

CLINICAL SCIENCE

# Anticardiolipin and other antiphospholipid antibodies in critically ill COVID-19 positive and negative patients

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# 背景

重症COVID-19においてしばしば致命的な血栓症を発症する。一方、そのような患者で高リン脂質抗体が陽性となる報告が複数あるが、COVID-19でない同じ重症度の比較対象が設定されておらず、抗リン脂質抗体とCOVID-19の関係は明らかでなかった。

# 目的

1. 抗リン脂質抗体の頻度を重症COVID-19肺障害患者と重症non-COVID-19肺障害患者で比較する
2. 抗リン脂質抗体と臨床所見（血栓症、重症度など）の関係をCOVID-19(+)およびCOVID-19(-)患者で明らかにする

# PECO

P: ICUで加療中のCOVID-19(+)呼吸不全の患者

E: 抗リン脂質抗体を測定

C: ICUで加療中のCOVID-19(-)呼吸不全の患者

O: 抗リン脂質抗体の頻度

P: ICUで加療中の 抗リン脂質抗体(+)呼吸不全の患者

E: 血栓症のsurrogate markerの測定

C: ICUで加療中の抗リン脂質抗体(-)呼吸不全の患者

O: 抗凝固薬使用頻度、血小板数、死亡率、

# COVID-19(+) vs (-)重症肺炎の患者背景 抗リン脂質抗体頻度、血栓治療の有無

**Table 1** Patient demographics, clinical and autoantibody status

	Cohort	All	COVID <sup>+</sup>	COVID <sup>-</sup>
	N	42	22	20
Age	Mean (CI)	58.2 (62.7 to 54.1)	60.9 (66.6 to 55.3)	55.7 (62 to 48.7)
Sex	N male (%)	29/42 (69)	17/22 (77)	12/20 (60)
Censored?	N (%)	5/42 (12)	4/22 (18)	1/20 (5)
No of days before censoring	Mean (CI)	39.4 (59.4 to 19.4)	44.3 (66.2 to 22.3)	20 (NA)
Days from symptom onset to ICU	Mean (CI)	6 (8.3 to 3.7)	7.5 (9.9 to 5.2)	4.2 (8.5 to 0)
APACHE II on ICU admission	Mean (CI)	25.3 (27.6 to 22.9)	23.7 (27 to 20.4)	27 (30.5 to 23.5)
Mean of SOFA score for first 3 days	Mean (CI)	9.6 (10.7 to 8.5)	9.3 (11 to 7.7)	9.9 (11.6 to 8.3)
Mean of SOFA score for first 7 days	Mean (CI)	8.9 (10.1 to 7.8)	9.1 (11 to 7.3)	8.7 (10.3 to 7.2)
ICU days (censored)	Mean (CI)	14.1 (17.3 to 10.8)	14.2 (20.5 to 7.8)	14 (16.9 to 11.1)
Death in ICU	N (%)	13/42 (31)	7/22 (32)	6/20 (30)
Mechanical ventilation days (censored)	Mean (CI)	14.4 (18.9 to 10)	16.8 (25.1 to 8.6)	11.8 (14.9 to 8.7)
Total days of ventilation rescue measures	Mean (CI)	2.9 (4.3 to 1.4)	4.4 (7 to 1.8)	1.2 (2 to 0.4)
Therapeutic anticoagulation used	N (%)	8/42 (19)	3/22 (14)	5/20 (25)
Mean platelet count	Mean (CI)	239 (269 to 209)	264 (313 to 214)	212 (245 to 179)
Mean platelet to neutrophil ratio	Mean (CI)	35.2 (42 to 28.4)	38.7 (48.4 to 29)	31.4 (41.6 to 21.2)
aCL IgG	N (%)	20/42 (48)	13/22 (59)	7/20 (35)
aCL IgM	N (%)	9/42 (21)	7/22 (32)	2/20 (10)
Anti-β2GPI IgG	N (%)	0	0	0
Anti-β2GPI IgM	N (%)	0	0	0
Anti-domain 1 β2GP1 IgG	N (%)	0	0	0
Anti-PS/PT IgG	N (%)	0	0	0
Anti-PS/PT IgM	N (%)	1/42 (2)	1/22 (5)	0

# COVID-19(+) vs (-)重症肺炎の患者背景(Table 1の一部抜粋)

	COVID <sup>+</sup>	COVID <sup>-</sup>
	22	20
Age	60.9 (66.6 to 55.3)	55.7 (62 to 48.7)
Sex	17/22 (77)	12/20 (60)
Censored?	4/22 (18)	1/20 (5)
No of days before censoring	44.3 (66.2 to 22.3)	20 (NA)
Days from symptom onset to ICU	7.5 (9.9 to 5.2)	4.2 (8.5 to 0)
APACHE II on ICU admission	23.7 (27 to 20.4)	27 (30.5 to 23.5)
Mean of SOFA score for first 3 days	9.3 (11 to 7.7)	9.9 (11.6 to 8.3)
Mean of SOFA score for first 7 days	9.1 (11 to 7.3)	8.7 (10.3 to 7.2)
ICU days (censored)	14.2 (20.5 to 7.8)	14 (16.9 to 11.1)
Death in ICU	7/22 (32)	6/20 (30)
Mechanical ventilation days (censored)	16.8 (25.1 to 8.6)	11.8 (14.9 to 8.7)
Total days of ventilation rescue measures	4.4 (7 to 1.8)	1.2 (2 to 0.4)

重症度や背景に差はない

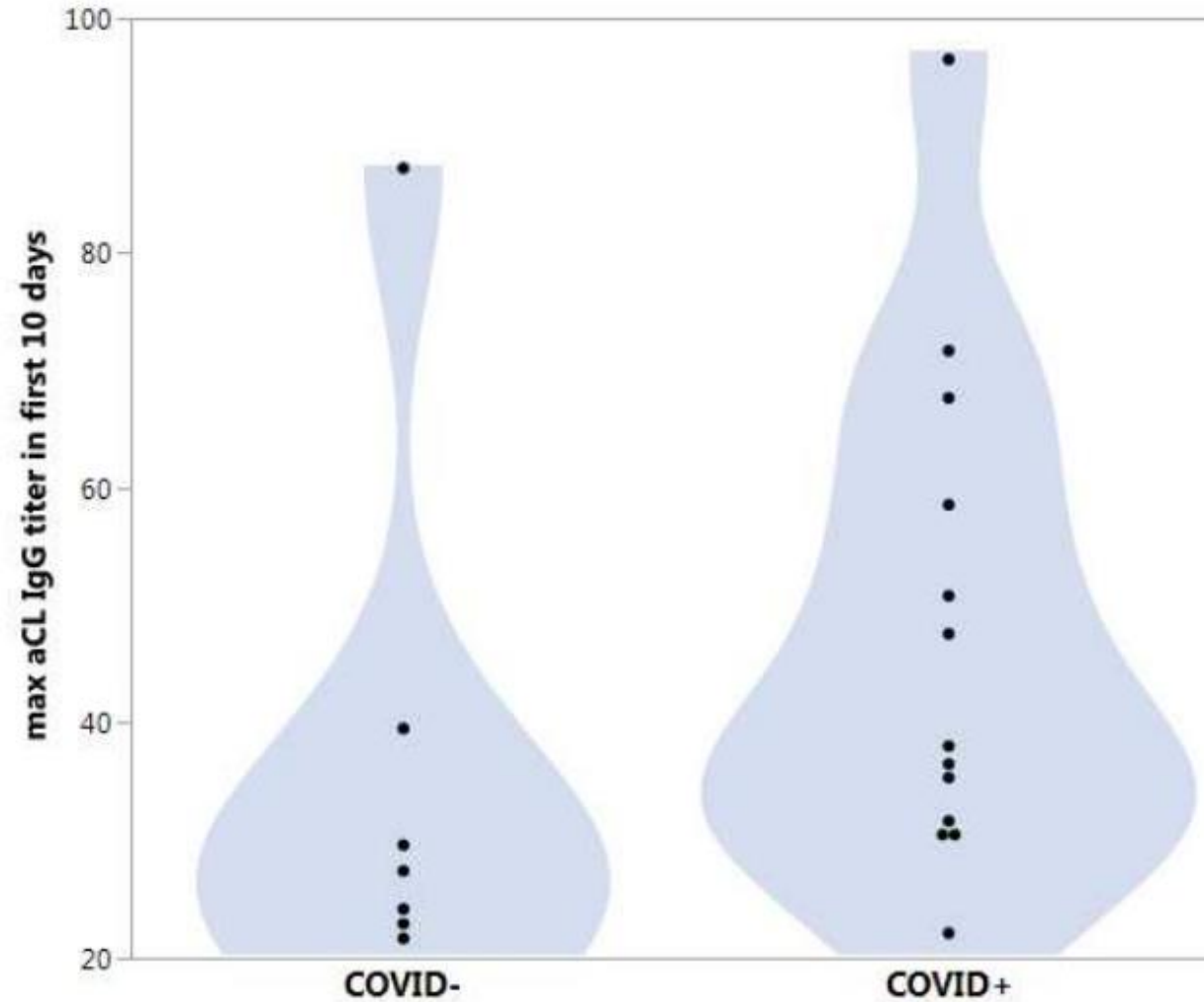
# COVID-19(+) vs (-)重症肺炎で 抗リン脂質抗体の頻度と血栓症surrogate markerの比較 (Table 1の一部抜粋)

	COVID <sup>+</sup>	COVID <sup>-</sup>
	22	20
Therapeutic anticoagulation used	3/22 (14)	5/20 (25)
Mean platelet count	264 (313 to 214)	212 (245 to 179)
Mean platelet to neutrophil ratio	38.7 (48.4 to 29)	31.4 (41.6 to 21.2)
aCL IgG	13/22 (59)	7/20 (35)
aCL IgM	7/22 (32)	2/20 (10)
Anti-β2GPI IgG	0	0
Anti-β2GPI IgM	0	0
Anti-domain 1 β2GP1 IgG	0	0
Anti-PS/PT IgG	0	0
Anti-PS/PT IgM	1/22 (5)	0

抗凝固治療頻度に差はなく、抗リン脂質抗体頻度も差がない（ややCOVID+で多い傾向）

# COVID-19(+) vs (-)重症肺炎で抗リン脂質抗体価の比較

Supplemental Figure 1: aCL titers according to COVID status



抗リン脂質抗体価に差がない（ややCOVID+で高い傾向）

# 抗カルジオリピン抗体頻度の経時的変化

**Table 2** Development of ACL IgG and IgM over time

Cohort		aCL detected on admission	aCL developed within 10 days	Late appearing aCL (after 10 days)
aCL IgG positive	COVID <sup>+</sup>	4	9	2
	COVID <sup>-</sup>	3	4	0
aCL IgM positive	COVID <sup>+</sup>	1	6	2
	COVID <sup>-</sup>	1	1	1



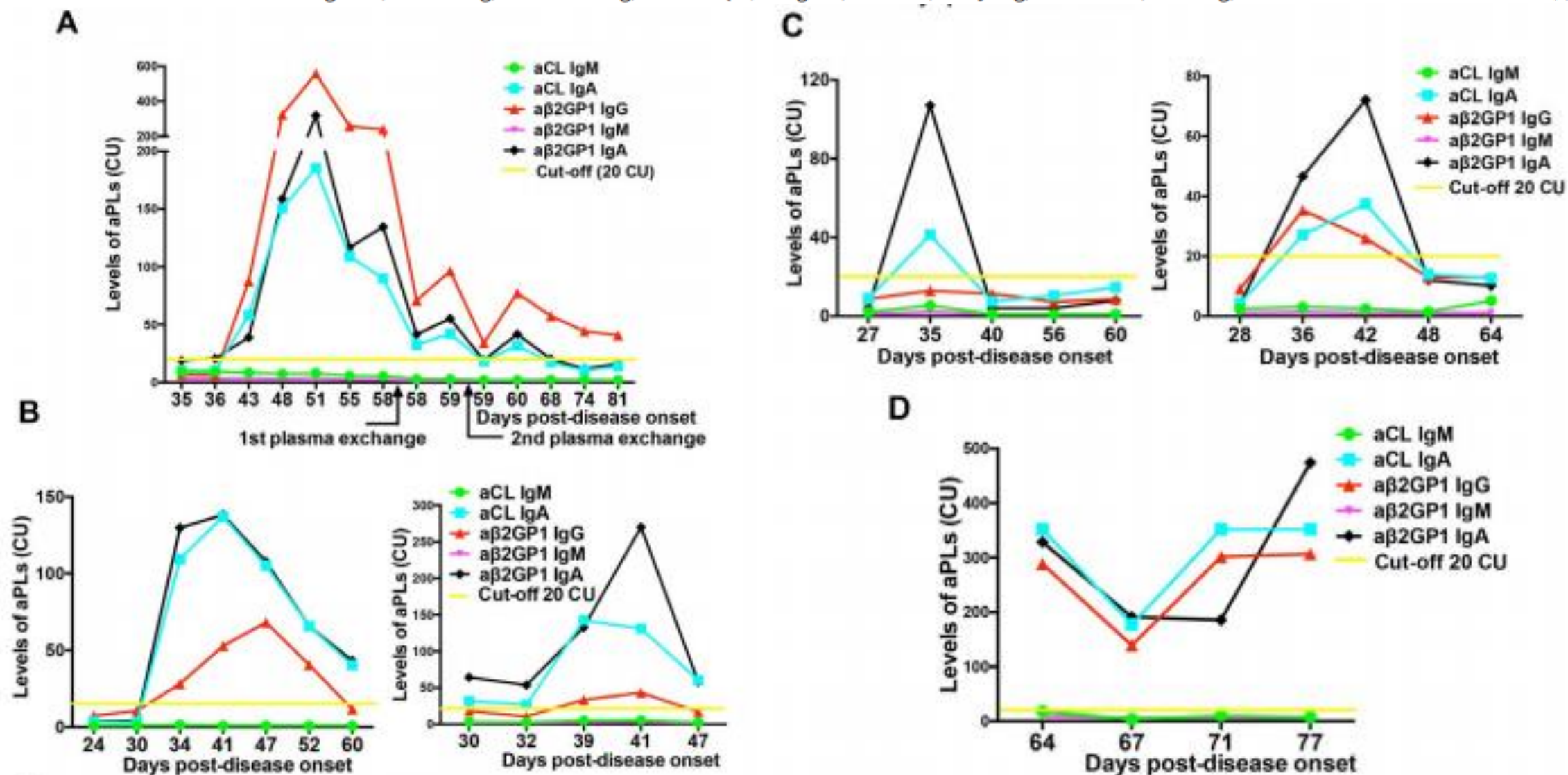
(参考)

## Antiphospholipid Antibodies in Critically Ill Patients With COVID-19

Meng Xiao, Yan Zhang, Shulan Zhang, Xuzhen Qin, Peng Xia, Wei Cao, Wei Jiang, Huan Chen, Xin Ding,

Arthritis &amp; Rheumatology

Vol. 72, No. 12, December 2020, pp 1998-2004



# 抗カルジオリピン抗体と重症度の関係

**Table 3** Association between ACL IgG and disease severity, platelet counts and need for anticoagulation

	Cohort	All	aCL IgG positive	aCL IgG negative
	N	42	20	22
Age	Mean (CI)	58.2 (62.7 to 54.1)	55.9 (62.9 to 49)	60.7 (66.4 to 55)
Sex	N male (%)	29/42 (69)	13/20 (65)	16/22 (73)
Days from symptom onset to ICU	Mean (CI)	6 (8.3 to 3.7)	8.7 (12.8 to 4.6)	3.4 (5.4 to 1.5)
APACHE II on ICU admission	Mean (CI)	25.3 (27.6 to 22.9)	25.7 (28.5 to 22.9)	24.9 (28.8 to 20.9)
Mean of SOFA score for first 3 days	Mean (CI)	9.6 (10.7 to 8.5)	10.6 (12.2 to 9.1)	8.7 (10.3 to 7)
Mean of SOFA score for first 7 days	Mean (CI)	8.9 (10.1 to 7.8)	10 (11.7 to 8.4)	8 (9.5 to 6.4)
ICU days (censored)	Mean (CI)	14.1 (17.3 to 10.8)	16.6 (21.9 to 11.3)	12.1 (16.5 to 7.6)
Death in ICU	N (%)	13/42 (31)	8/20 (40)	5/22 (23)
Mechanical ventilation days (censored)	Mean (CI)	14.4 (18.9 to 10)	18.2 (25.5 to 10.8)	11.1 (16.4 to 5.7)
Total days of ventilation rescue measures	Mean (CI)	2.9 (4.3 to 1.4)	3.6 (5.6 to 1.5)	2.3 (4.4 to 0.1)
Therapeutic anticoagulation used	N (%)	8	4/20 (20)	4/22 (18)
Mean platelet count	Mean (CI)	239 (269 to 209)	268 (321 to 216)	212 (246 to 179)
Mean platelet to neutrophil ratio	Mean (CI)	35.2 (42 to 28.4)	34.8 (45.2 to 24.3)	35.6 (45.4 to 28.9)

# Table 3の一部抜粋

	aCL IgG positive	aCL IgG negative
	20	22
Age	55.9 (62.9 to 49)	60.7 (66.4 to 55)
Sex	13/20 (65)	16/22 (73)
Days from symptom onset to ICU	8.7 (12.8 to 4.6)	3.4 (5.4 to 1.5)
APACHE II on ICU admission	25.7 (28.5 to 22.9)	24.9 (28.8 to 20.9)
Mean of SOFA score for first 3 days	10.6 (12.2 to 9.1)	8.7 (10.3 to 7)
Mean of SOFA score for first 7 days	10 (11.7 to 8.4)	8 (9.5 to 6.4)
ICU days (censored)	16.6 (21.9 to 11.3)	12.1 (16.5 to 7.6)
Death in ICU	8/20 (40)	5/22 (23)
Mechanical ventilation days (censored)	18.2 (25.5 to 10.8)	11.1 (16.4 to 5.7)
Total days of ventilation rescue measures	3.6 (5.6 to 1.5)	2.3 (4.4 to 0.1)
Therapeutic anticoagulation used	4/20 (20)	4/22 (18)
Mean platelet count	268 (321 to 216)	212 (246 to 179)
Mean platelet to neutrophil ratio	34.8 (45.2 to 24.3)	35.6 (45.4 to 28.9)

aCL抗体の有無で抗凝固治療頻度に差はなく、重症度にも有意差はない（ややaCL+で多い傾向）

# 本論文のまとめ

- 抗リン脂質抗体の検出頻度は、COVID-19の有無によらず重症肺炎で同等
- 抗リン脂質抗体の中では抗カルジオリピン抗体(IgG)の頻度が高い
- 抗リン脂質抗体は経過中に陽性となる症例が少ない
- 血栓eventのsurrogate markerでみて、抗リン脂質抗体と血栓症の関連はなさそう

# (参考)抗リン脂質抗体とCOVID-19の関連のメタ解析

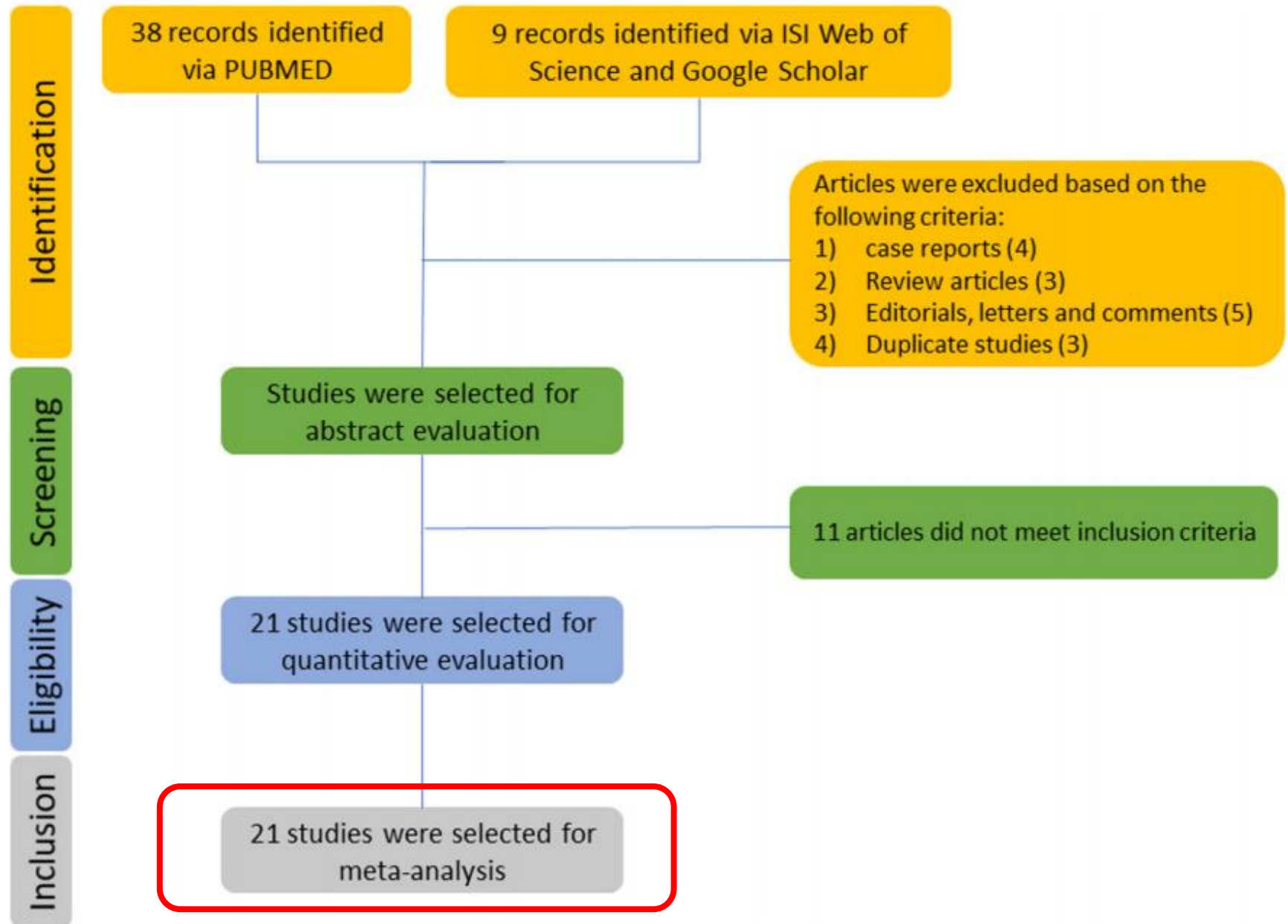


ORIGINAL RESEARCH

## Antiphospholipid antibodies in COVID-19: a meta-analysis and systematic review

Muhanad Taha , Lobelia Samavati

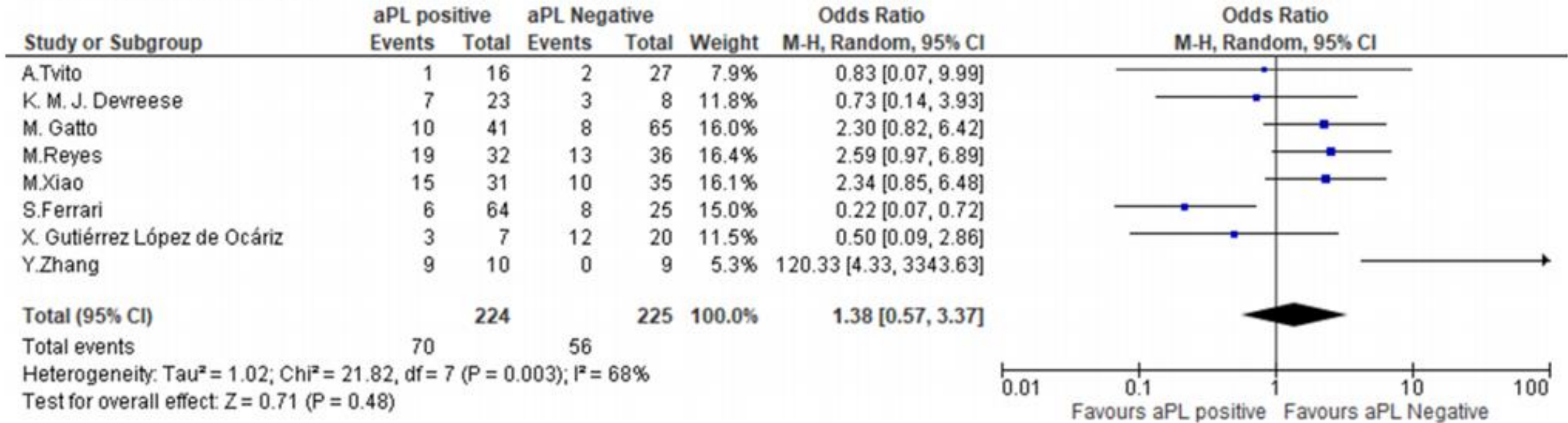
Taha M, Samavati L. *RMD Open* 2021;**7**:e001580.



**Figure 1** Searching and selection process.

# COVID-19において抗リン脂質抗体と血栓症は関連なさそう

## Venous thromboembolism



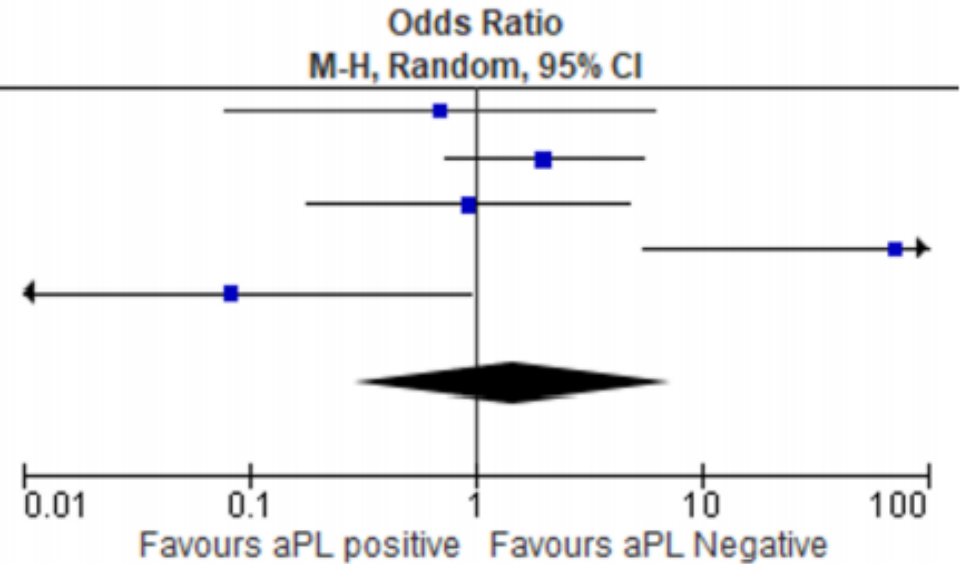
**Figure 5** Forest plot on the odds of venous thromboembolism in aPL-positive patients with COVID-19 compared with aPL-negative patients with COVID-19. aPL, anticardiolipin antibodies.

# 抗リン脂質抗体と重症度も関係なさそう

## A. Mortality

Study or Subgroup	aPL positive		aPL Negative		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Amezcu-GuerraLM	2	12	2	9	18.7%	0.70 [0.08, 6.22]
M.Reyes	14	32	10	36	25.6%	2.02 [0.74, 5.55]
S.Ferrari	7	22	3	9	21.9%	0.93 [0.18, 4.86]
S.Pascolini	6	8	1	25	16.5%	72.00 [5.56, 933.00]
Y.Zhang	4	10	8	9	17.2%	0.08 [0.01, 0.95]
<b>Total (95% CI)</b>		<b>84</b>		<b>88</b>	<b>100.0%</b>	<b>1.46 [0.29, 7.29]</b>
Total events	33		24			

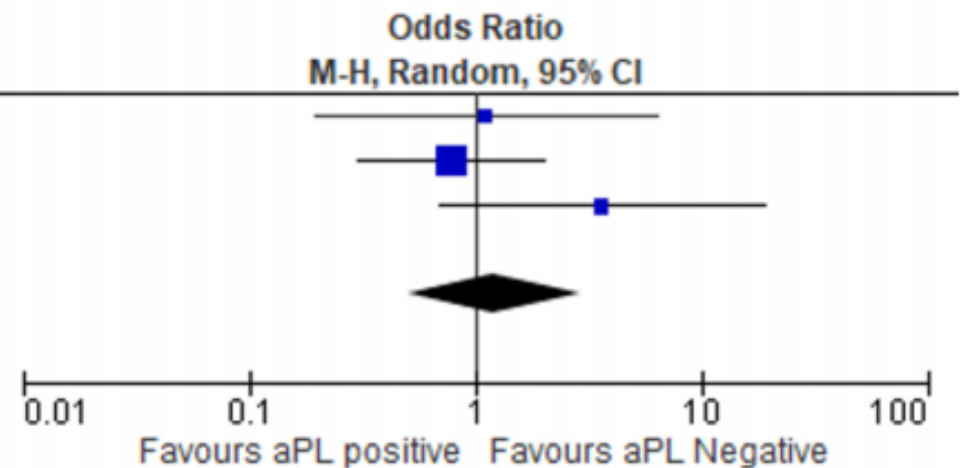
Heterogeneity:  $\tau^2 = 2.37$ ;  $\chi^2 = 15.31$ ,  $df = 4$  ( $P = 0.004$ );  $I^2 = 74\%$   
 Test for overall effect:  $Z = 0.46$  ( $P = 0.65$ )



## B. Invasive ventilation

Study or Subgroup	aPL positive		aPL Negative		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Amezcu-GuerraLM	7	12	5	9	21.5%	1.12 [0.20, 6.41]
M.Reyes	15	32	19	36	54.9%	0.79 [0.30, 2.05]
M.Xiao	29	31	28	35	23.6%	3.63 [0.69, 18.97]
<b>Total (95% CI)</b>		<b>75</b>		<b>80</b>	<b>100.0%</b>	<b>1.22 [0.51, 2.91]</b>
Total events	51		52			

Heterogeneity:  $\tau^2 = 0.12$ ;  $\chi^2 = 2.46$ ,  $df = 2$  ( $P = 0.29$ );  $I^2 = 19\%$   
 Test for overall effect:  $Z = 0.45$  ( $P = 0.65$ )





# COVID(+) ARDS vs COVID(-) ARDSを比較した論文が最近でている

**Table 1.** Characteristics and outcomes of patients with COVID-19-related ARDS and those with non-COVID-19-related ARDS\*

	COVID-19-related ARDS (n = 37)	Non-COVID-19-related ARDS (n = 31)	P†
Demographic characteristics and comorbidities			
Age, median (IQR) years‡	63 (50–73)	57 (42–70)	0.378
Male sex	31 (84)	24 (77)	0.506
Obesity§	13 (37)	4 (13)	0.025
Characteristics upon ICU admission			
SOFA score, median (IQR)	9 (6–10)	9 (6–11)	0.483
SAPS II score, median (IQR)	38 (32–45)	39 (31–54)	0.808
Invasive mechanical ventilation	19 (51)	18 (58)	0.176
Pao <sub>2</sub> /Fio <sub>2</sub> ratio, median (IQR) mm Hg	126 (97–175)	91 (70–130)	0.017
PaCo <sub>2</sub> , median (IQR) mm Hg§	40 (37–48)	46 (40–51)	0.110
Thrombotic events			
Any thromboembolic event	24 (65)	8 (26)	0.001
Pulmonary embolism	9 (24)	2 (7)	0.046
Thromboembolic disease¶	12 (32)	3 (10)	0.024
Renal replacement therapy circuit thrombosis#	11 (55)	0 (0)	0.001
aPL			
IgA aCL or IgA anti-β <sub>2</sub> GPI	7 (19)	6 (19)	0.964
IgM or IgG aCL or IgM or IgG anti-β <sub>2</sub> GPI	6 (16)	4 (13)	0.745
Any aPL	11 (30)	9 (29)	0.950
Outcomes			
Invasive mechanical ventilation	36 (97)	31 (100)	>0.99
Ventilator-associated pneumonia‡	27 (75)	13 (42)	0.006
Shock	28 (76)	21 (68)	0.468
Renal replacement therapy	20 (54)	15 (48)	0.641
Extracorporeal membrane oxygenation	9 (24)	8 (26)	0.888
No. organ failure-free days at day 28, median (IQR)**	0 (0–15)	14 (0–20)	0.004
Day-28 mortality††	12 (32)	3 (11)	0.040
ICU mortality‡‡	13 (50)	5 (16)	0.006

Frapard T. et al.,  
Arthritis Rheumatol.  
2021; 73: 897

血栓はCOVIDで多い

aPLはCOVID有無で  
差がない

\*Frapard T, et al. Characteristics and outcomes of patients with COVID-19-related ARDS and those with non-COVID-19-related ARDS. Arthritis Rheumatol. 2021; 73: 897.

# 全体のまとめ

- 抗リン脂質抗体はCOVID-19の有無にかかわらず重症肺炎で約半数で陽性となる
- 抗リン脂質抗体産生は一過性に上昇し、消失する
- 抗リン脂質抗体と血栓症のeventの関連はなさそう
- 抗リン脂質抗体と重症化の関連もおそらくなさそう

# コメント

抗 $\beta$ 2GPI抗体の病原性については、in vivo, in vitroの実験からも明らかですが、抗カルジオリピン抗体についてはよくわかりません。急性肺障害で出てくる抗リン脂質抗体と血栓症の関連がなさそうなのは、抗リン脂質抗体の種類も影響しているかもしれません。もちろん、抗体の量も影響すると思います。

現時点では、急性肺障害で出てくる抗リン脂質抗体は血栓症の原因ではなく、内皮等の細胞障害の結果と考えるのが妥当そうで、血栓症は肺内の血管内皮障害修復機転から起こっていると考えべきでしょう。