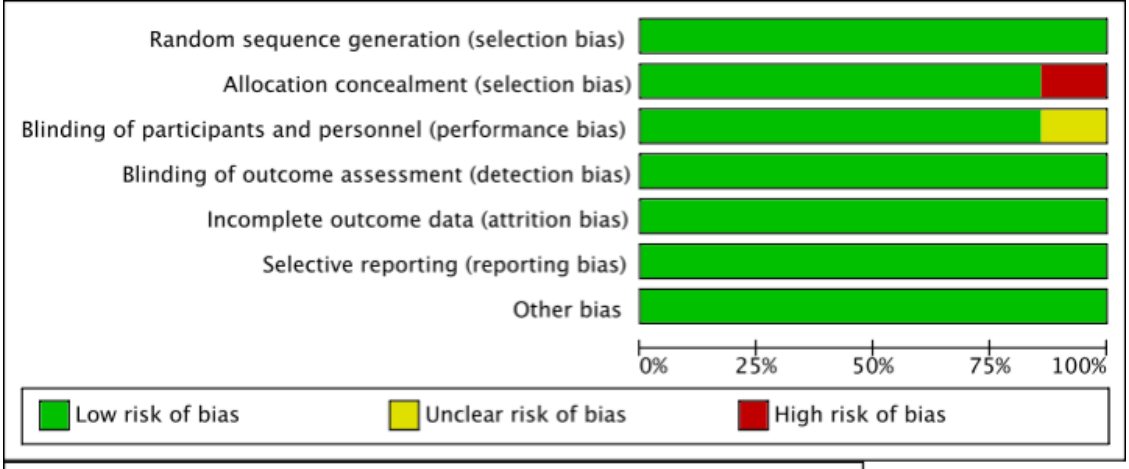
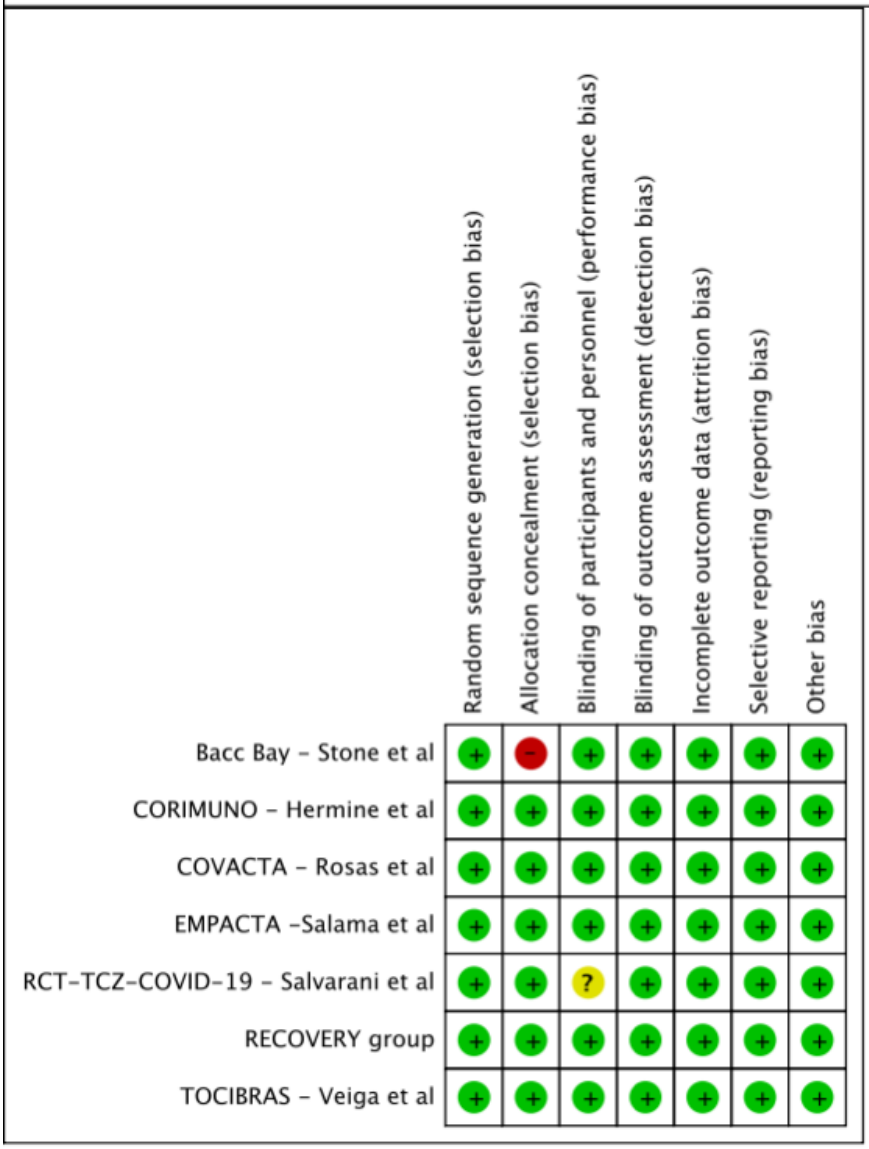
A





B

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%) With ST	Study event rates (%) With ST+TCZ	Relative effect (95% CI)	Anticipated absolute effects Risk with ST	Anticipated absolute effects Risk difference with ST+TCZ
Mortality (follow up: mean 28 days)											
5555 (7 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	749/2641 (28.4%)	711/2914 (24.4%)	**OR 0.89** (0.79 to 1.00)	284 per 1.000	**23 fewer per 1.000** (from 45 fewer to 0 fewer)

CI: Confidence interval; **OR:** Odds ratio

Summary of findings:

TCZ+ST compared to ST for COVID-19

Patient or population: COVID-19
Setting: hospital
Intervention: TCZ+ST
Comparison: ST

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)		Difference	Certainty	What happens
Mortality follow up: mean 28 days № of participants: 5555 (7 RCTs)	**OR 0.89** (0.79 to 1.00)	28.4%	**26.1%** (23.8 to 28.4)	**2.3% fewer** (4,5 fewer to 0 fewer)	⨁⨁⨁⨁ HIGH	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Suppl Fig. 1

A

	Albertini	Balena	Biran	Campochiaro	Canziani	Capra	Colaneri	Eimer	Galvan Roman	Garcia	Gokhale	Guaraldi	Hill	Holt	Kewan	Kimmig	Klopfenstein	Klopfenstein (a)	Mattew	Menzella	Mikulska	Pan Li	Patel	Potere	Quartuccio	Ramaswamy	Rodriguez Bano	Rojas-Marte	Roumier	Ruiz antoran	Somers	Van der Eynde	Wadud
Selection																																	
1) Is the case definition adequate?	*	*	*	*	--	*	*	--	*	--	--	*	*	*	--	*	*	*	*	*	*	*	--	--	*	*	*	*	--	*	*	*	*
2) Representativeness of the cases	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
3) Selection of controls	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
4) Definition of controls	*	*	*	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Comparability																																	
1) Comparability of cases and controls on the basis of the design or analysis	*	**	**	**	**	*	*	*	*	*	*	**	**	**	*	**	**	*	*	**	**	**	*	*	*	**	**	*	**	*	*	*	**
Exposure																																	
1) Ascertainment of exposure	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
2) Same method of ascertainment for cases and controls	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
3) Non-response rate	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Total	**8**	**9**	**9**	**9**	**8**	**8**	**8**	**8**	**7**	**7**	**7**	**9**	**9**	**8**	**7**	**9**	**9**	**8**	**8**	**9**	**9**	**9**	**7**	**7**	**8**	**9**	**9**	**8**	**8**	**8**	**8**	**8**	**9**

B

Summary of findings:

[ST+TCZ] compared to [ST] in [COVID-19 positive subjects]

Patient or population: [COVID-19 positive subjects]
Setting:
Intervention: [ST+TCZ]
Comparison: [ST]

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)		Difference	Certainty	What happens
Mortality № of participants: 5125 (33 observational studies)	**OR 0.54** (0.47 to 0.62)	38.4%	**25.2%** (22.7 to 27.9)	**13.2% fewer** (15,8 fewer to 10,5 fewer)	⨁⨁⨁◯ MODERATE	[ST+TCZ] likely reduces mortality.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

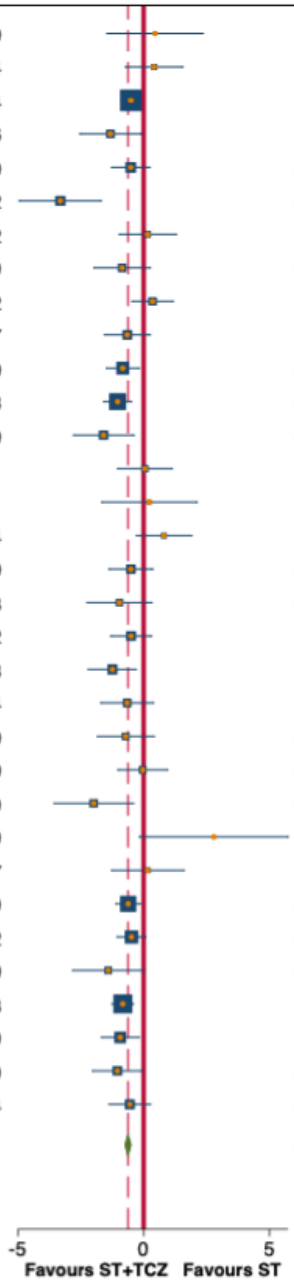
Suppl Fig. 2

A

Study	ST+TCZ Died	ST+TCZ Alive	ST Died	ST Alive	Log Odds-Ratio with 95% CI	Weight (%)
Albertini et al	3	19	2	20	0.46 [-1.44, 2.35]	0.30
Balena et al	5	11	34	114	0.42 [-0.70, 1.55]	0.79
Biran et al	102	108	256	164	-0.50 [-0.84, -0.17]	15.18
Campochiaro et al	5	27	11	16	-1.31 [-2.54, -0.09]	1.74
Canziani et al	17	47	24	40	-0.51 [-1.26, 0.24]	3.05
Capra et al	2	60	11	12	-3.31 [-4.94, -1.69]	2.69
Colaneri et al	5	16	19	72	0.17 [-0.96, 1.29]	0.94
Eimer et al	5	24	19	39	-0.85 [-1.96, 0.26]	1.81
Galvan-Roman et al	14	44	16	72	0.36 [-0.45, 1.17]	1.67
Garcia Moreno et al	8	69	17	77	-0.64 [-1.55, 0.26]	2.37
Gokhale et al	33	37	61	30	-0.82 [-1.47, -0.18]	4.85
Guaraldi et al	18	161	87	278	-1.03 [-1.57, -0.49]	8.90
Hill et al	4	39	15	30	-1.58 [-2.79, -0.38]	2.30
Holt et al	10	22	9	21	0.06 [-1.02, 1.14]	1.10
Kewan et al	3	25	2	21	0.23 [-1.65, 2.11]	0.34
Kimming et al	12	16	8	24	0.81 [-0.28, 1.91]	0.74
Klopfenstein et al	8	22	66	110	-0.50 [-1.37, 0.36]	2.44
Klopfenstein et al (a)	5	14	12	13	-0.95 [-2.24, 0.34]	1.32
Mattew et al 2021	13	32	28	42	-0.50 [-1.30, 0.31]	2.69
Menzella et al 2020	10	31	20	18	-1.24 [-2.19, -0.28]	2.71
Mikulska et al	6	23	22	44	-0.65 [-1.68, 0.38]	1.84
Pan-li et al 2021	12	27	9	10	-0.71 [-1.83, 0.42]	1.45
Patel et al	11	31	11	30	-0.03 [-1.01, 0.94]	1.42
Potere et al	2	38	11	29	-1.98 [-3.56, -0.39]	1.81
Quartuccio et al	4	38	0	69	2.79 [-0.16, 5.74]	0.06
Ramaswamy et al	3	18	8	57	0.17 [-1.26, 1.60]	0.58
Rodríguez-Baño et al 2021	34	54	184	159	-0.61 [-1.09, -0.13]	7.97
Rojas-Marte et al	43	53	55	42	-0.48 [-1.05, 0.09]	5.22
Roumier et al	3	27	9	20	-1.40 [-2.83, 0.03]	1.42
Ruiz-Antoran et al	45	223	75	163	-0.82 [-1.25, -0.40]	11.43
Somers et al	14	64	27	49	-0.92 [-1.67, -0.18]	3.88
Van den Eynde et al	7	14	69	49	-1.04 [-2.01, -0.06]	2.40
Wadud et al	17	27	26	24	-0.54 [-1.36, 0.28]	2.58
Overall					-0.62 [-0.75, -0.48]	

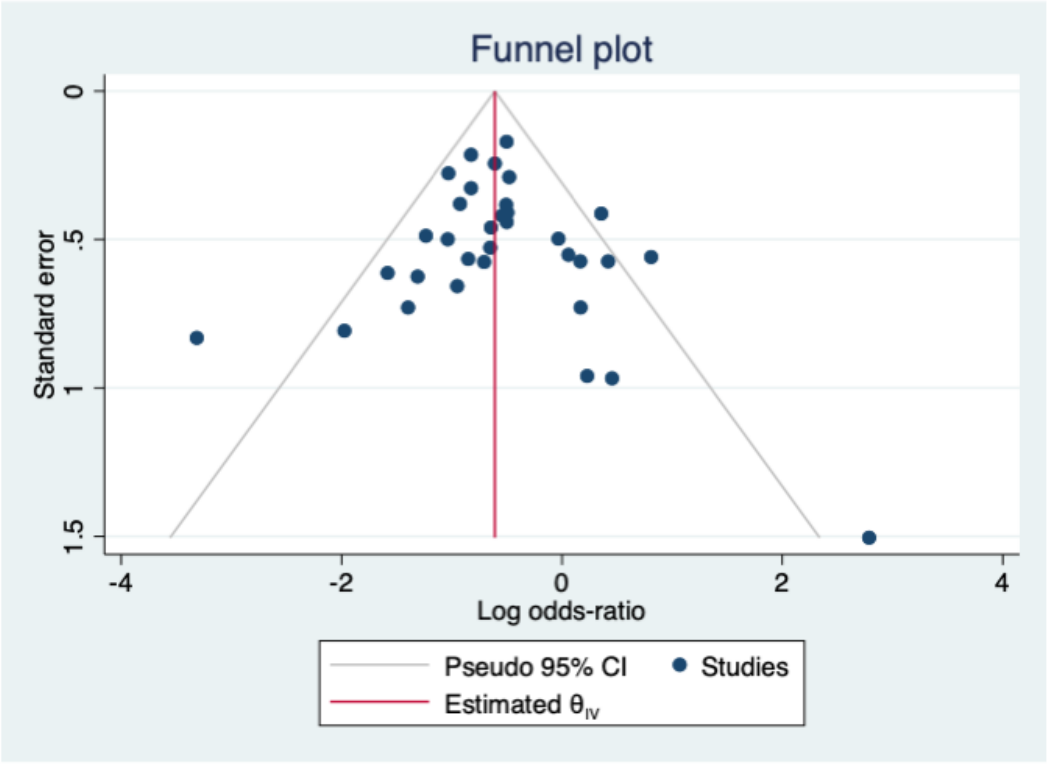
Heterogeneity: I^2 = 41.40%, H^2 = 1.71

Test of θ = 0: z = -8.88, p = 0.00



Fixed-effects Mantel-Haenszel model

B



Suppl Fig. 3

A

Random-effects meta-regression
Method: REML

Number of obs = **39**
Residual heterogeneity:
tau2 = **.7111**
I2 (%) = **84.17**
H2 = **6.32**
R-squared (%) = **0.00**
Wald chi2(**1**) = **0.03**
Prob > chi2 = **0.8544**

_meta_es	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Age_total_mean	**.0052704**	**.0287134**	**0.18**	**0.854**	**-.0510068**	**.0615477**
_cons	**-.8373497**	**1.858384**	**-0.45**	**0.652**	**-4.479715**	**2.805016**

B

Random-effects meta-regression
Method: REML

Number of obs = **37**
Residual heterogeneity:
tau2 = **.7153**
I2 (%) = **84.17**
H2 = **6.32**
R-squared (%) = **3.03**
Wald chi2(**2**) = **3.20**
Prob > chi2 = **0.2016**

_meta_es	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Age_total_mean	**-.0053736**	**.0324479**	**-0.17**	**0.868**	**-.0689703**	**.0582232**
Female_tot_perc	**.0338997**	**.0192361**	**1.76**	**0.078**	**-.0038023**	**.0716017**
_cons	**-1.266051**	**2.026761**	**-0.62**	**0.532**	**-5.23843**	**2.706328**

C

Random-effects meta-regression
Method: REML

Number of obs = **35**
Residual heterogeneity:
tau2 = **.8224**
I2 (%) = **85.96**
H2 = **7.12**
R-squared (%) = **0.00**
Wald chi2(**3**) = **3.00**
Prob > chi2 = **0.3912**

_meta_es	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Age_total_mean	**-.0055345**	**.0390578**	**-0.14**	**0.887**	**-.0820864**	**.0710174**
Female_tot_perc	**.0337998**	**.0204396**	**1.65**	**0.098**	**-.006261**	**.0738605**
IMV_cat	**-.1208417**	**.6808665**	**-0.18**	**0.859**	**-1.455315**	**1.213632**
_cons	**-1.238272**	**2.514126**	**-0.49**	**0.622**	**-6.165869**	**3.689325**

D

Random-effects meta-regression
Method: REML

Number of obs = **37**
Residual heterogeneity:
tau2 = **.7255**
I2 (%) = **83.23**
H2 = **5.96**
R-squared (%) = **1.65**
Wald chi2(**3**) = **3.42**
Prob > chi2 = **0.3317**

_meta_es	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Age_total_mean	**-.0033884**	**.0328899**	**-0.10**	**0.918**	**-.0678514**	**.0610746**
Female_tot_perc	**.031897**	**.0197744**	**1.61**	**0.107**	**-.00686**	**.0706541**
Dose_cat	**.1253835**	**.2550035**	**0.49**	**0.623**	**-.3744142**	**.6251812**
_cons	**-1.4229**	**2.06364**	**-0.69**	**0.491**	**-5.46756**	**2.62176**

E

Random-effects meta-regression
Method: REML

Number of obs = **25**
Residual heterogeneity:
tau2 = **.7314**
I2 (%) = **82.47**
H2 = **5.70**
R-squared (%) = **0.00**
Wald chi2(**3**) = **2.41**
Prob > chi2 = **0.4926**

_meta_es	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Age_total_mean	**-.0153946**	**.0415938**	**-0.37**	**0.711**	**-.096917**	**.0661278**
Female_tot_perc	**.038115**	**.0265789**	**1.43**	**0.152**	**-.0139787**	**.0902088**
Timing_TCZ	**-.0081562**	**.0587429**	**-0.14**	**0.890**	**-.1232902**	**.1069778**
_cons	**-.7211457**	**2.75289**	**-0.26**	**0.793**	**-6.116711**	**4.674419**

F

Random-effects meta-regression
Method: REML

Number of obs = **32**
Residual heterogeneity:
tau2 = **.2786**
I2 (%) = **60.53**
H2 = **2.53**
R-squared (%) = **53.74**
Wald chi2(**3**) = **23.84**
Prob > chi2 = **0.0000**

_meta_es	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Age_total_mean	**-.0114922**	**.0248185**	**-0.46**	**0.643**	**-.0601356**	**.0371511**
Female_tot_perc	**.0518066**	**.01654**	**3.13**	**0.002**	**.0193888**	**.0842244**
Mode_injection	**-.5746726**	**.171245**	**-3.36**	**0.001**	**-.9103066**	**-.2390386**
_cons	**-1.295176**	**1.533695**	**-0.84**	**0.398**	**-4.301164**	**1.710812**

G

Random-effects meta-regression
Method: REML

Number of obs = **40**
Residual heterogeneity:
tau2 = **.6905**
I2 (%) = **83.58**
H2 = **6.09**
R-squared (%) = **0.00**
Wald chi2(**1**) = **0.80**
Prob > chi2 = **0.3697**

_meta_es	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Corticost_cat	**.2347404**	**.2616668**	**0.90**	**0.370**	**-.2781172**	**.7475979**
_cons	**-.6887763**	**.2419221**	**-2.85**	**0.004**	**-1.162935**	**-.2146176**

H

Random-effects meta-regression
Method: REML

Number of obs = **37**
Residual heterogeneity:
tau2 = **.7447**
I2 (%) = **84.63**
H2 = **6.51**
R-squared (%) = **0.00**
Wald chi2(**3**) = **3.17**
Prob > chi2 = **0.3664**

_meta_es	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Corticost_cat	**.0621324**	**.291176**	**0.21**	**0.831**	**-.5085622**	**.632827**
Age_total_mean	**-.0044416**	**.033387**	**-0.13**	**0.894**	**-.0698789**	**.0609956**
Female_tot_perc	**.0325839**	**.0206067**	**1.58**	**0.114**	**-.0078045**	**.0729724**
_cons	**-1.326711**	**2.085264**	**-0.64**	**0.525**	**-5.413753**	**2.760331**

Random-effects meta-regression
Method: REML

Number of obs	**23**
Residual heterogeneity:	
tau2 =	**.4674**
I2 (%) =	**69.60**
H2 =	**3.29**
R-squared (%) =	**9.48**
Wald chi2(**7**) =	**13.25**
Prob > chi2 =	**0.0663**

_meta_es	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Age_total_mean	**-.0143186**	**.042169**	**-0.34**	**0.734**	**-.0969684**	**.0683311**
Female_tot_perc	**.0381356**	**.0273911**	**1.39**	**0.164**	**-.01555**	**.0918211**
Corticost_cat	**-.2286777**	**.3767779**	**-0.61**	**0.544**	**-.9671488**	**.5097934**
IMV_cat	**-.5189578**	**.680771**	**-0.76**	**0.446**	**-1.853244**	**.8153287**
Dose_cat	**-.2485185**	**.4477769**	**-0.56**	**0.579**	**-1.126145**	**.629108**
Timing_TCZ	**-.0281051**	**.0657062**	**-0.43**	**0.669**	**-.1568869**	**.1006767**
Mode_injection	**-.8200898**	**.2729461**	**-3.00**	**0.003**	**-1.355054**	**-.2851253**
_cons	**-.0077662**	**3.090532**	**-0.00**	**0.998**	**-6.065097**	**6.049565**

Suppl Table