

Efficacy and safety of levosimendan in patients with sepsis: a systematic review and network meta-analysis

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Supplementary Material 1 Statistical Analysis Protocol and Results

I Cardiac index

In this part, we used "gemtc" package(version 1.0-1) in R(version 4.2.3) to conduct the Bayesian Meta analysis.

1 Building Network

1.1 **Function used:** *mtc.network*

1.2 **Results:**

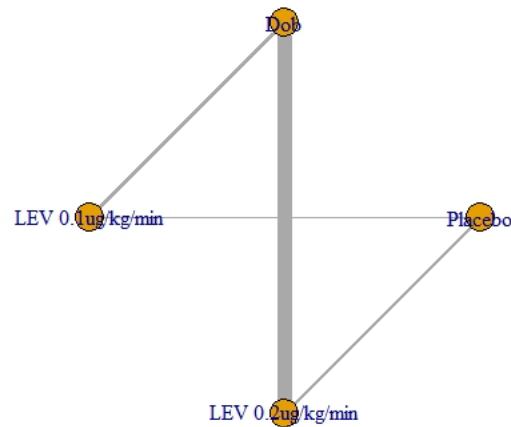


Figure SI-1 Network of Cardiac index

2 Modelling and Running

2.1 **Function used:** *mtc.model*, *mtc.run*

3 Results Presentation:

3.1 **Forest plot (Placebo was set as the baseline to calculate the relative effect among arms)**

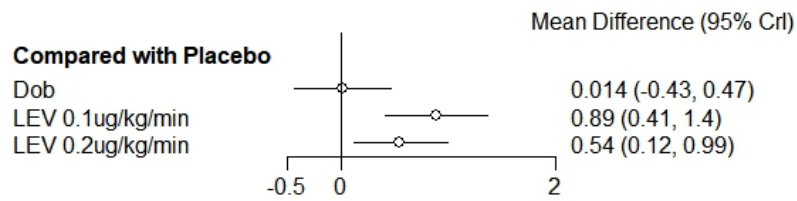


Figure SI-3.1 Relative Effect Forest Plot of Cardiac index (baseline: placebo)

Abbreviation: CrI, credible interval.

3.2 League table

Table SI-3.2 League Table of Cardiac index

Placebo			
-0.01 (-0.47, 0.43)	Dob		
-0.89 (-1.36, -0.41)	-0.87 (-1.22, -0.52)	LEV 0.1ug/kg/min	
-0.54 (-0.99, -0.12)	-0.53 (-0.74, -0.33)	0.34 (-0.06, 0.72)	LEV 0.2ug/kg/min

3.3 Rank of probability

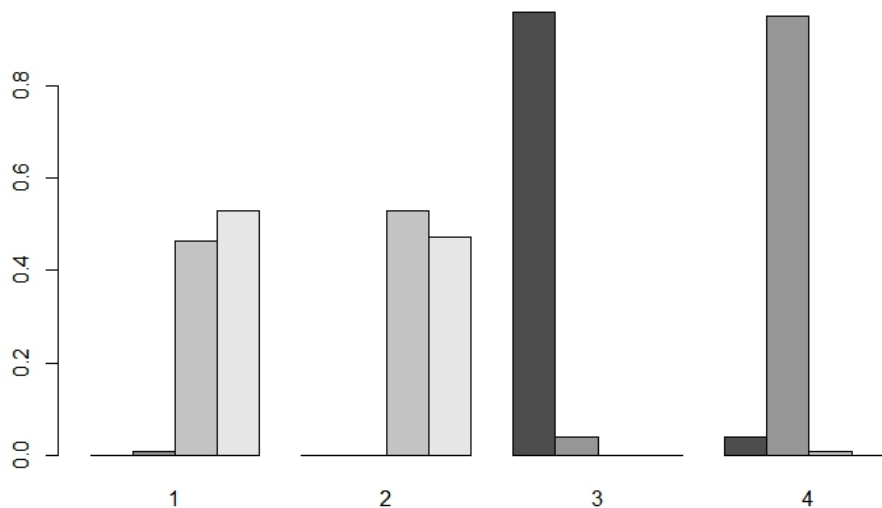


Figure SI-3.3 Bar chart of rank of probability of cardiac index.

Notes: 1, Placebo; 2, Dob; 3, LEV 0.1ug/kg/min; 4, LEV 0.2ug/kg/min.

3.4 SUCRA rank of probability

Table SI-3.4 SUCRA rank of probability of cardiac index.

Intervention	SUCRA
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Placebo	16.02%
Dob	17.61%
LEV 0.1ug/kg/min	98.57%
LEV 0.2ug/kg/min	67.80%

Abbreviation: SUCRA, surface area under the cumulative ranking curve.

4 Quality Control

4.1 Convergence test: PSRF value

Potential scale reduction factors:

	Point est.	Upper C.I.
d.1.3	1	1
d.1.4	1	1
d.3.2	1	1
sd.d	1	1

Multivariate psrf

Figure SI-4.1 PSRF of the Bayesian analysis of cardiac index

Abbreviation: PSRF, Potential scale reduction factors.

Note: The closer the PSRF value is to 1, the better. >1.05 indicates unsatisfactory convergence.

4.2 Consistency hypothesis: inconsistency test.

4.2.1 Function used: *mtc.nodesplit*

4.2.2 Results:

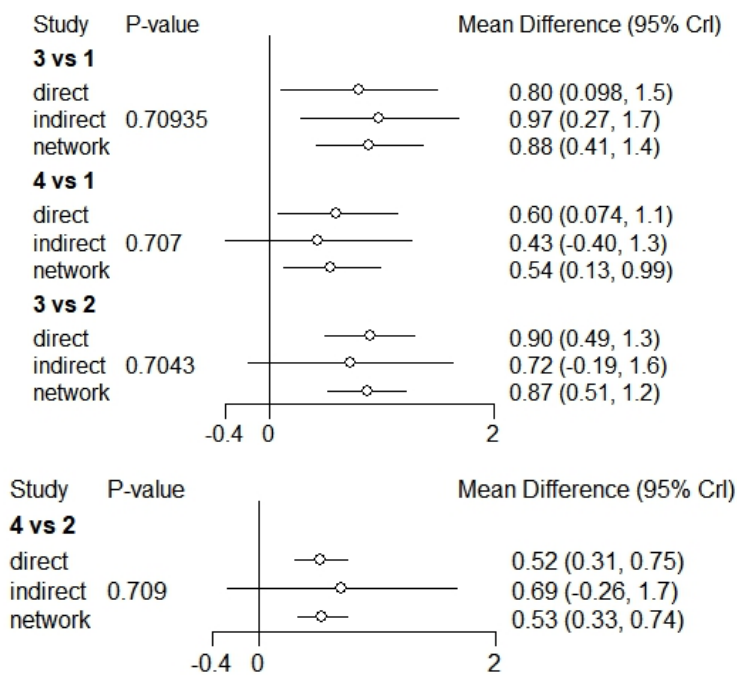


Figure SI-4.2.2 Inconsistency test of the Bayesian analysis of cardiac index

Note: 1, Placebo; 2, Dob; 3, LEV 0.1ug/kg/min;4, LEV 0.2ug/kg/min. *P* value > 0.05 indicates that there is no significant inconsistency which means the direct, indirect and network comparison is consistent.

4.3 Homogeneity hypothesis: Heterogeneity analysis

4.3.1 Function used: *mtc.anohe*

4.3.2 Results

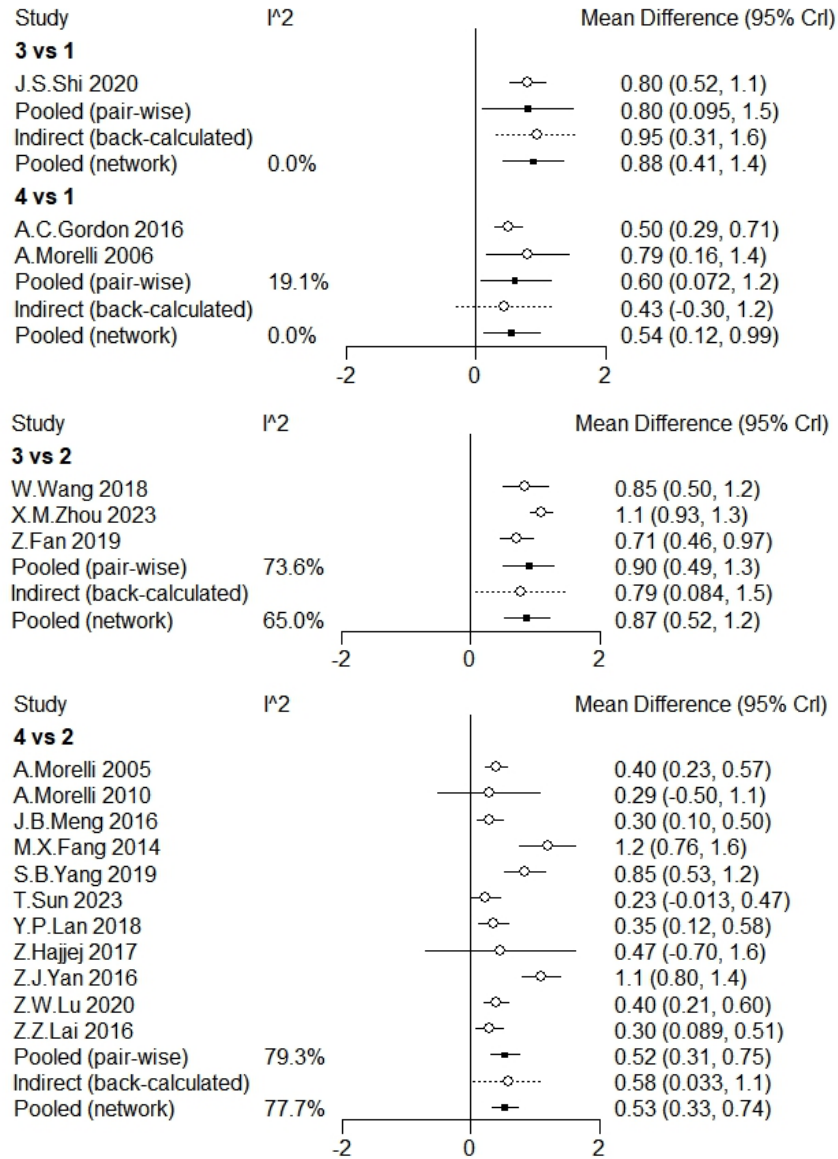


Figure SI-4.3.2 Heterogeneity analysis of the Bayesian analysis of cardiac index

Note: From the figure we could see, there exists no significant heterogeneity between any two arms, which allows the use of fixed effect model to estimate the pooling results.

II Lactic acid

In this part, we used "gemtc" package(version 1.0-1) in R(version 4.2.3) to conduct the Bayesian Meta analysis.

1 Building Network

1.1 Function used: *mtc.network*

1.2 Results:

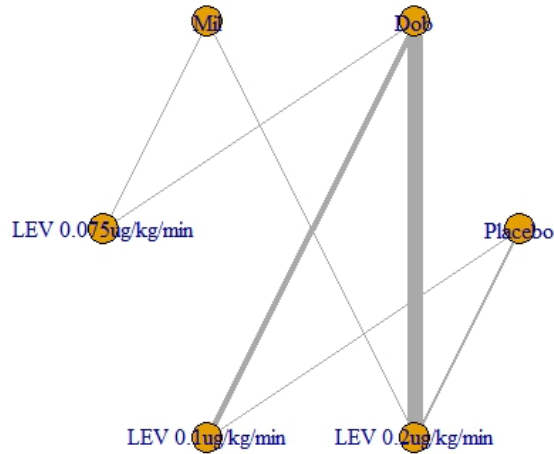


Figure SII-1 Network of Lactic acid

2 Modelling and Running

2.1 Function used: *mtc.model*, *mtc.run*

3 Results Presentation:

3.1 Forest plot (Placebo was set as the baseline to calculate the relative effect among arms)

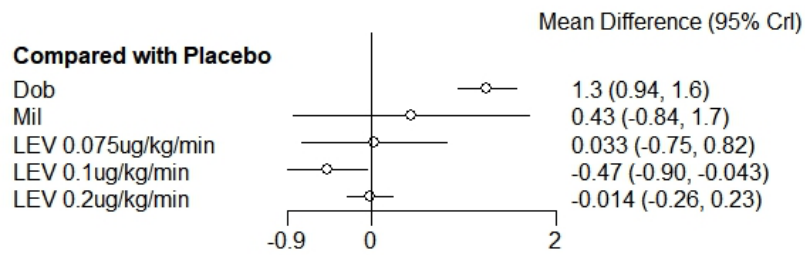


Figure SII-3.1 Relative Effect Forest Plot of Lactic acid

Abbreviation: CrI, credible interval.

3.2 League table

Table SII-3.2 League Table of Lactic acid

Placebo					
-1.25 (-1.57, -0.94)	Dob				
-0.43 (-1.71, 0.84)	0.82 (-0.44, 2.08)	Mil			
-0.03 (-0.82, 0.75)	1.22 (0.5, 1.94)	0.4 (-0.88, 1.68)	LEV 0.075ug/kg/min		
0.47 (0.04, 0.9)	1.72 (1.4, 2.04)	0.9 (-0.39, 2.2)	0.5 (-0.29, 1.29)	LEV 0.1ug/kg/min	
0.01 (-0.23, 0.26)	1.27 (1.05, 1.49)	0.44 (-0.8, 1.7)	0.05 (-0.7, 0.8)	-0.45 (-0.83, -0.08)	LEV 0.2ug/kg/min

3.3 Rank of probability

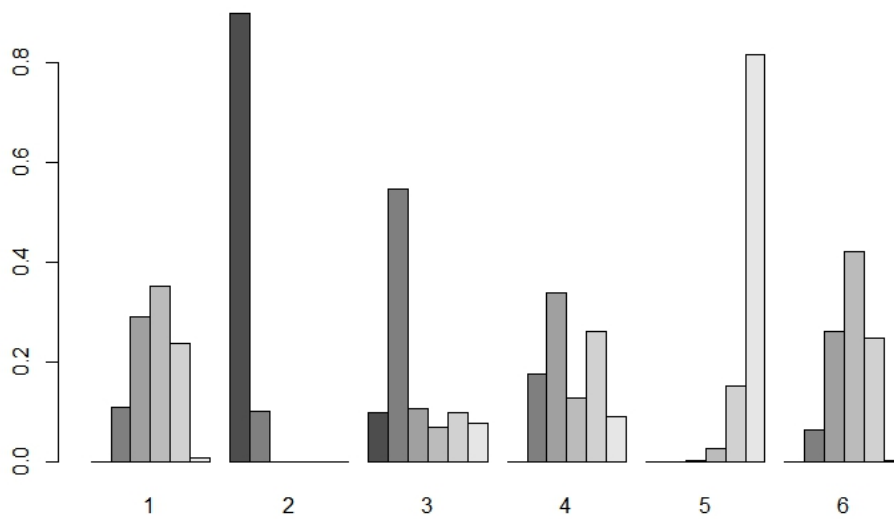


Figure SII-3.3 Bar chart of rank of probability of lactic acid.

Notes: 1, Placebo; 2, Dob; 3, Mil; 4, LEV 0.075ug/kg/min;5, LEV 0.1ug/kg/min;6, LEV 0.2ug/kg/min.

3.4 SUCRA rank of probability

Table SII-3.4 SUCRA rank of probability of lactic acid.

Intervention	SUCRA
Placebo	45.00%
Dob	97.98%
Mil	65.04%
LEV 0.075ug/kg/min	44.92%
LEV 0.1ug/kg/min	4.34%
LEV 0.2ug/kg/min	42.73%

Abbreviation: SUCRA, surface area under the cumulative ranking curve.

4 Quality Control

4.1 Convergence test: PSRF value

Potential scale reduction factors:

	Point est.	Upper C.I.
d.2.4	1	1
d.2.5	1	1
d.2.6	1	1
d.6.1	1	1
d.6.3	1	1

Multivariate psrf

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Figure SII-4.1 PSRF of the Bayesian analysis of lactic acid

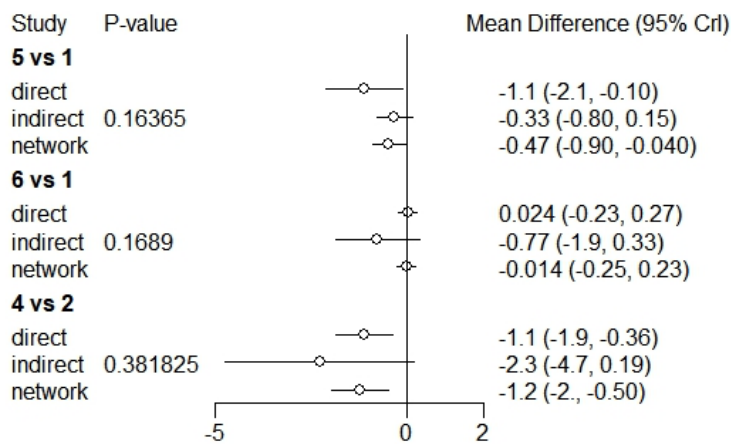
Abbreviation: PSRF, Potential scale reduction factors.

Note: The closer the PSRF value is to 1, the better. >1.05 indicates unsatisfactory convergence.

4.2 Consistency hypothesis: inconsistency test.

4.2.1 Function used: *mtc.nodesplit*

4.2.2 Results:



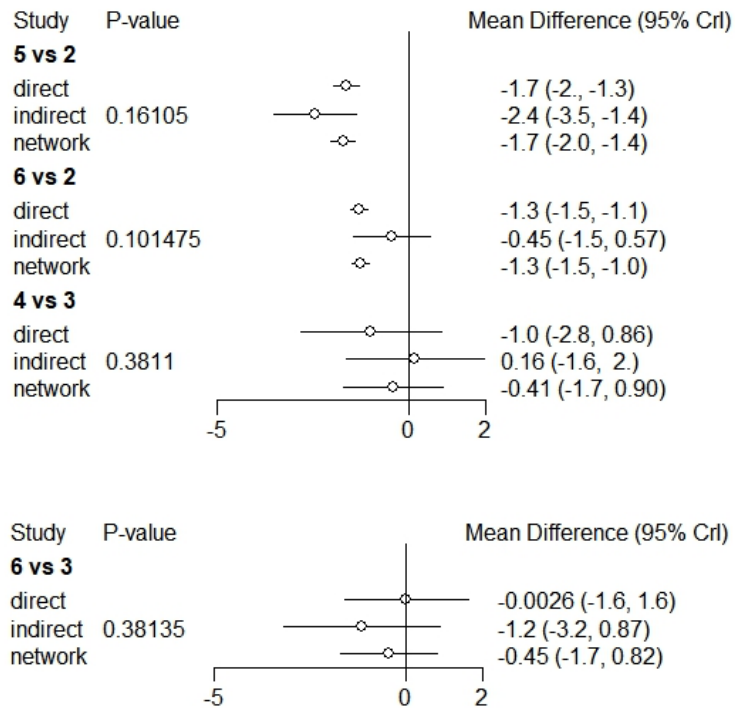


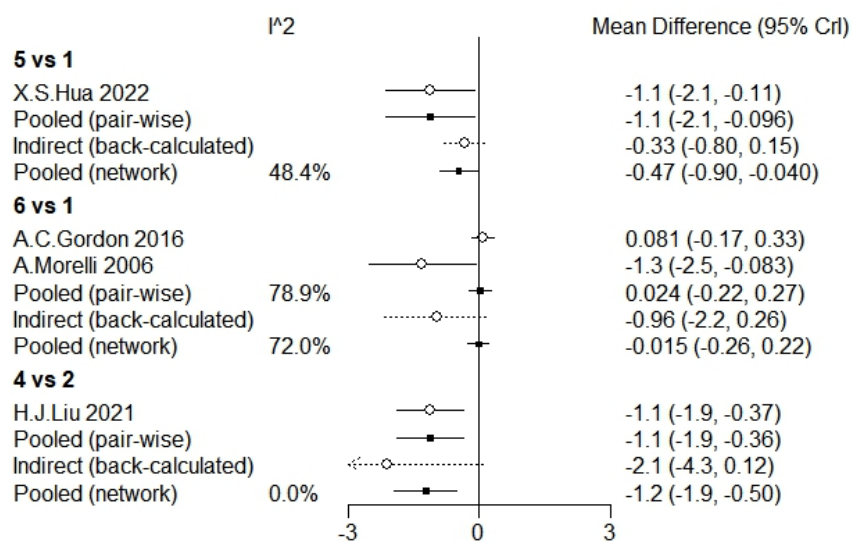
Figure SII-4.2.2 Inconsistency test of the Bayesian analysis of lactic acid

Note: 1, Placebo; 2, Dob; 3, Mil; 4, LEV 0.075ug/kg/min;5, LEV 0.1ug/kg/min;6, LEV 0.2ug/kg/min. *P* value > 0.05 indicates that there is no significant inconsistency which means the direct, indirect and network comparison is consistent.

4.3 Homogeneity hypothesis: Heterogeneity analysis

4.3.1 Function used: *mtc.anohe*

4.3.2 Results



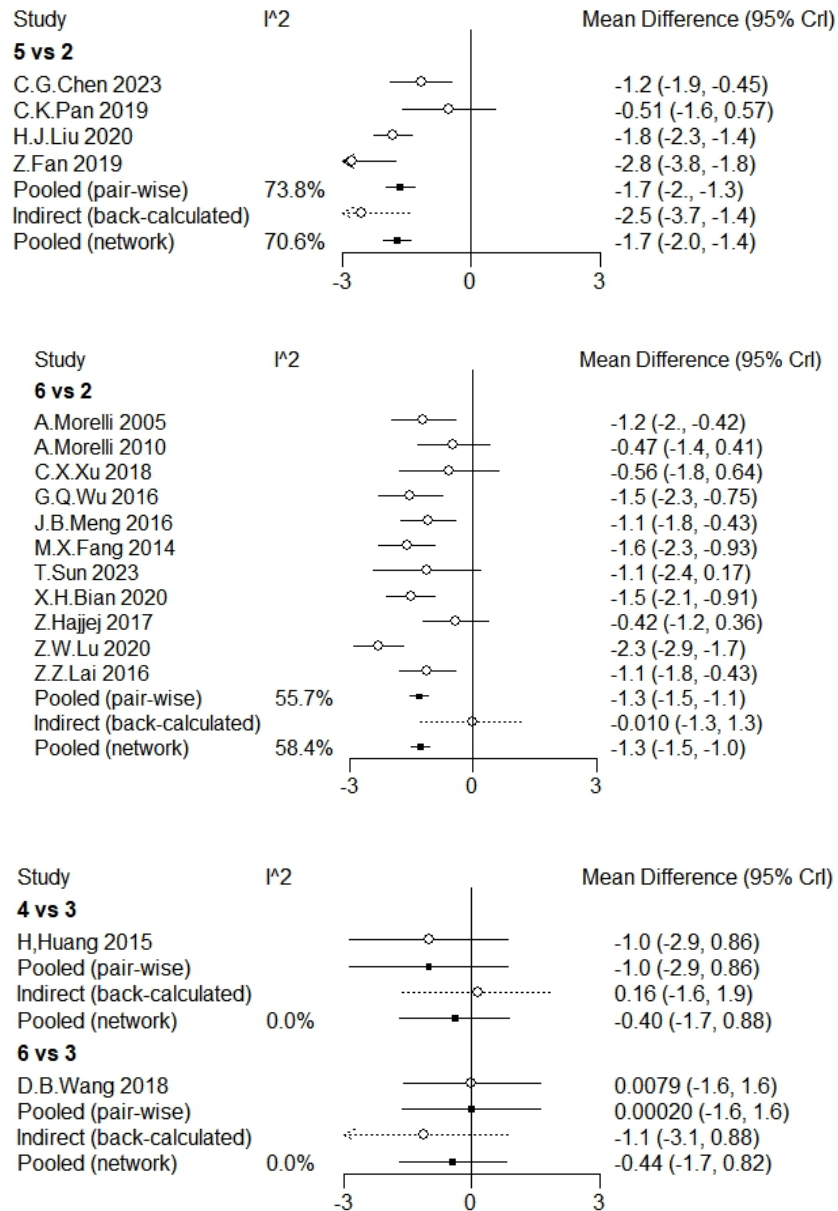


Figure SII-4.3.2 Heterogeneity analysis of the Bayesian analysis of lactic acid

Note: From the figure we could see, there exists no significant heterogeneity between any two arms, which allows the use of fixed effect model to estimate the pooling results.

III 28-day mortality

In this part, we used "gemtc" package(version 1.0-1) in R(version 4.2.3) to conduct the Bayesian Meta analysis.

1 Building Network

1.1 Function used: *mtc.network*

1.2 Results:

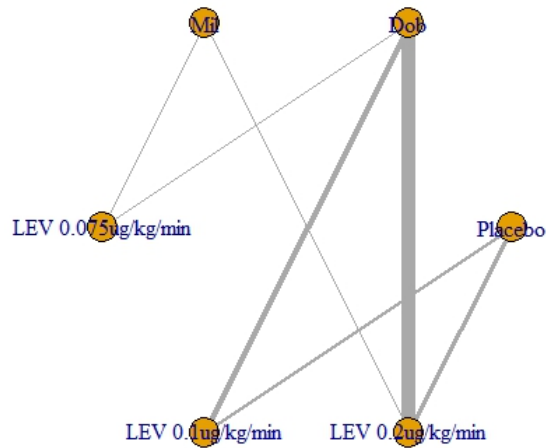


Figure SIII-1 Network of 28-day mortality

2 Modelling and Running

2.1 Function used: *mtc.model*, *mtc.run*

3 Results Presentation:

3.1 Forest plot (Placebo was set as the baseline to calculate the relative effect among arms)

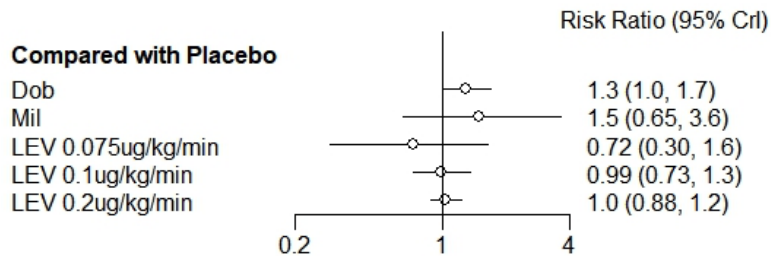


Figure SIII-3.1 Relative Effect Forest Plot of 28-day mortality (baseline: placebo)

Abbreviation: CrI, credible interval.

3.2 League table

Table SIII-3.2 League Table of 28-day mortality

Placebo			
0.77 (0.6, 0.99)	Dob		
0.67 (0.28, 1.53)	0.87 (0.36, 1.98)	Mil	
1.38 (0.61, 3.38)	1.78 (0.82, 4.26)	2.07 (0.77, 6.18)	LEV 0.075ug/kg/min

1.01 (0.74, 1.37)
0.96 (0.82, 1.13)

1.31 (1.01, 1.71)
1.25 (1.01, 1.55)

1.51 (0.64, 3.73)
1.44 (0.64, 3.42)

0.73 (0.3, 1.68)
0.7 (0.29, 1.57)

LEV 0.1ug/kg/min
0.95 (0.71, 1.29)

LEV 0.2ug/kg/min

3.3 Rank of probability

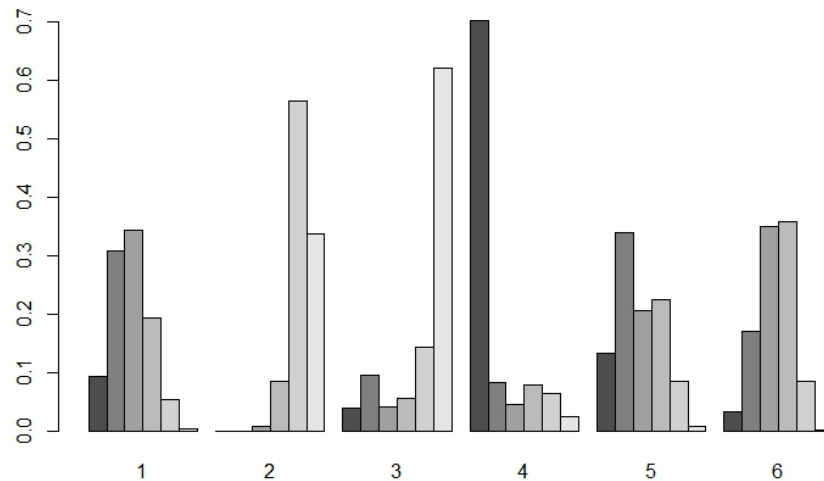


Figure SIII-3.3 Bar chart of rank of probability of 28-day mortality.

Notes: 1, Placebo; 2, Dob; 3, Mil; 4, LEV 0.075ug/kg/min;5, LEV 0.1ug/kg/min;6, LEV 0.2ug/kg/min.

3.4 SUCRA rank of probability

Table SIII-3.4 SUCRA rank of probability of 28-day mortality.

Intervention	SUCRA
Placebo	63.57%
Dob	15.43%
Mil	19.31%
LEV 0.075ug/kg/min	84.05%
LEV 0.1ug/kg/min	63.69%
LEV 0.2ug/kg/min	53.94%

Abbreviation: SUCRA, surface area under the cumulative ranking curve.

4 Quality Control

4.1 Convergence test: PSRF value

Potential scale reduction factors:

	Point est.	Upper C.I.
d.2.4	1	1
d.2.5	1	1
d.2.6	1	1
d.6.1	1	1
d.6.3	1	1

Multivariate psrf

1

Figure SIII-4.1 PSRF of the Bayesian analysis of 28-day mortality

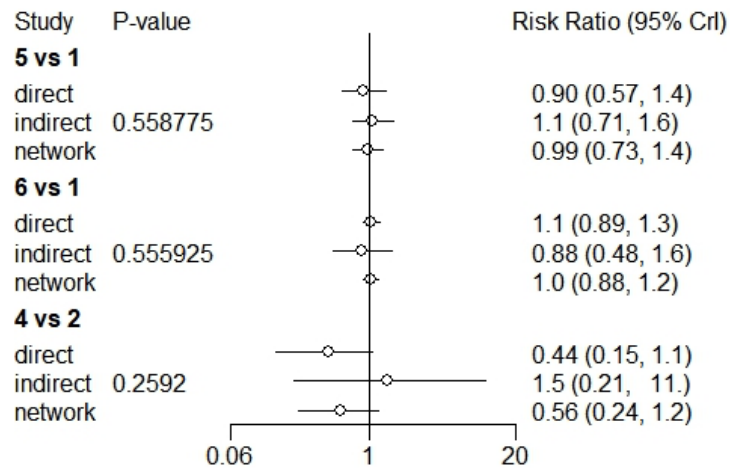
Abbreviation: PSRF, Potential scale reduction factors.

Note: The closer the PSRF value is to 1, the better. >1.05 indicates unsatisfactory convergence.

4.2 Consistency hypothesis: inconsistency test.

4.2.1 Function used: *mtc.nodesplit*

4.2.2 Results:



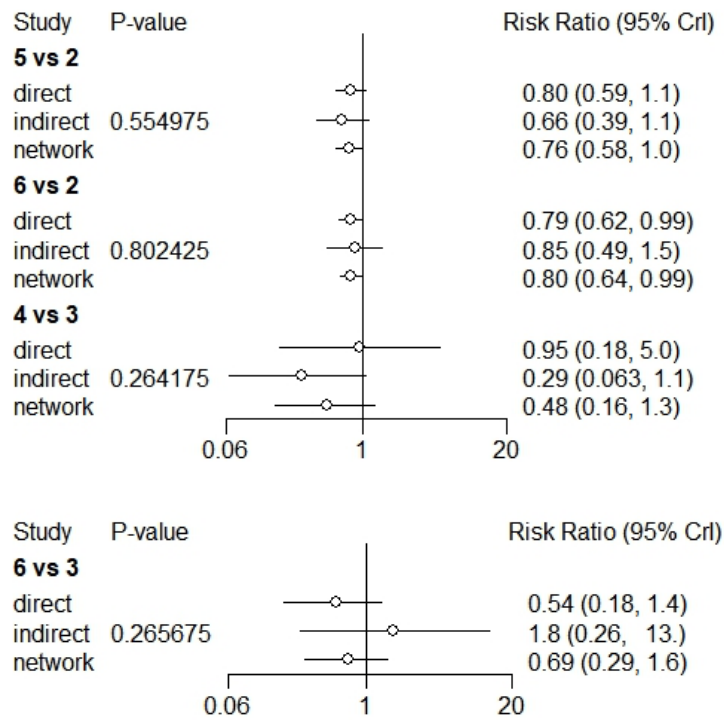


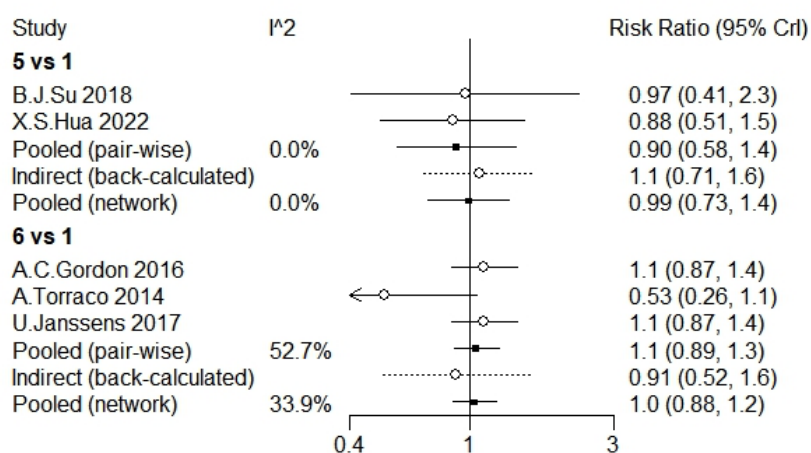
Figure SIII-4.2.2 Inconsistency test of the Bayesian analysis of 28-day mortality

Note: 1, Placebo; 2, Dob; 3, Mil; 4, LEV 0.075ug/kg/min;5, LEV 0.1ug/kg/min;6, LEV 0.2ug/kg/min. *P* value > 0.05 indicates that there is no significant inconsistency which means the direct, indirect and network comparison is consistent.

4.3 Homogeneity hypothesis: Heterogeneity analysis

4.3.1 Function used: *mtc.anohe*

4.3.2 Results



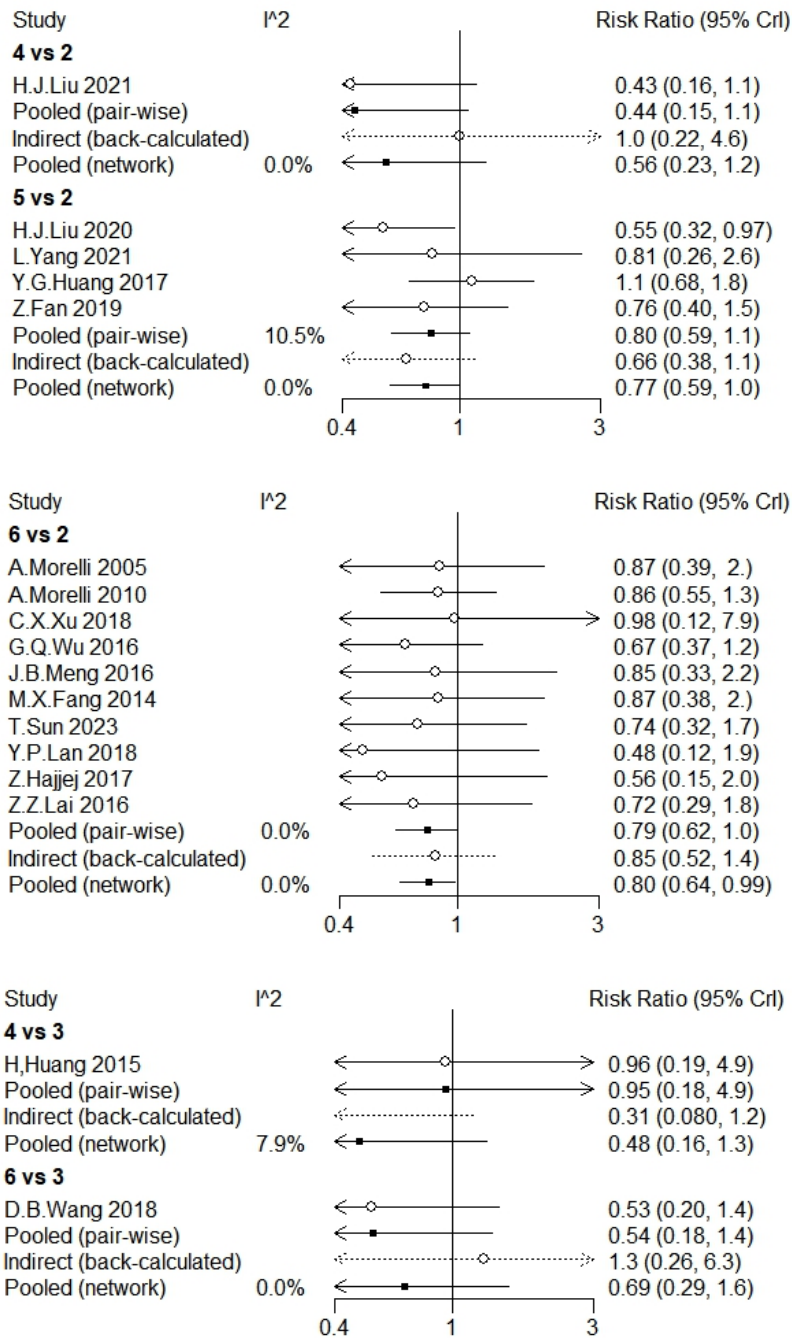


Figure SIII-4.3.2 Heterogeneity analysis of the Bayesian analysis of 28-day mortality

Note: From the figure we could see, there exists no significant heterogeneity between any two arms, which allows the use of fixed effect model to estimate the pooling results.