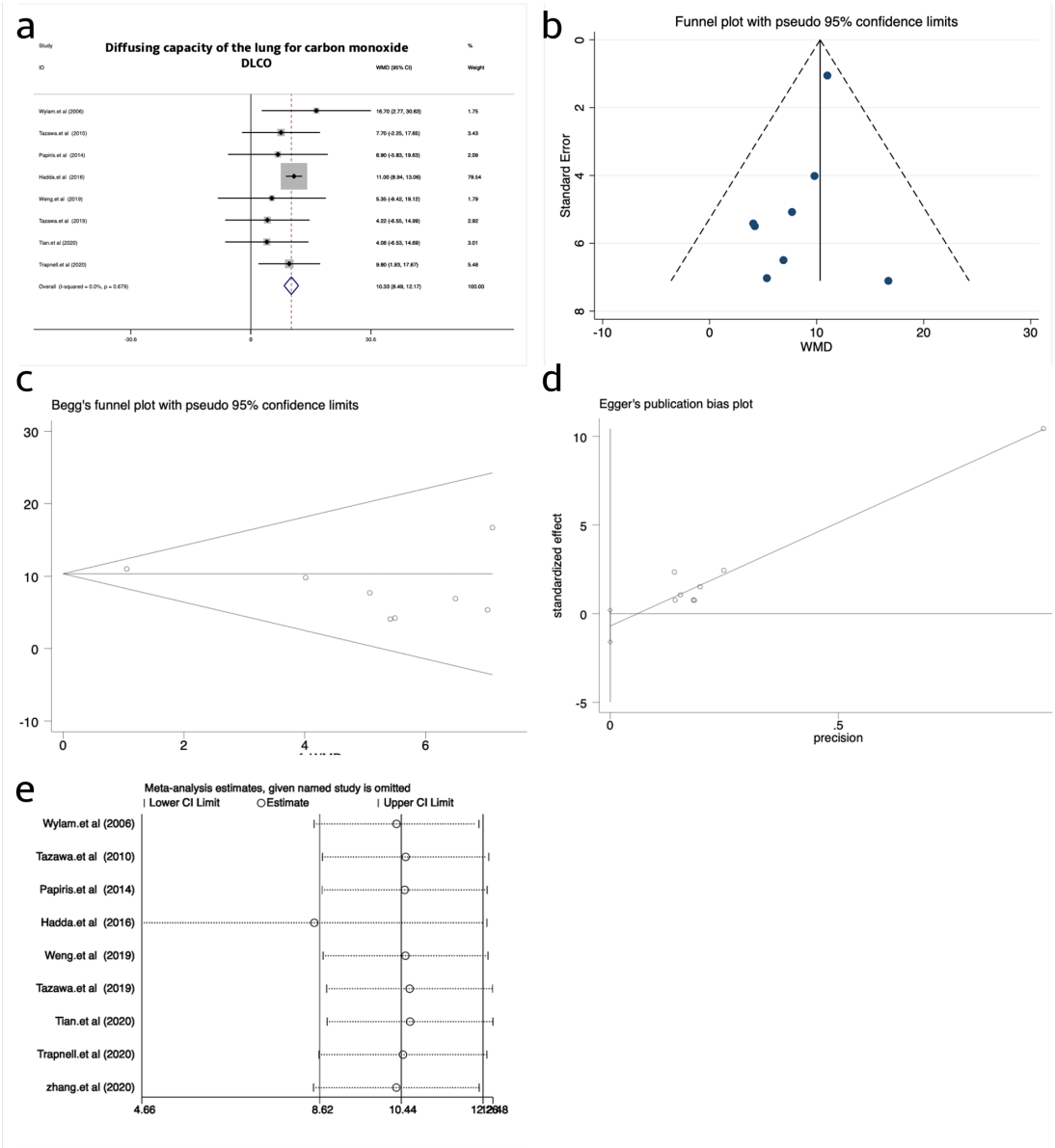

Figure S5: (a). Forest plot showing the pooled effect of DLCO. (b). Funnel plot showing no publication bias of DLCO. (c). Begg's funnel plot showing no publication bias of DLCO. (d). Egger's publication bias plot showing no publication bias of DLCO. (e). Sensitive analysis of DLCO shows no significant difference.

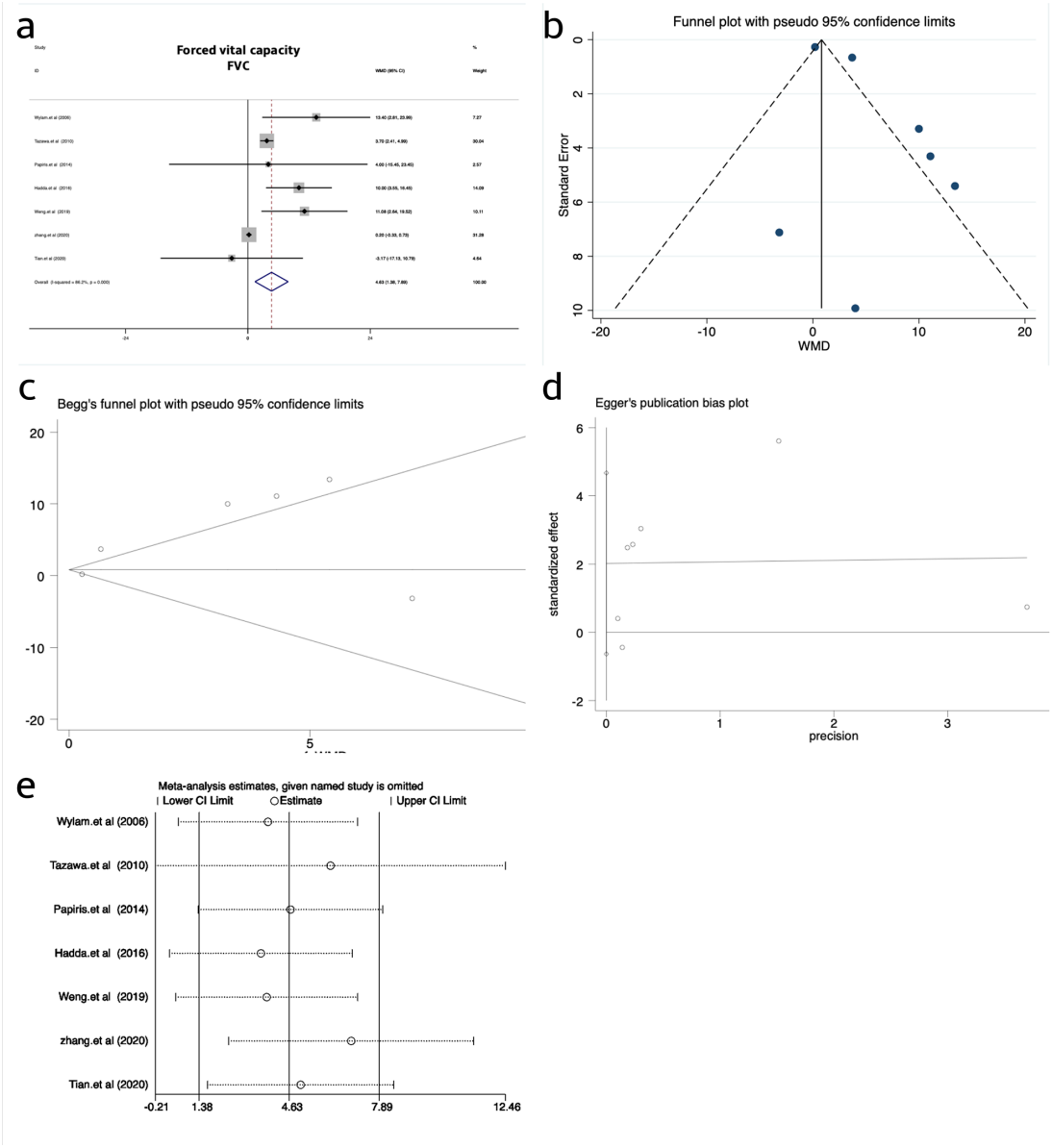

Figure S6: (a). Forest plot showing the pooled effect of FVC. (b). Funnel plot showing no publication bias of FVC. (c). Begg's funnel plot showing no publication bias of FVC. (d). Egger's publication bias plot showing no publication bias of FVC. (e). Sensitive analysis of FVC shows no significant difference.

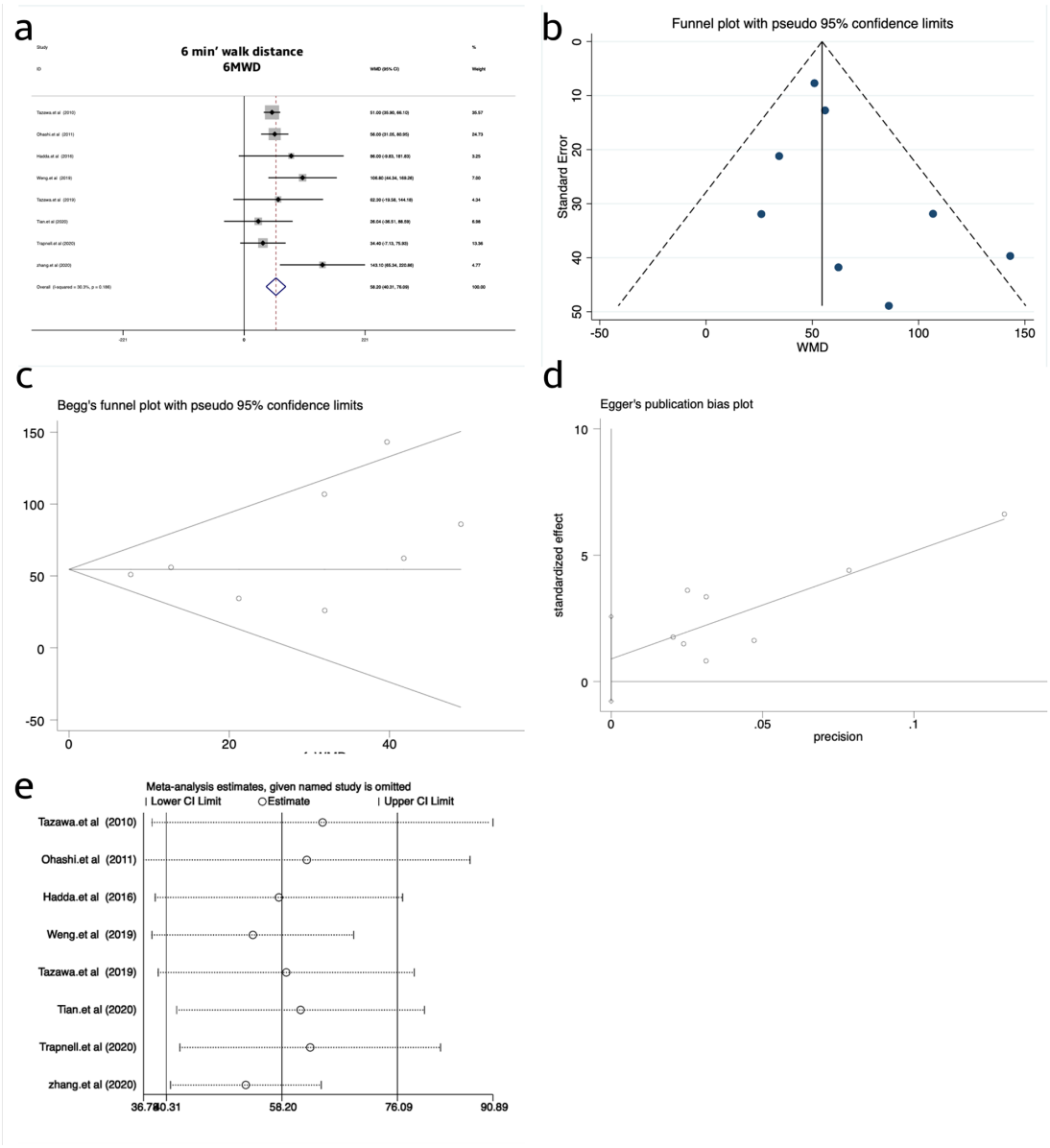

Figure S7: (a). Forest plot showing the pooled effect of 6MWD. (b). Funnel plot showing no publication bias of 6MWD. (c). Begg's funnel plot showing no publication bias of 6MWD. (d). Egger's publication bias plot showing no publication bias of 6MWD. (e). Sensitive analysis of 6MWD shows no significant difference.