

# **The Dynamics of Inflammatory Markers in Coronavirus Disease-2019 (COVID-19) Patients: A Systematic Review and Meta-analysis**

Roshan Kumar Mahat, Suchismita Panda, Vedika Rathore, Sharmistha Swain, Lalendra Yadav,  
Sumesh Prasad Sah

**Supplement 1:** Forest plot of inflammatory markers. Forest plot between severe and non-severe groups for levels of C-reactive protein (A), Erythrocyte sedimentation rate (B), Procalcitonin (C), Interleukin-6 (D), Interleukin-10 (E), Interleukin-2R (F), Tumor necrosis factor- $\alpha$  (G), Ferritin (H), Serum amyloid A (I), Neutrophil to lymphocyte ratio (J).

**Supplement 2:** Forest plot of inflammatory markers. Forest plot between survivor and non-survivor groups for levels of C-reactive protein (A), Erythrocyte sedimentation rate (B), Procalcitonin (C), Interleukin-6 (D), Ferritin (E), Neutrophil to lymphocyte ratio (F).

**Supplement-3:** Forest plot (A-I) showing subgroup analysis of inflammatory parameters (CRP, ESR, PCT, IL-6, IL-10, TNF- $\alpha$ , ferritin, SAA and NLR) by sample size in severity studies.

**Supplement-4:** Forest plot (A-E) showing subgroup analysis of inflammatory parameters (CRP, ESR, PCT, ferritin and NLR) by sample size in mortality studies.

**Supplement-5:** Funnel plots for inflammatory parameters in severity studies. (A, B) Funnel plot and adjusted funnel plot for CRP. (C, D) Funnel plot and adjusted funnel plot for ESR. (E, F) Funnel plot and adjusted funnel plot for PCT. (G, H) Funnel plot and adjusted funnel plot for IL-6. (I, J) Funnel plot and adjusted funnel plot for NLR.

**Supplement-6:** (A) Trim and fill method for CRP. (B) Trim and fill method for ESR. (C) Trim and fill method for PCT. (D) Trim and fill method for IL-6. (E) Trim and fill method for NLR

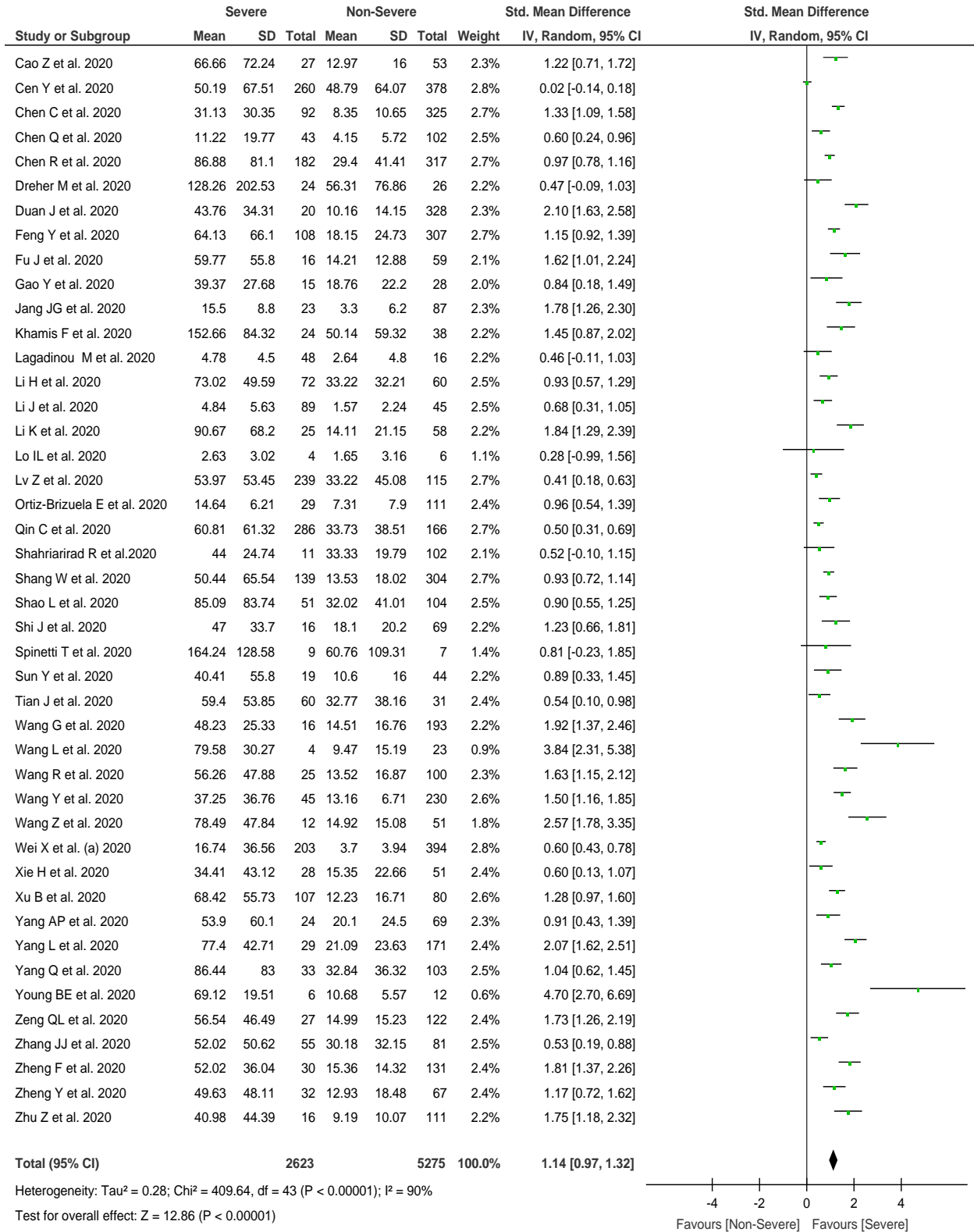
**Supplement-7:** Funnel plots for inflammatory parameters in mortality studies. (A) Funnel plot for CRP. (B, C) Funnel plot and adjusted funnel plot for PCT. (D, E) Funnel plot and adjusted funnel plot for ferritin.

**Supplement-8:** (A) Trim and fill method for PCT. (B) Trim and fill method for ferritin.

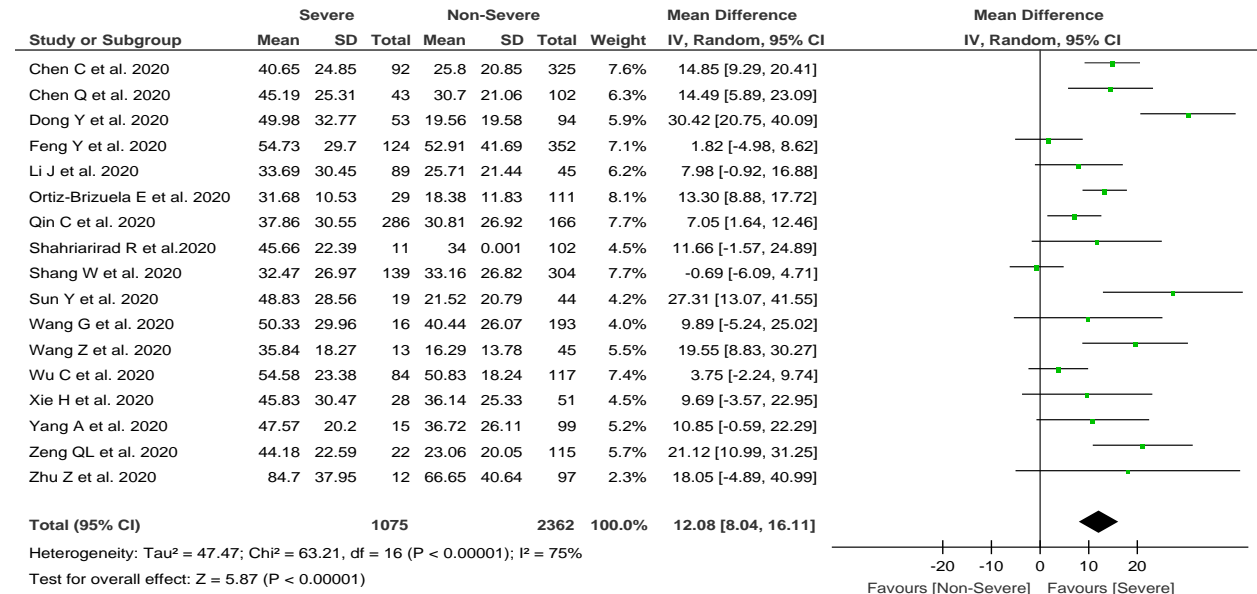
**Supplement-9:** Sensitivity analysis (A-I). Sensitivity analysis between severe and non-severe groups for levels of CRP (A), ESR (B), PCT (C), IL-6 (D), IL-10 (E), TNF- $\alpha$  (F), ferritin (G), SAA (H) and NLR (I).

**Supplement-10:** Sensitivity analysis (A-F). Sensitivity analysis between survivor and non-survivor groups for levels of CRP (A), ESR (B), PCT (C), IL-6 (D), ferritin (E) and NLR (F)

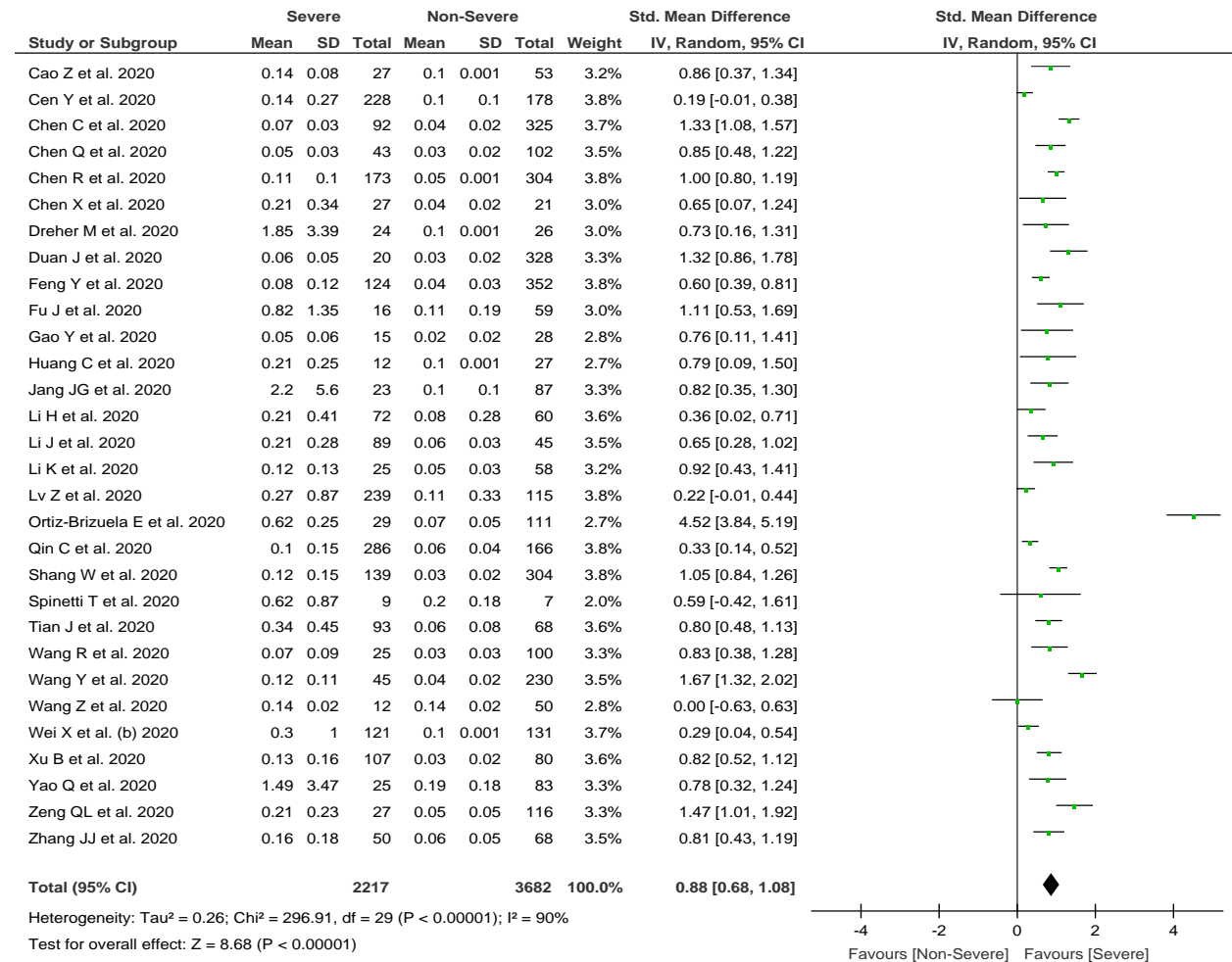
## A. C-reactive protein (CRP)



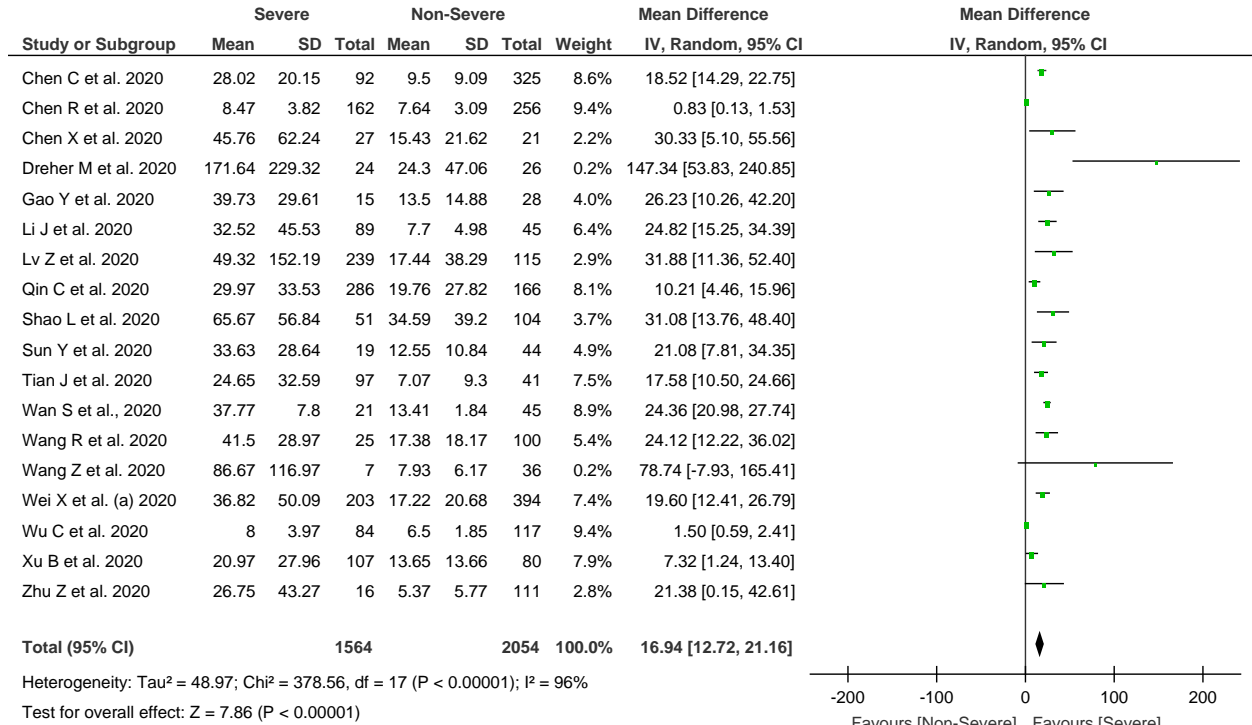
## B. Erythrocyte sedimentation rate (ESR)



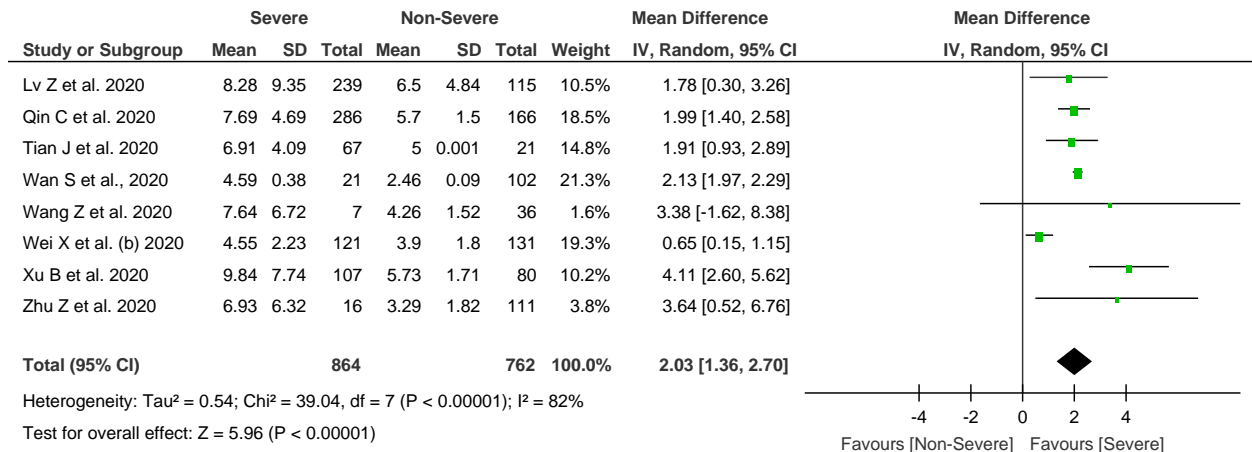
## C. Procalcitonin (PCT)



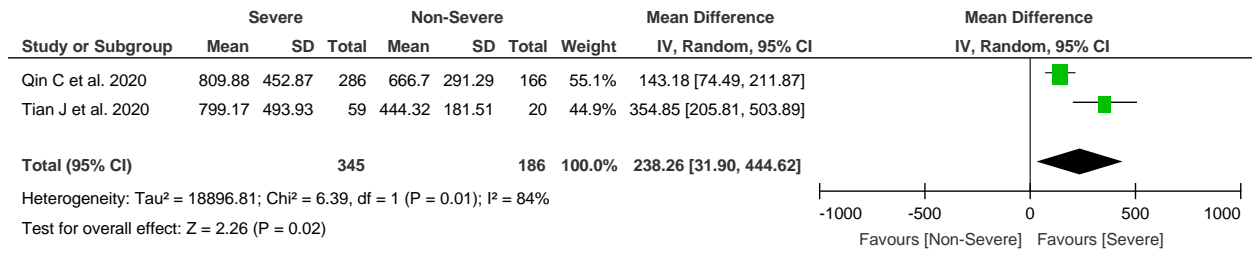
### D. Interleukin-6 (IL-6)



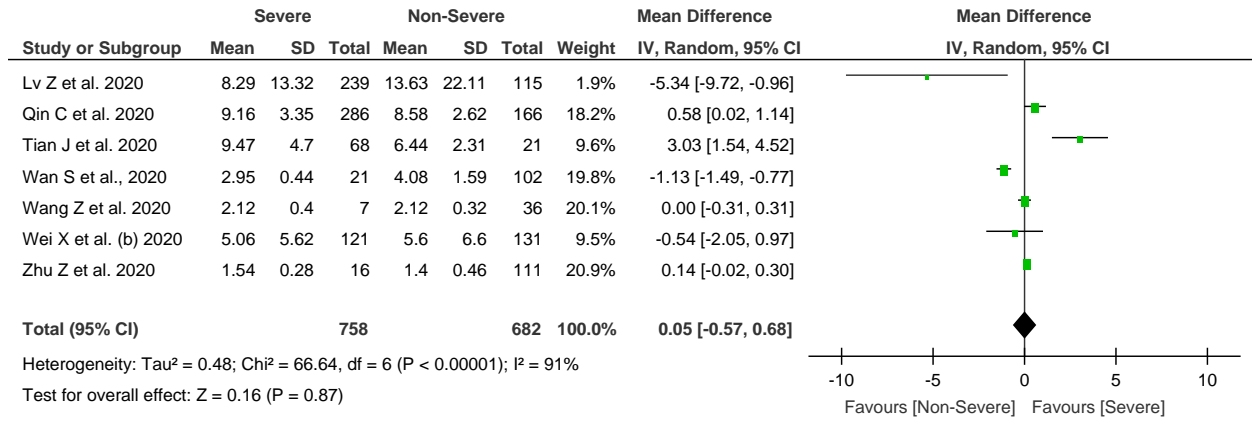
### E. Interleukin 10 (IL-10)



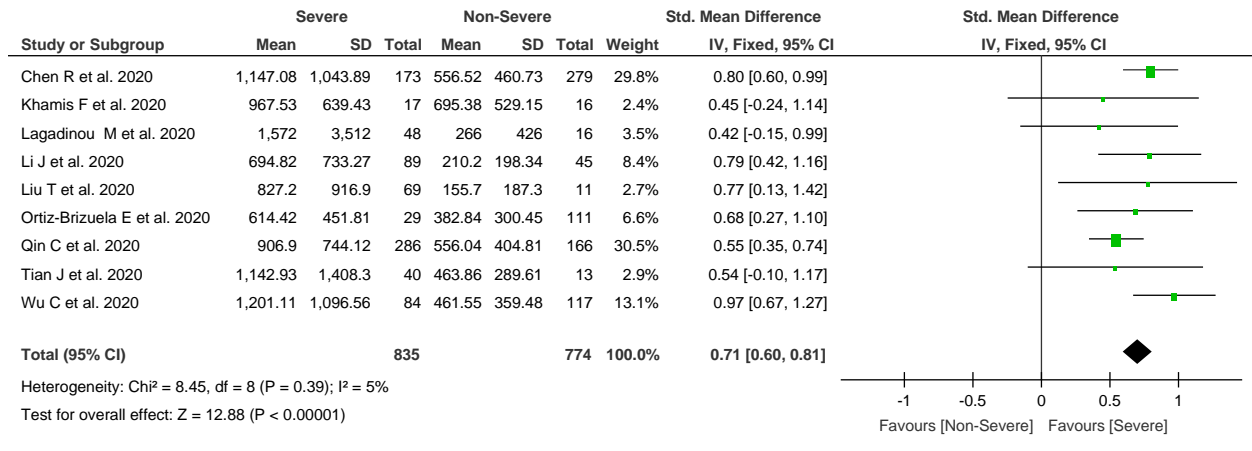
### F. Interleukin 2R (IL-2R)



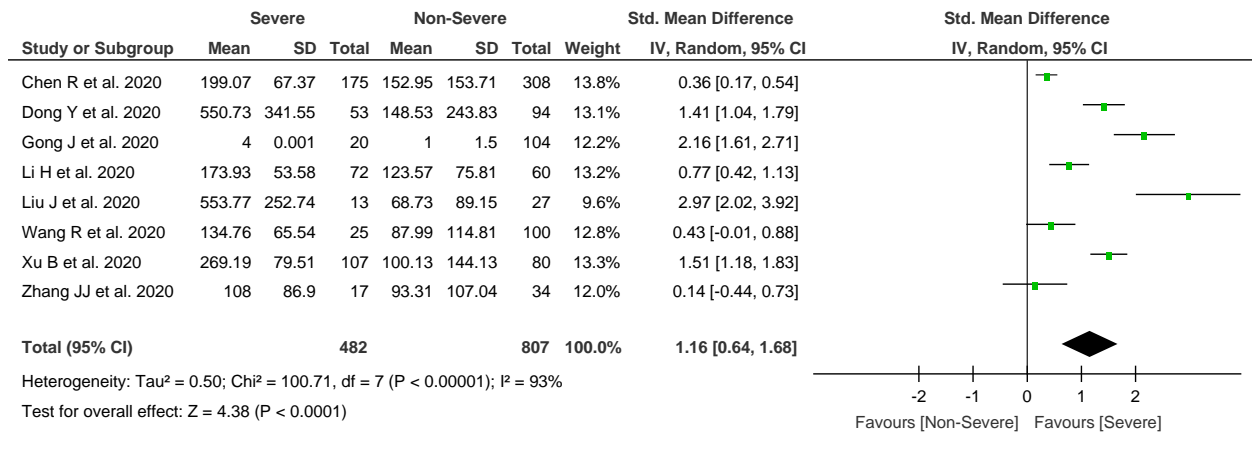
### G. Tumor necrosis factor- $\alpha$ (TNF- $\alpha$ )



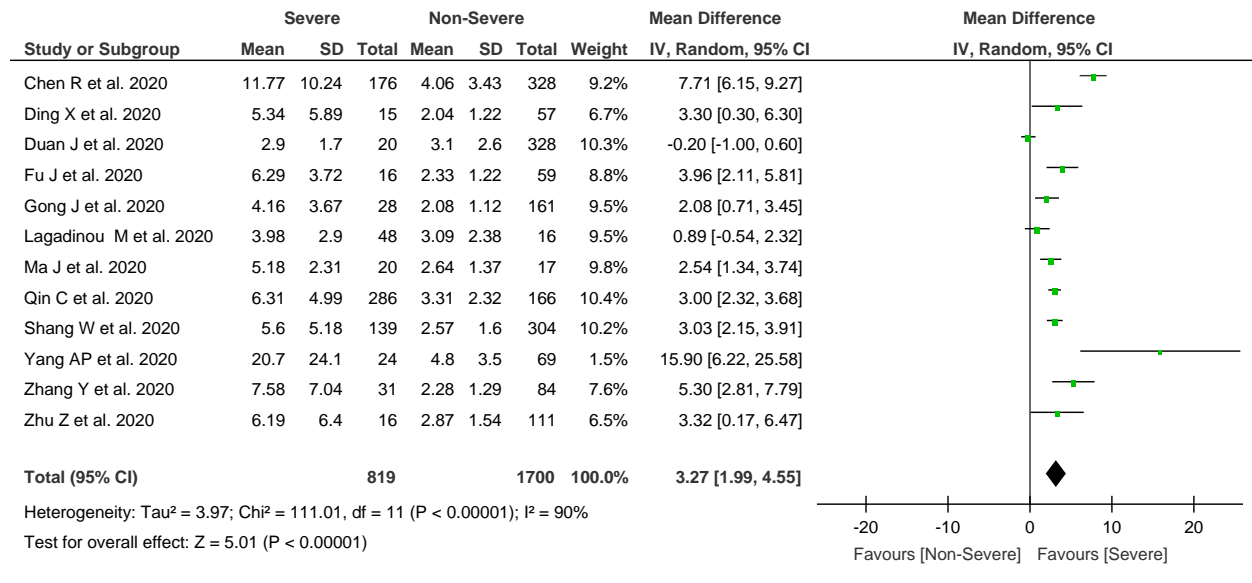
### H. Ferritin



### I. Serum amyloid A (SAA)

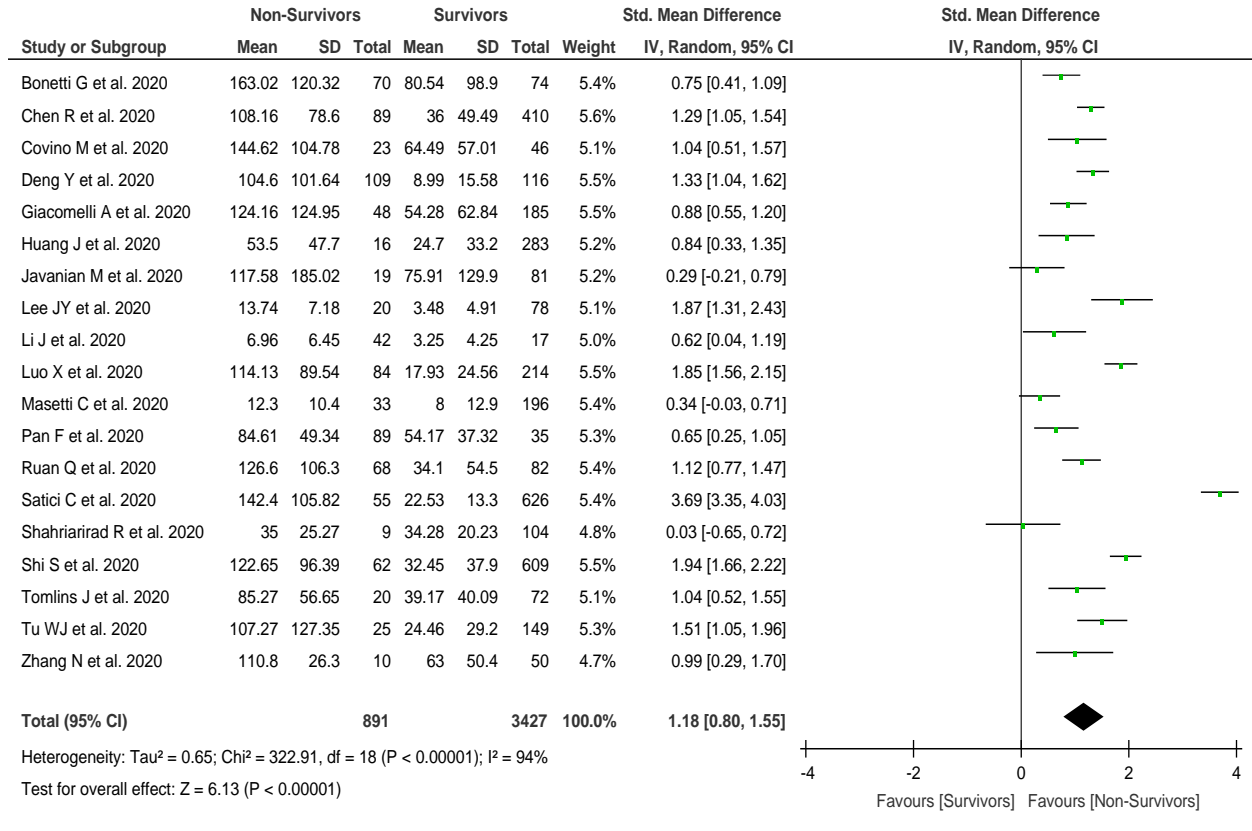


### J. Neutrophil to lymphocyte ratio (NLR):

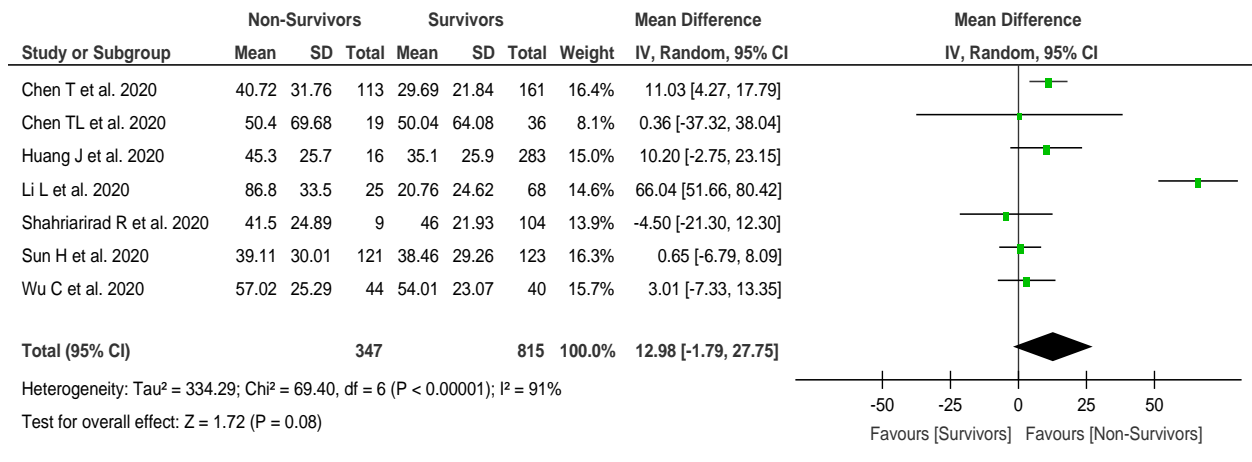


**Supplement 1:** Forest plot of inflammatory markers. Forest plot between severe and non-severe groups for levels of C-reactive protein (A), Erythrocyte sedimentation rate (B), Procalcitonin (C), Interleukin-6 (D), Interleukin-10 (E), Interleukin-2R (F), Tumor necrosis factor- $\alpha$  (G), Ferritin (H), Serum amyloid A (I), Neutrophil to lymphocyte ratio (J).

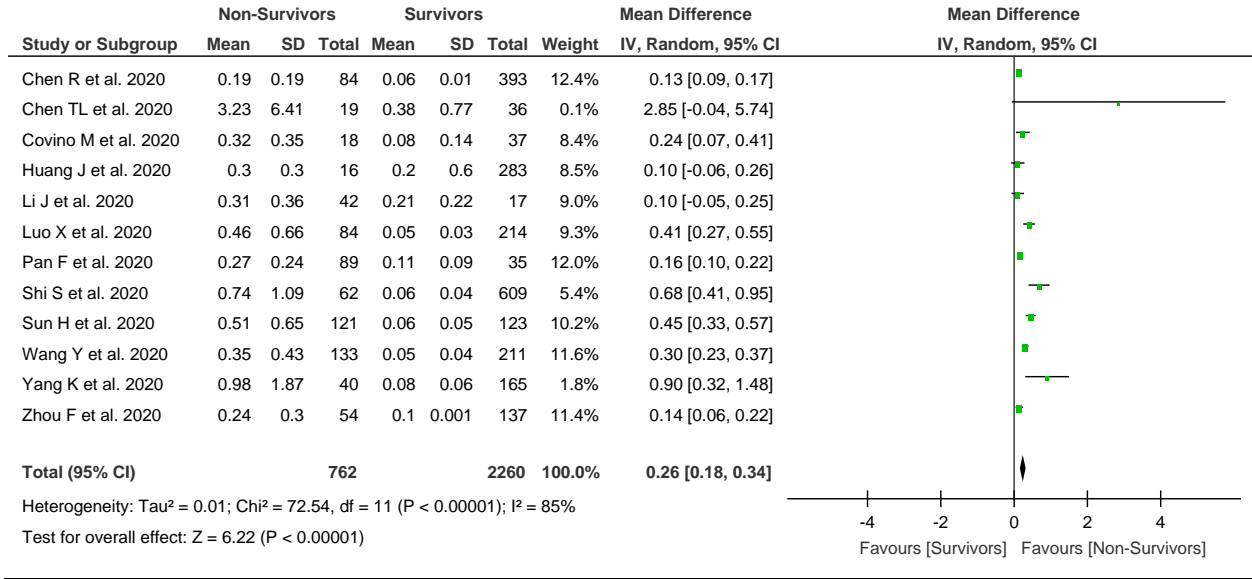
### A. C-reactive protein (CRP)



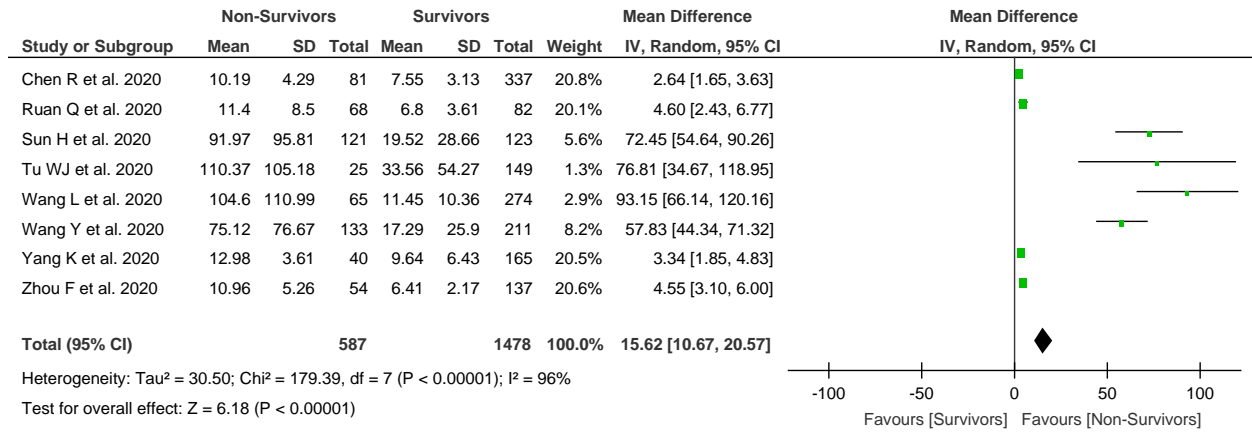
### B. Erythrocyte sedimentation rate (ESR)



### C. Procalcitonin (PCT)

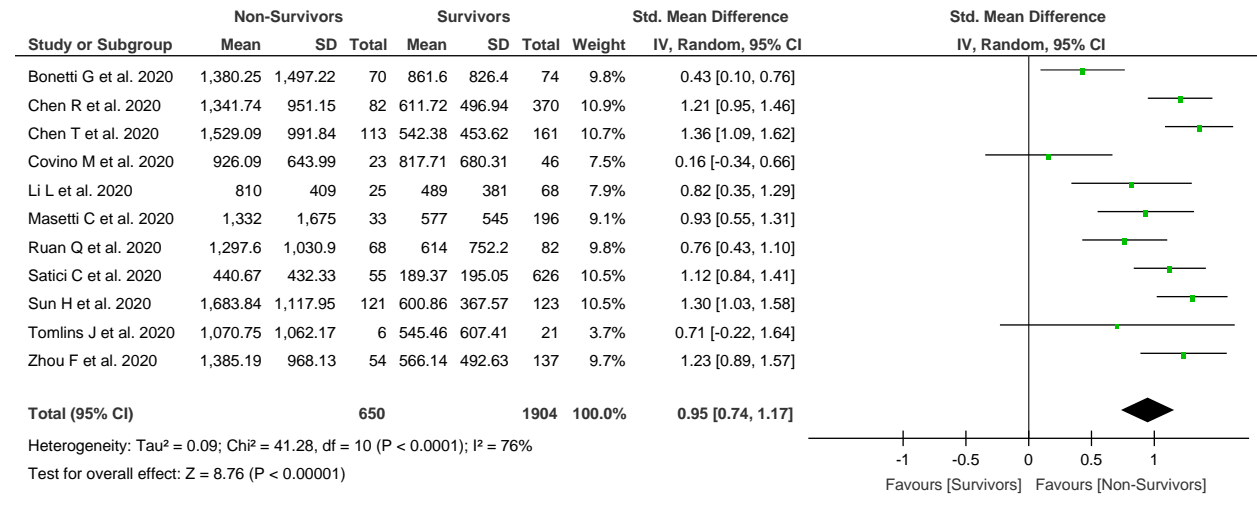


### D. Interleukin-6 (IL-6)

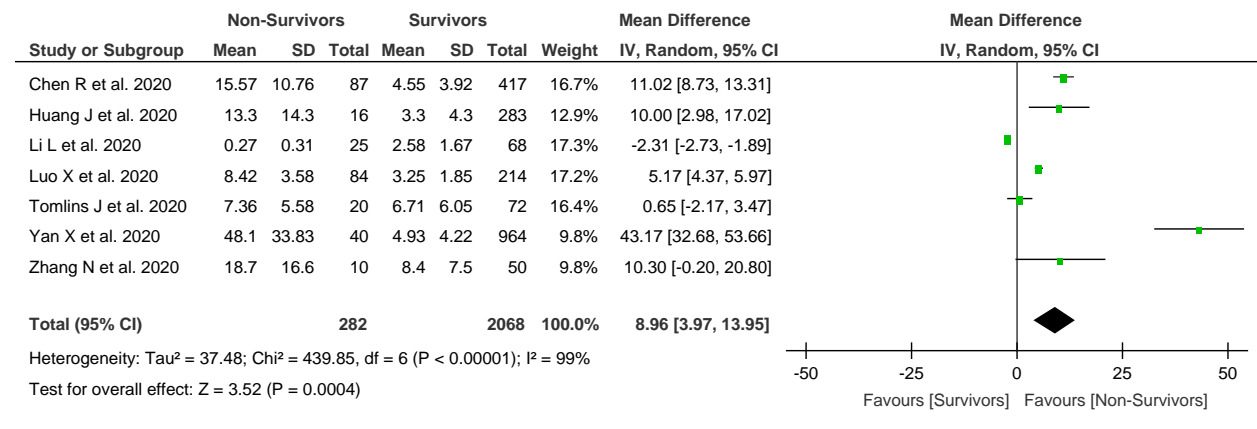




## E. Ferritin

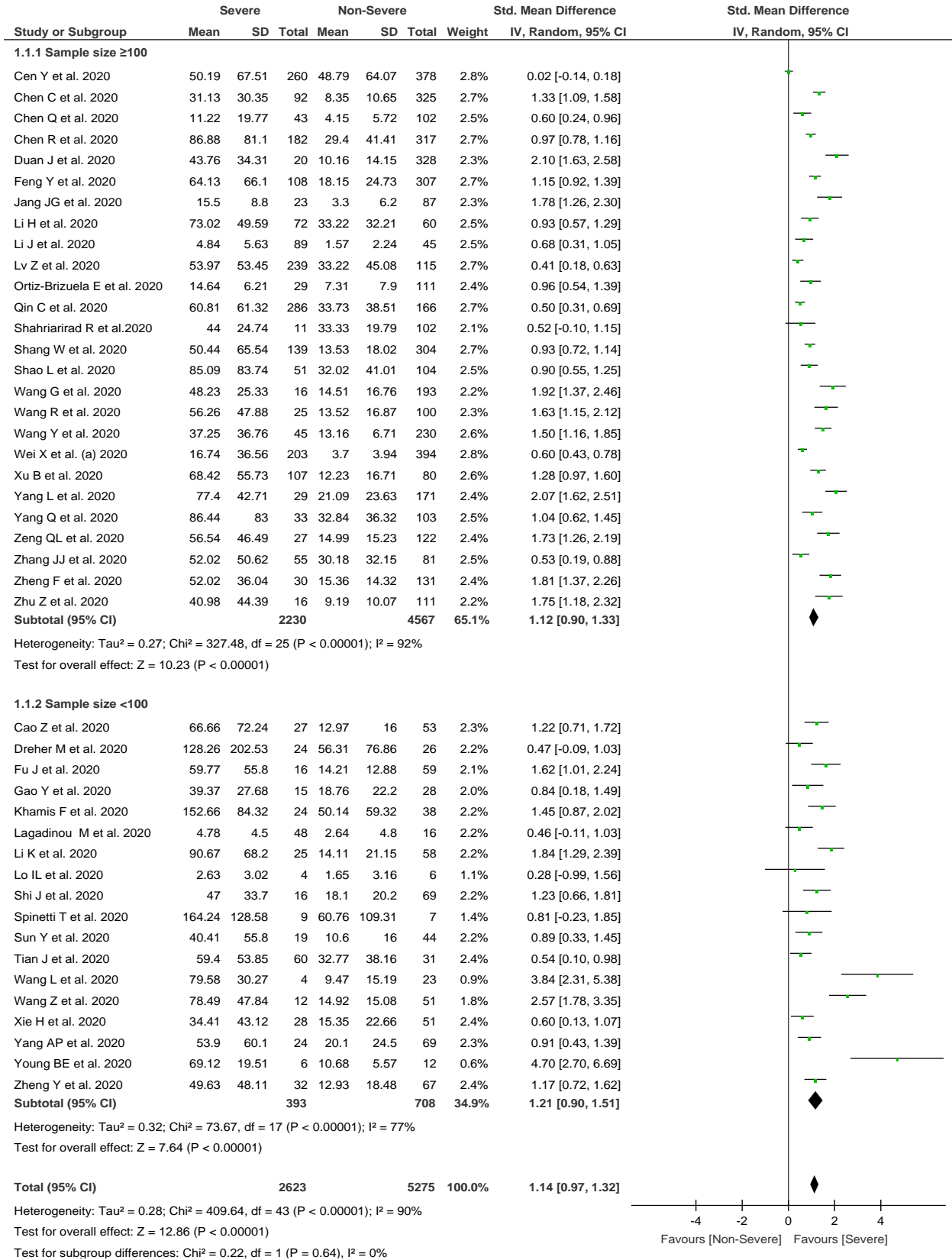


## F. Neutrophil to lymphocyte ratio (NLR):

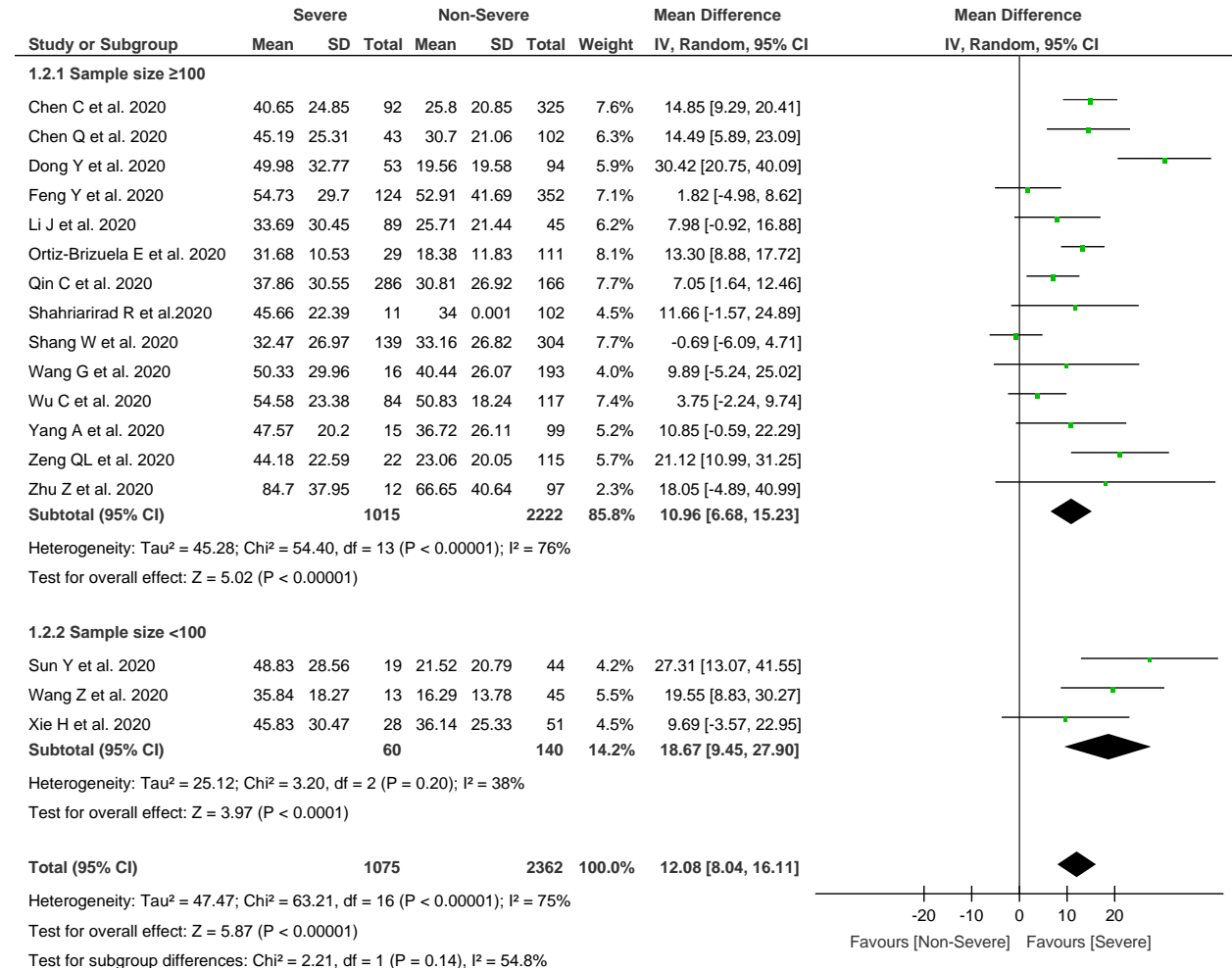


**Supplement 2:** Forest plot of inflammatory markers. Forest plot between survivor and non-survivor groups for levels of C-reactive protein (A), Erythrocyte sedimentation rate (B), Procalcitonin (C), Interleukin-6 (D), Ferritin (E), Neutrophil to lymphocyte ratio (F).

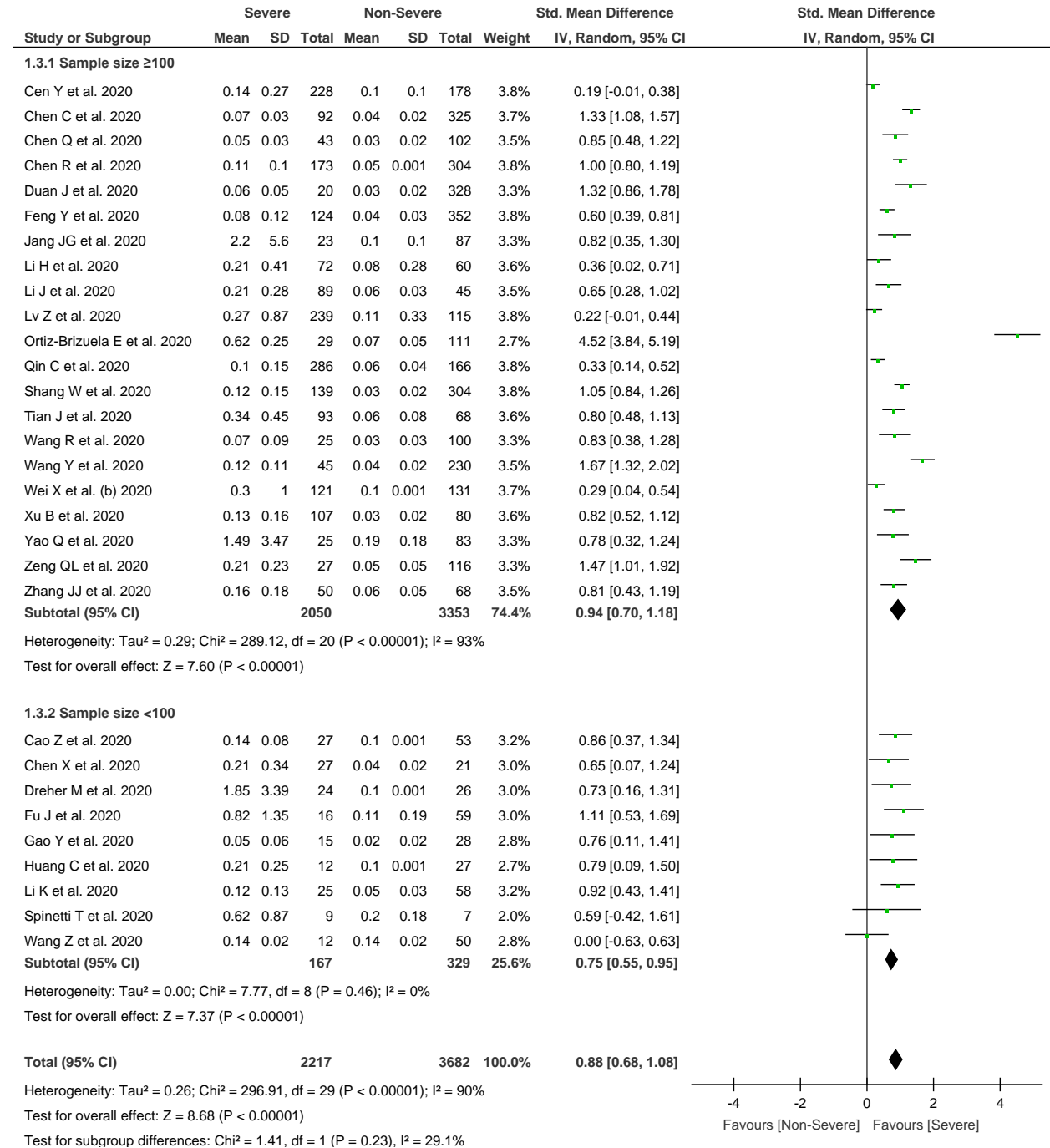
## A. C-reactive protein (CRP)



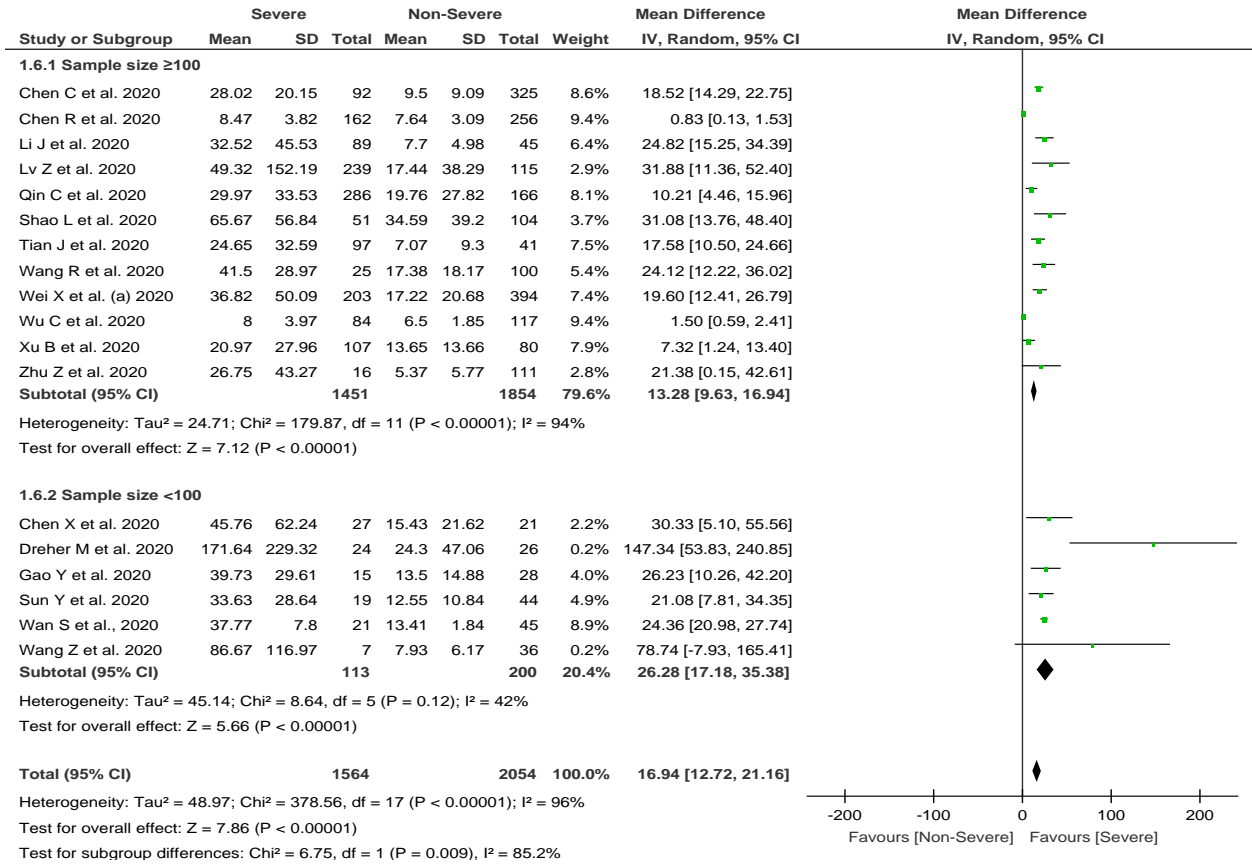
## B. Erythrocyte sedimentation rate (ESR)



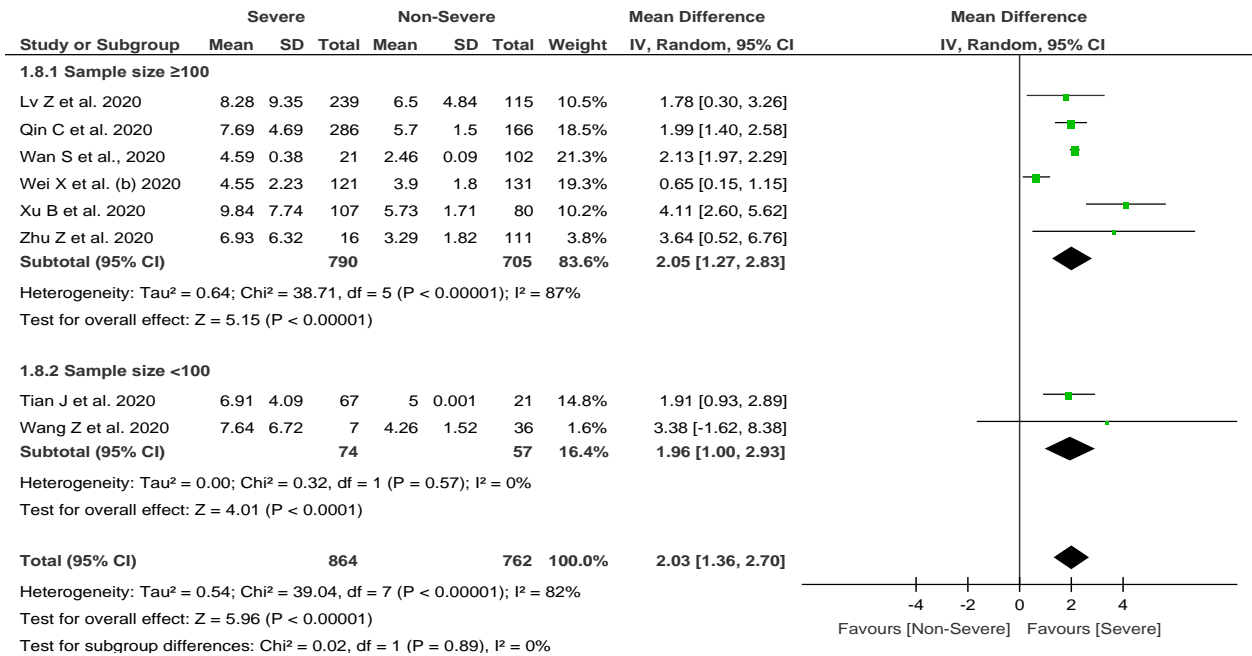
## C. Procalcitonin (PCT)



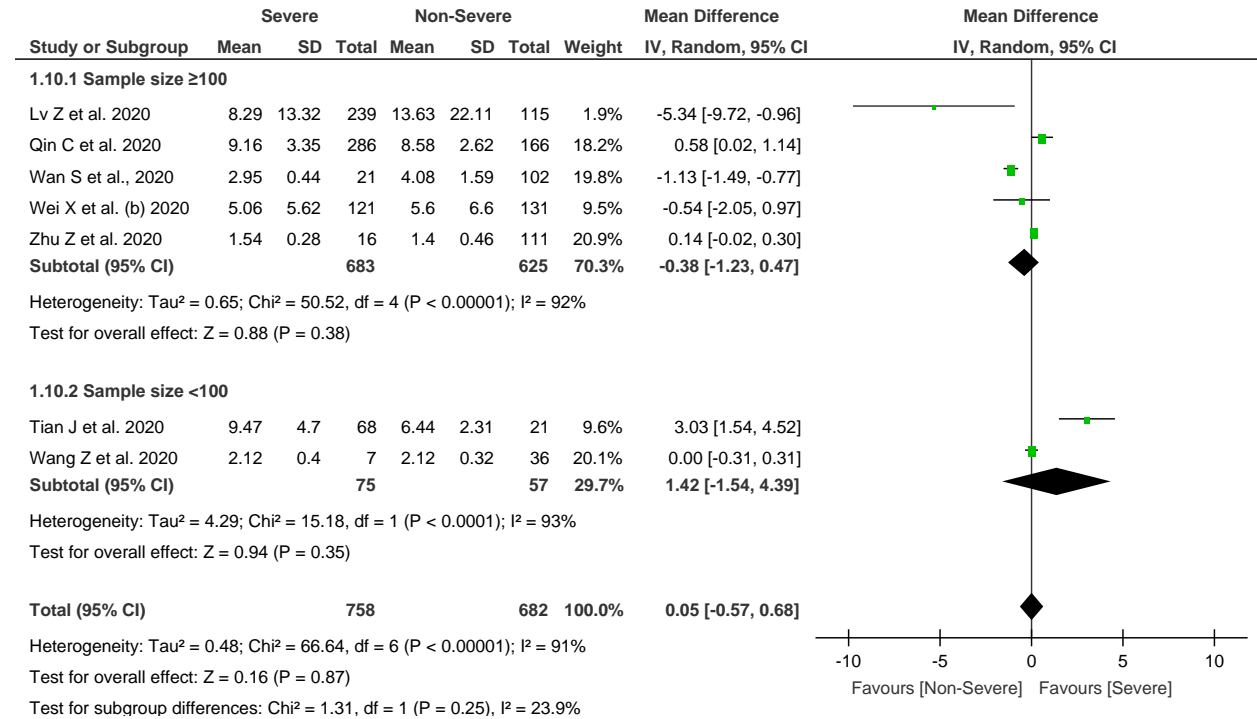
## D. Interleukin-6 (IL-6)



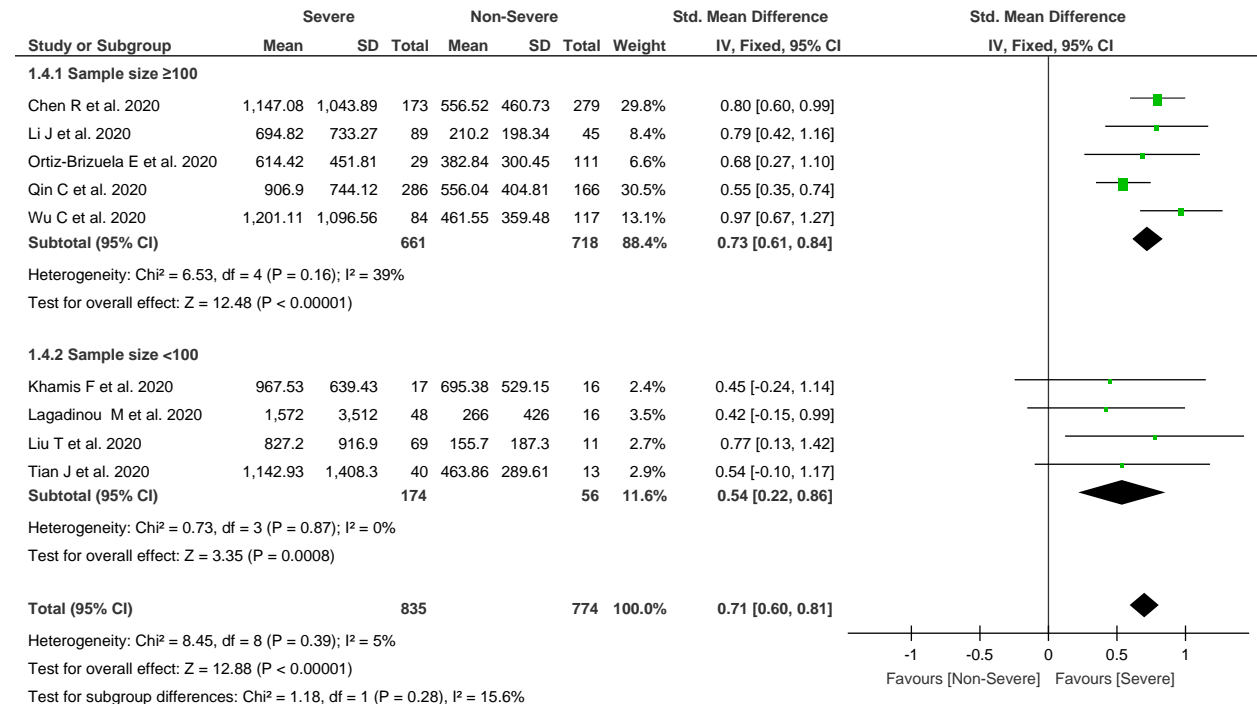
## E. Interleukin-10 (IL-10)



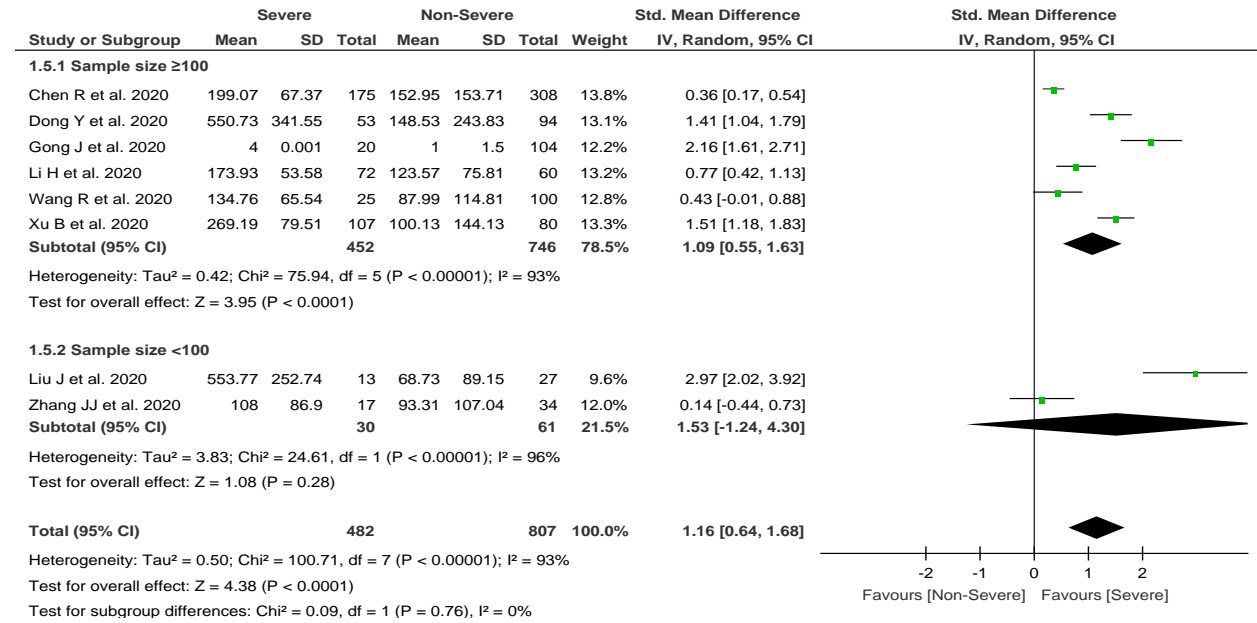
## F. Tumor necrosis factor- $\alpha$ (TNF- $\alpha$ )



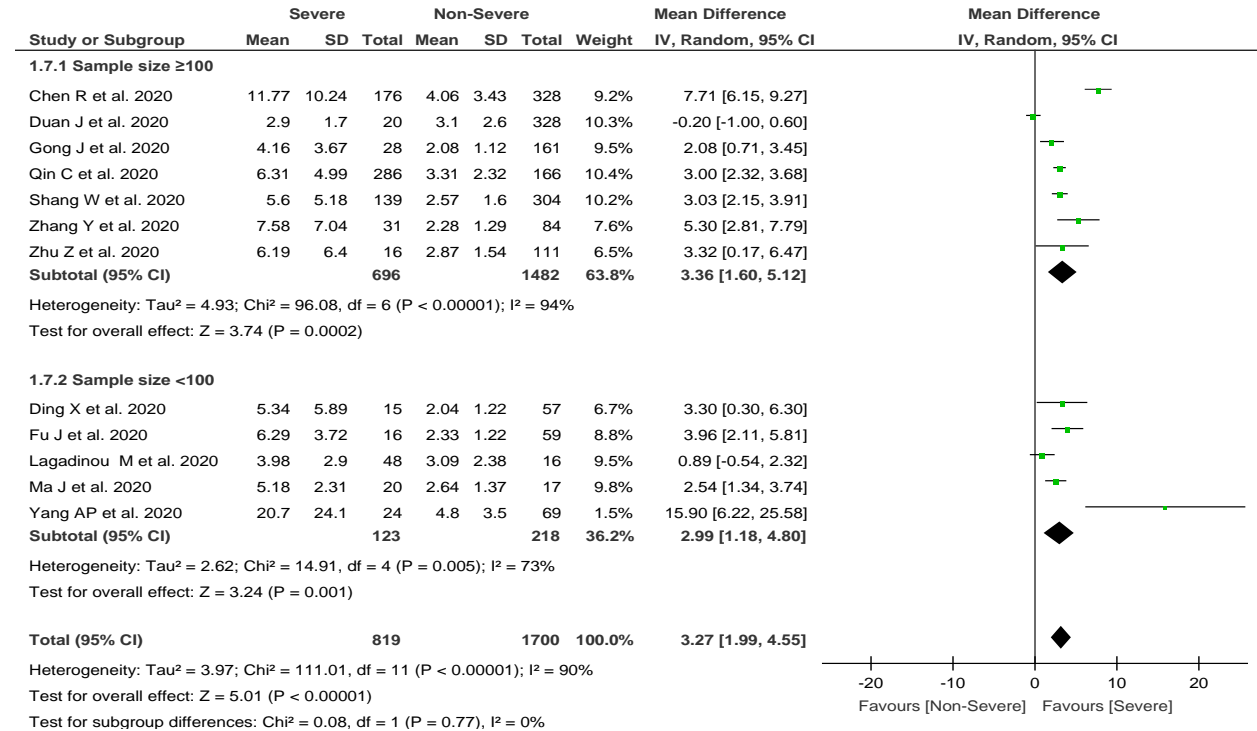
## G. Ferritin



## H. Serum amyloid A (SAA)

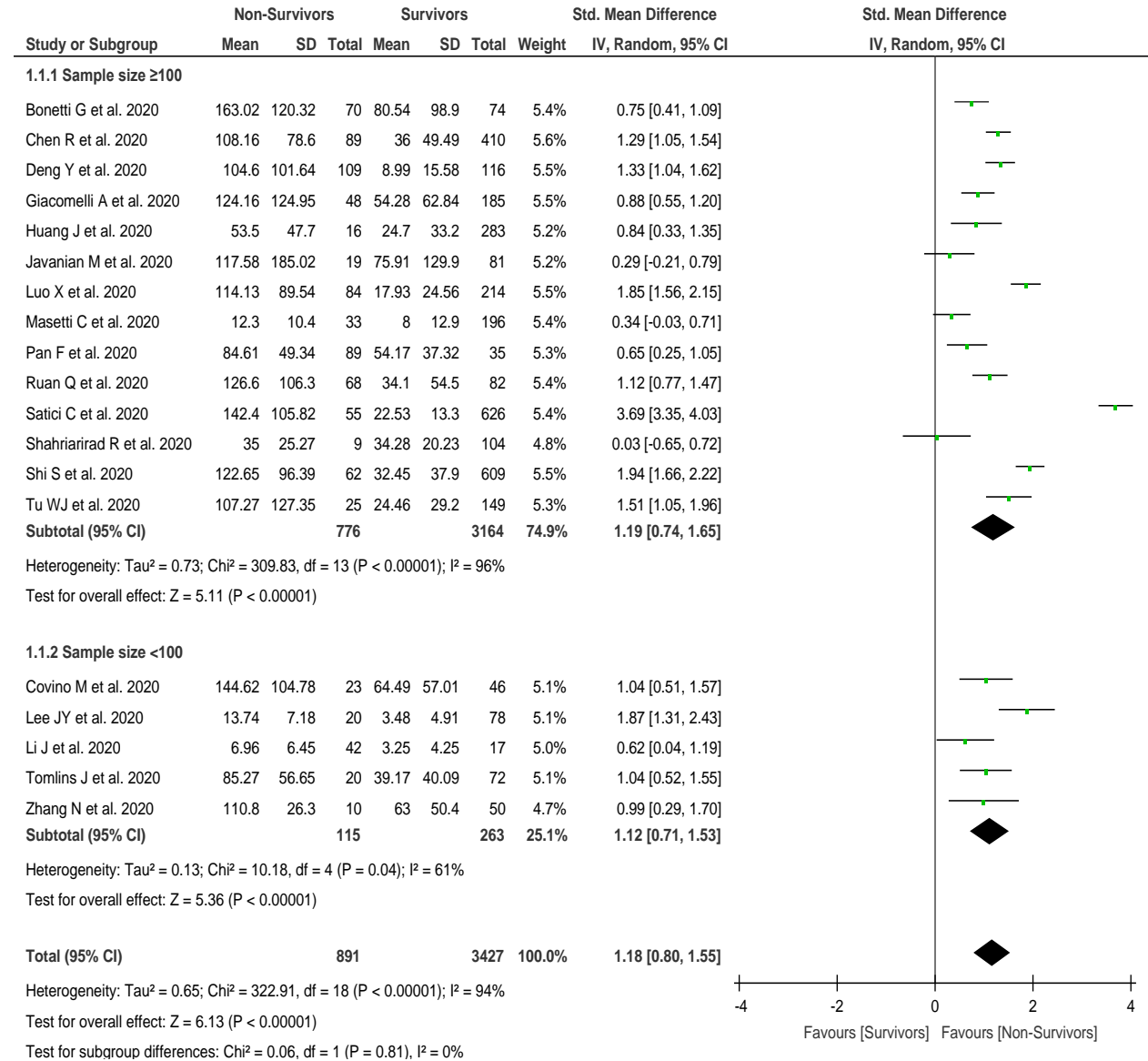


## I. Neutrophil to lymphocyte ratio (NLR)



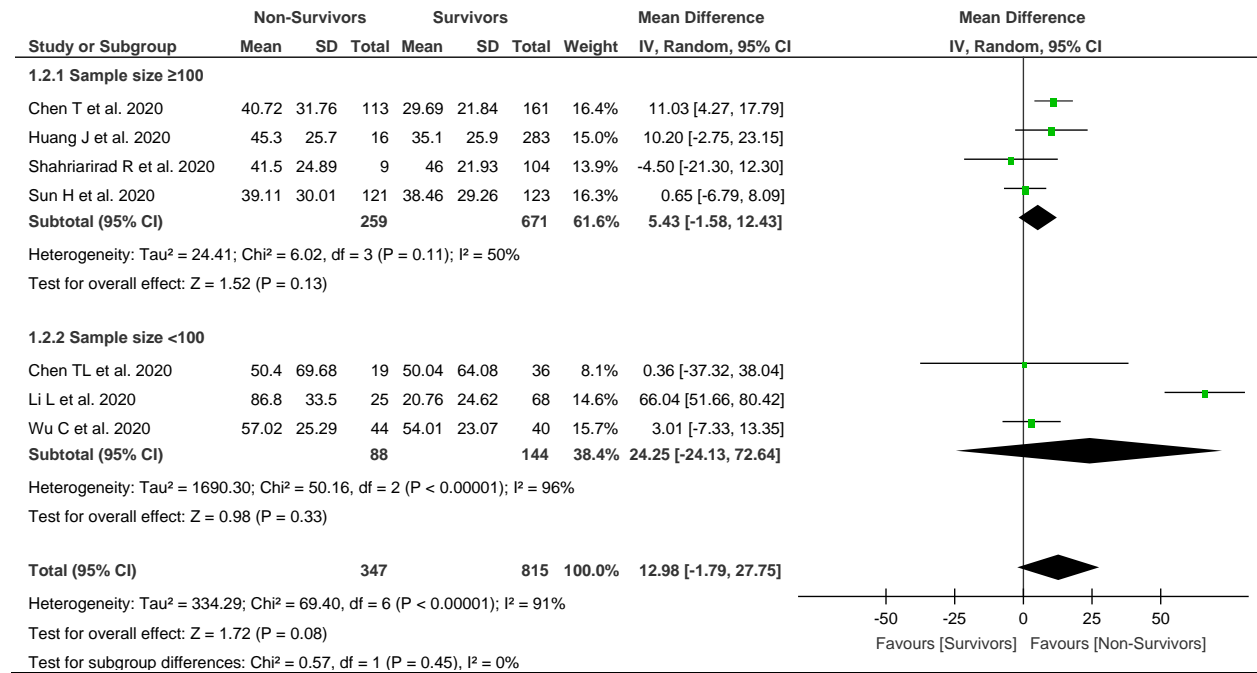
**Supplement-3:** Forest plot (A-I) showing subgroup analysis of inflammatory parameters (CRP, ESR, PCT, IL-6, IL-10, TNF- $\alpha$ , ferritin, SAA and NLR) by sample size in severity studies.

## A. C-reactive protein (CRP)

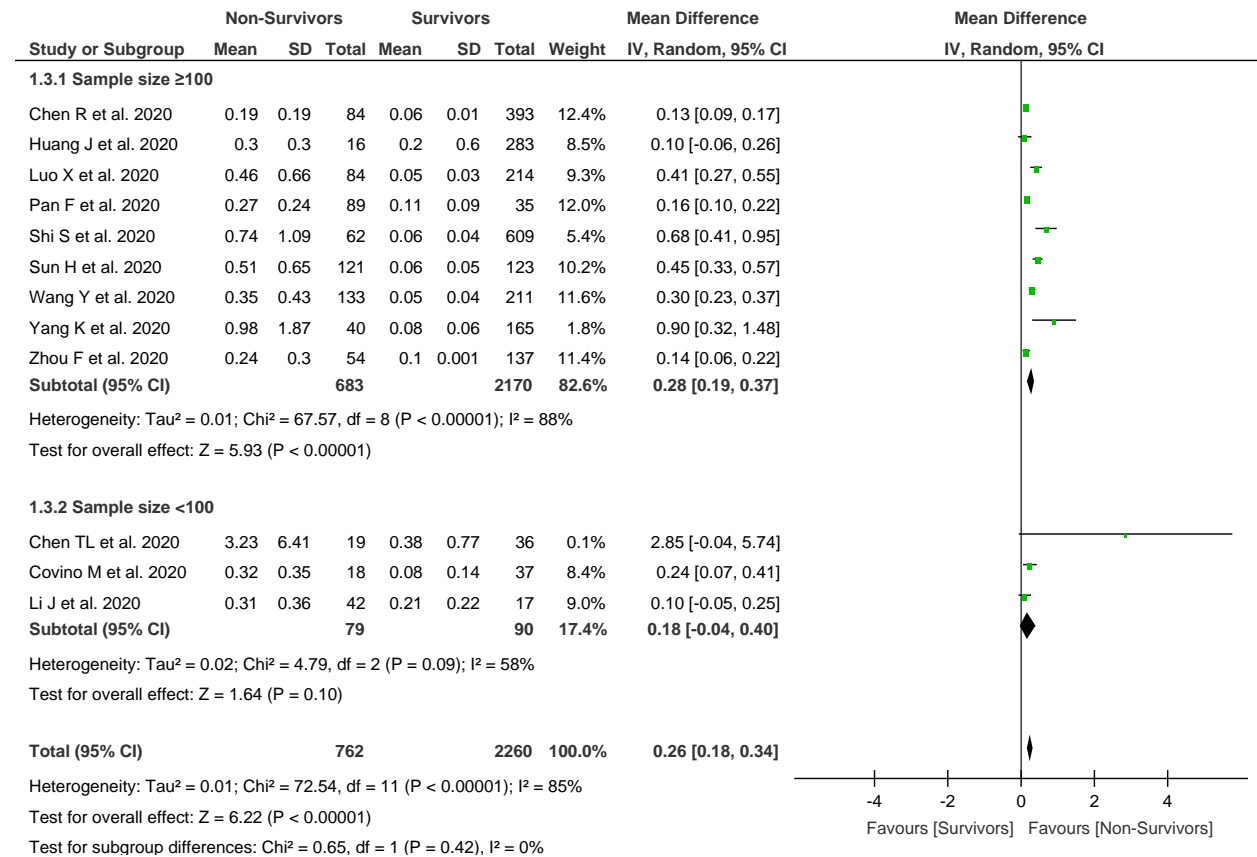




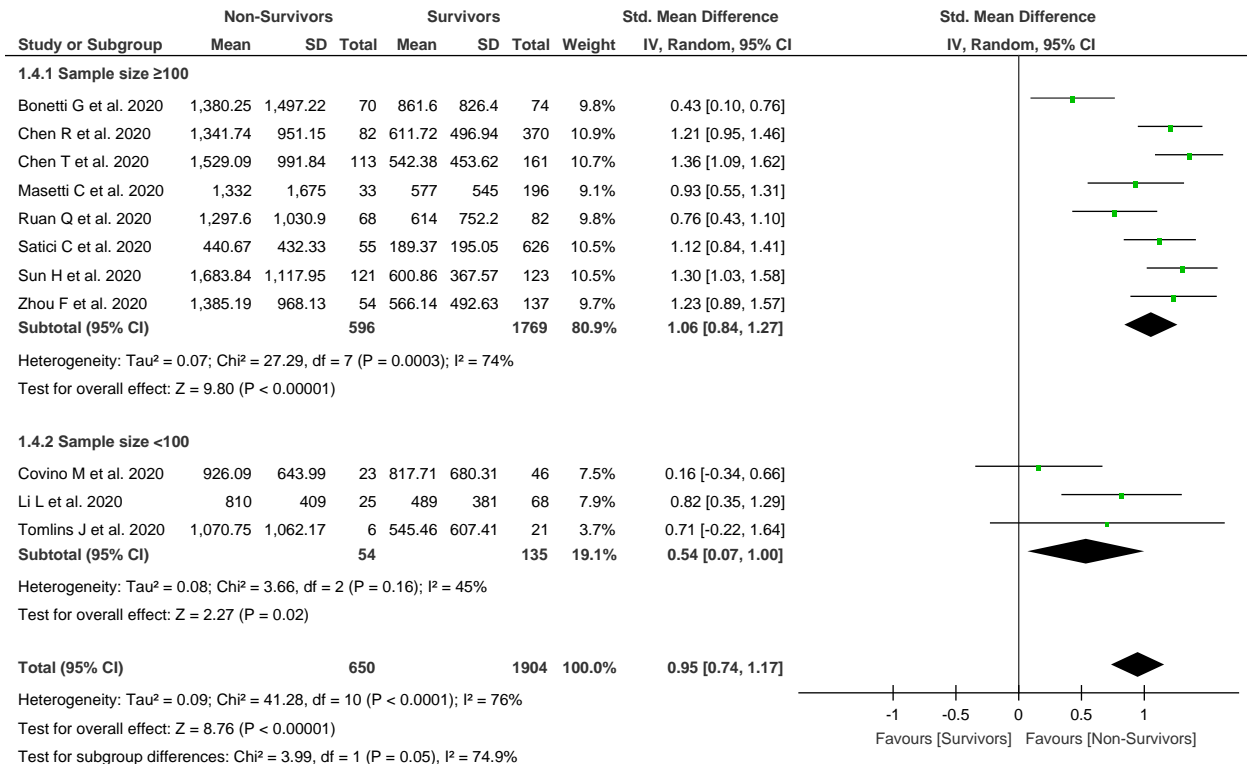
## B. Erythrocyte sedimentation rate (ESR)



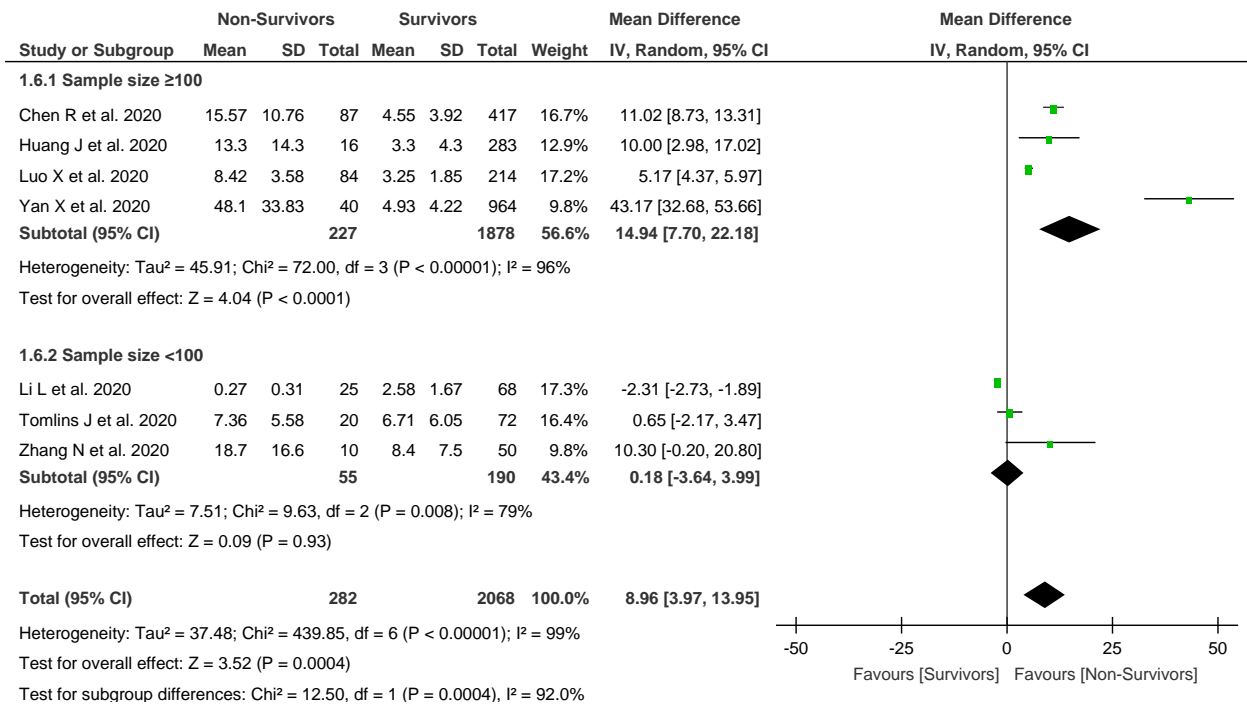
## C. Procalcitonin (PCT)



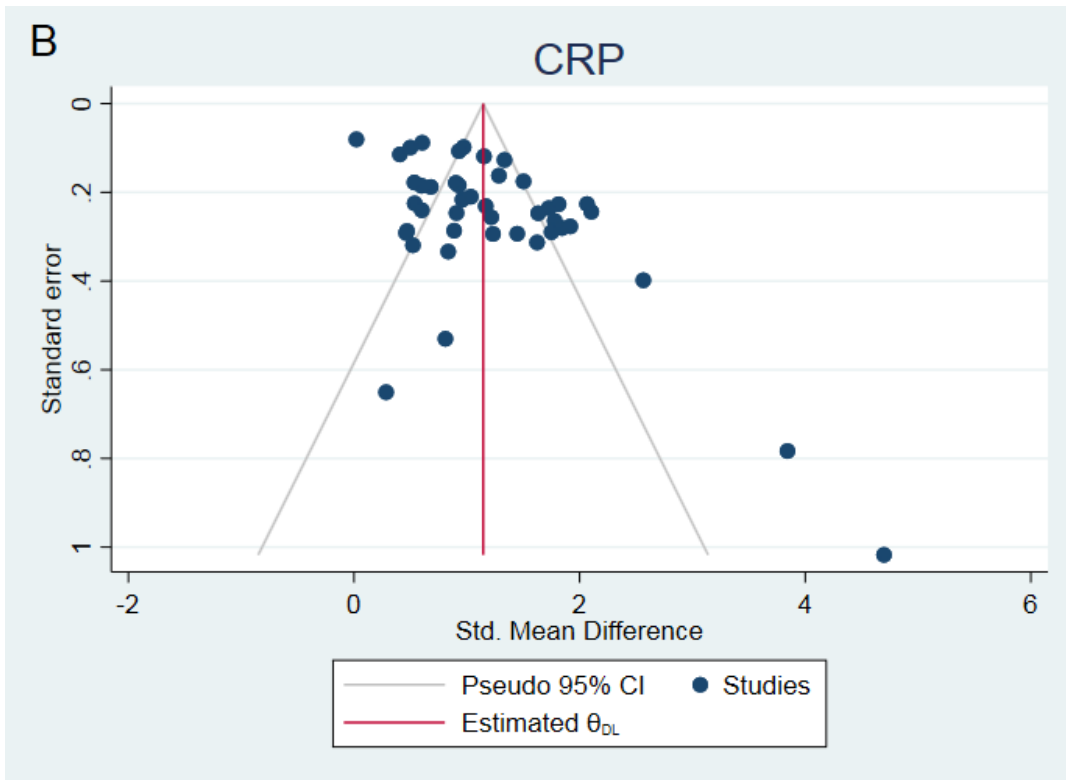
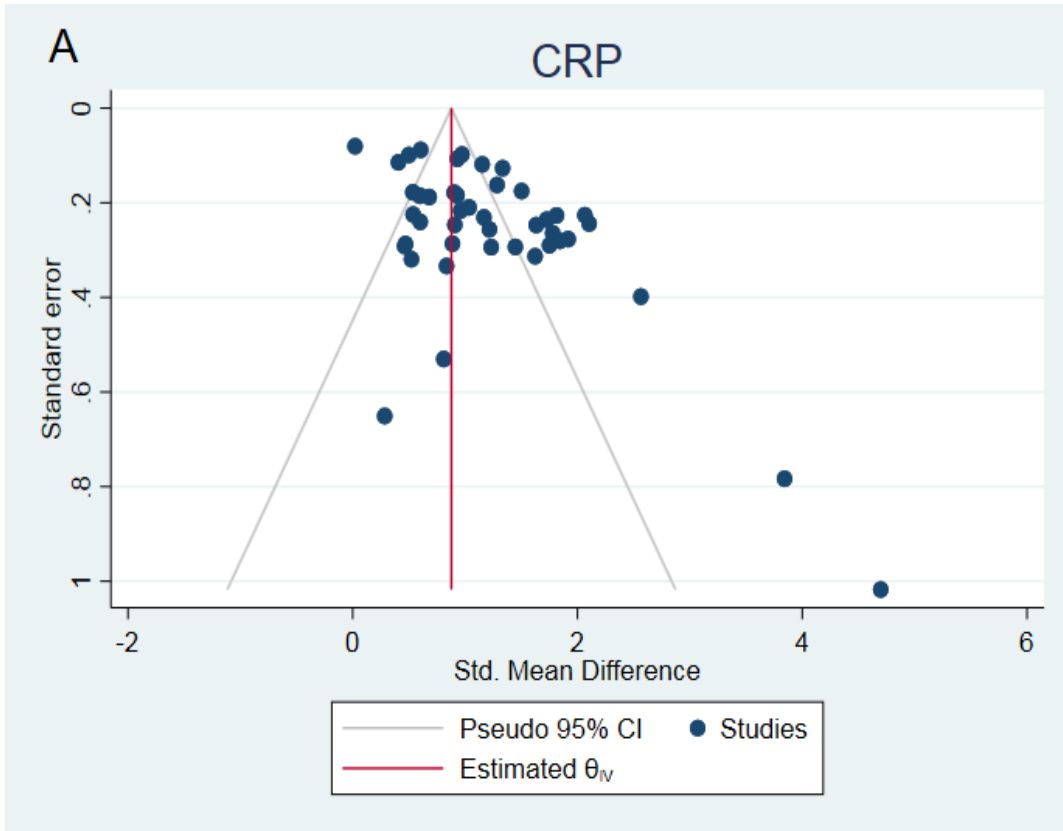
## D. Ferritin

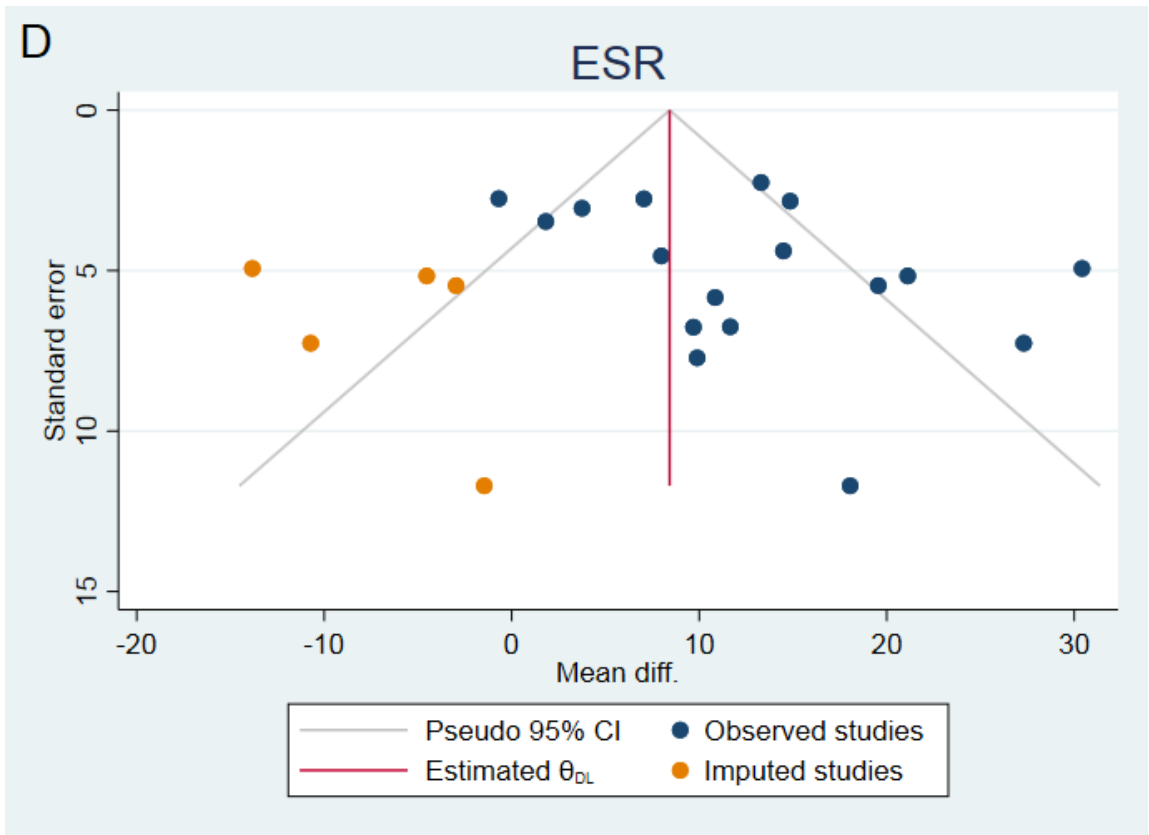
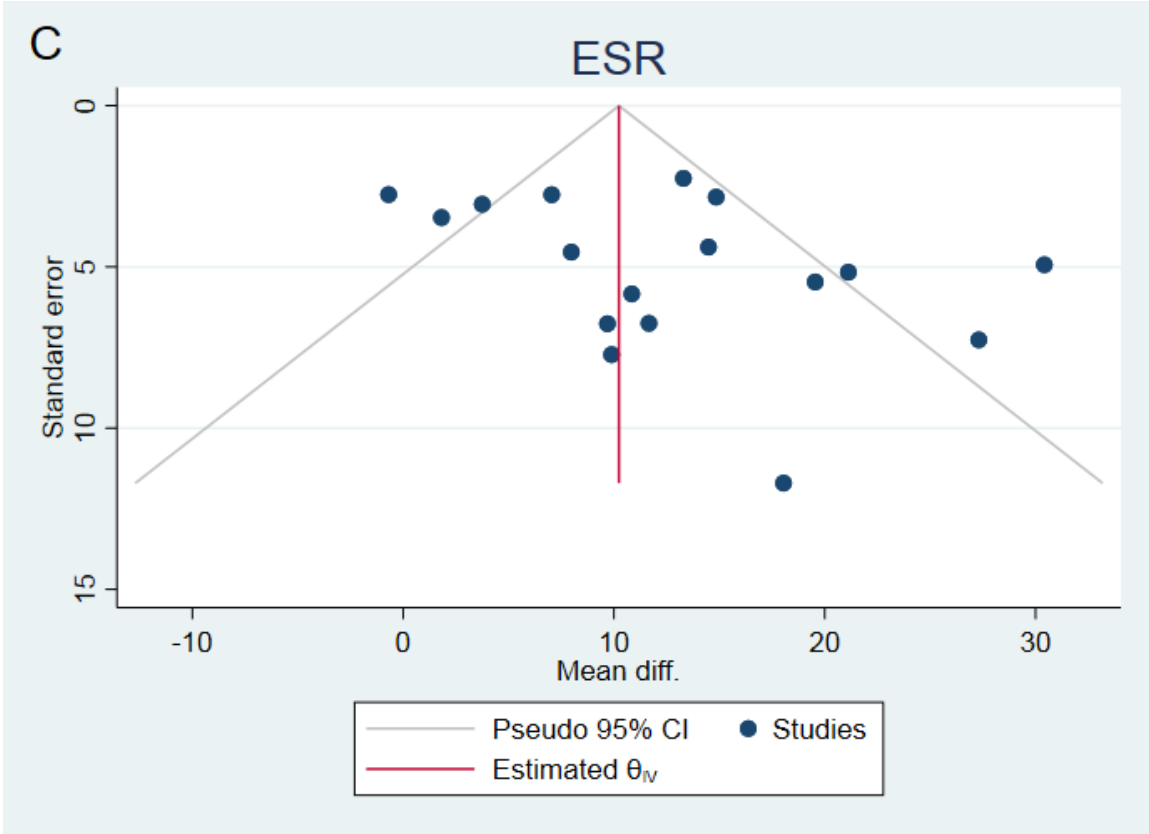


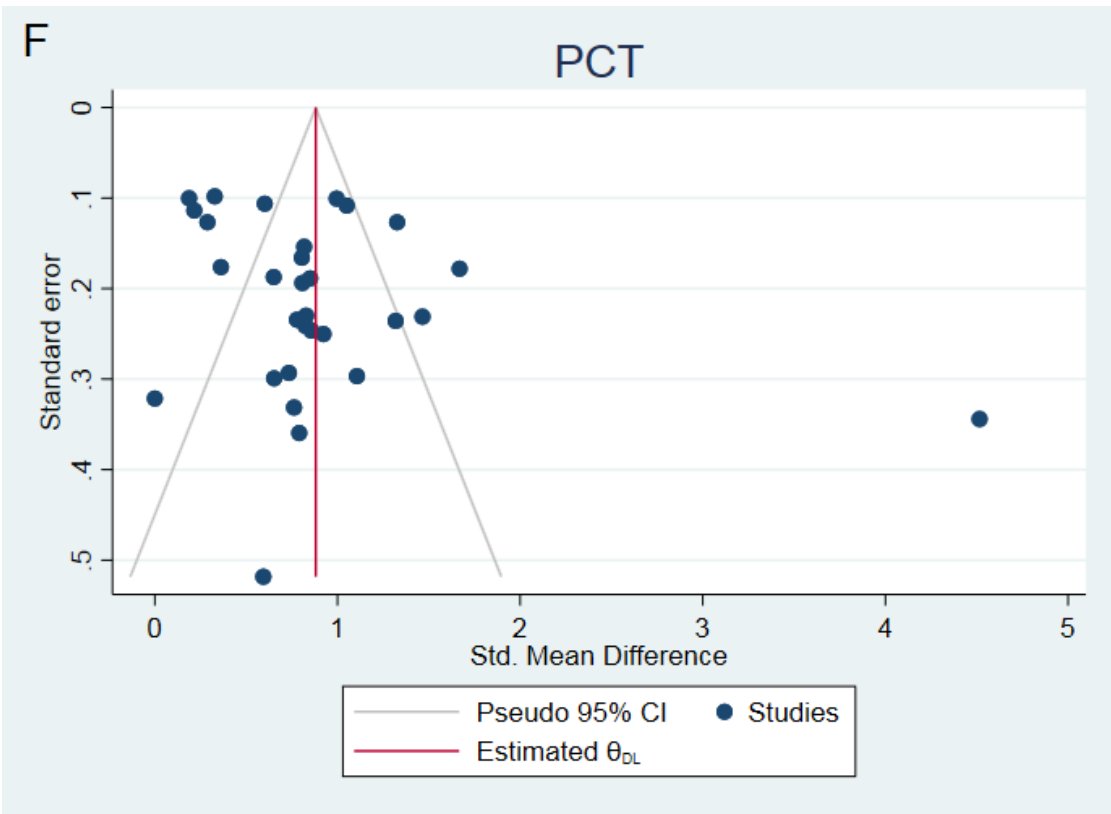
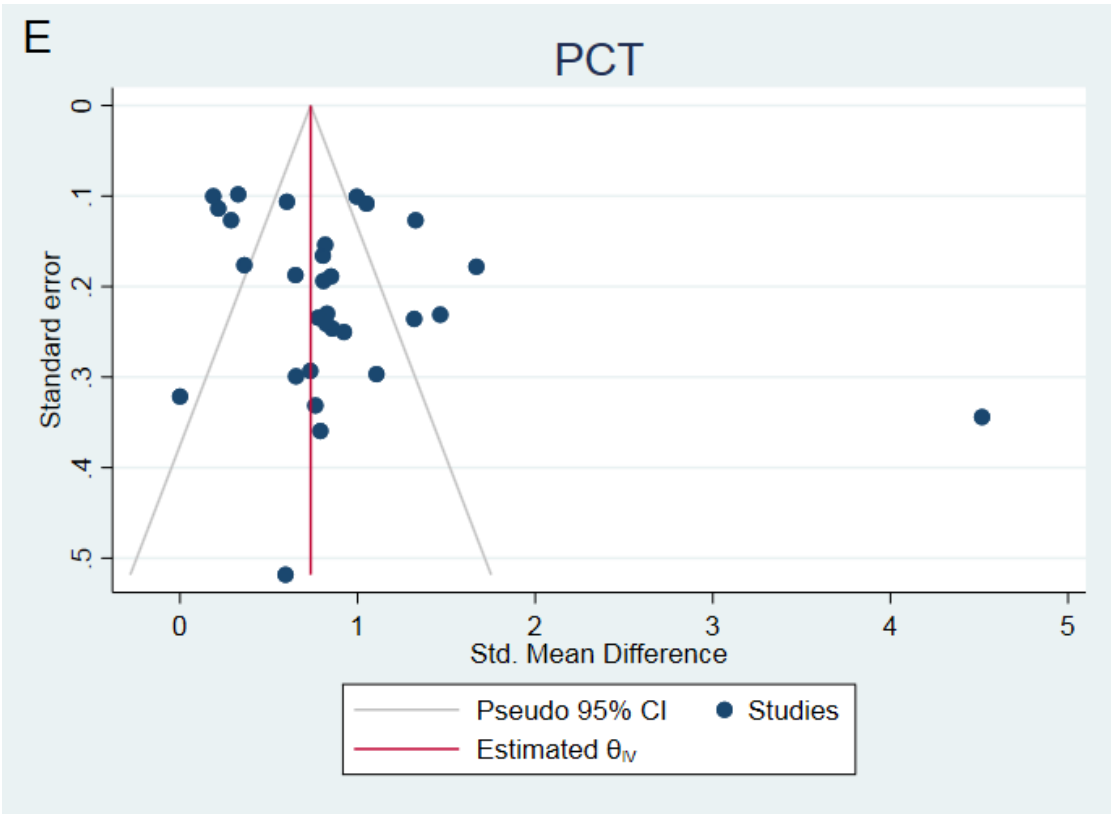
## E. Neutrophil to lymphocyte ratio (NLR)

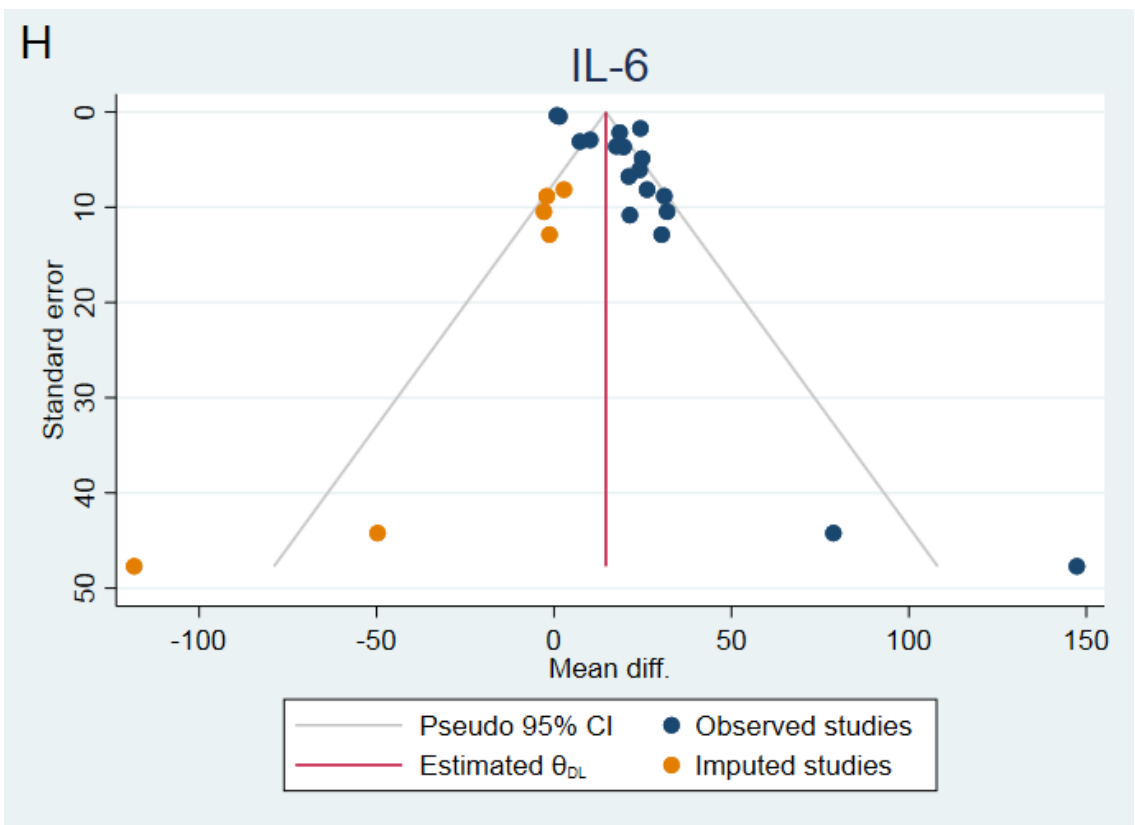
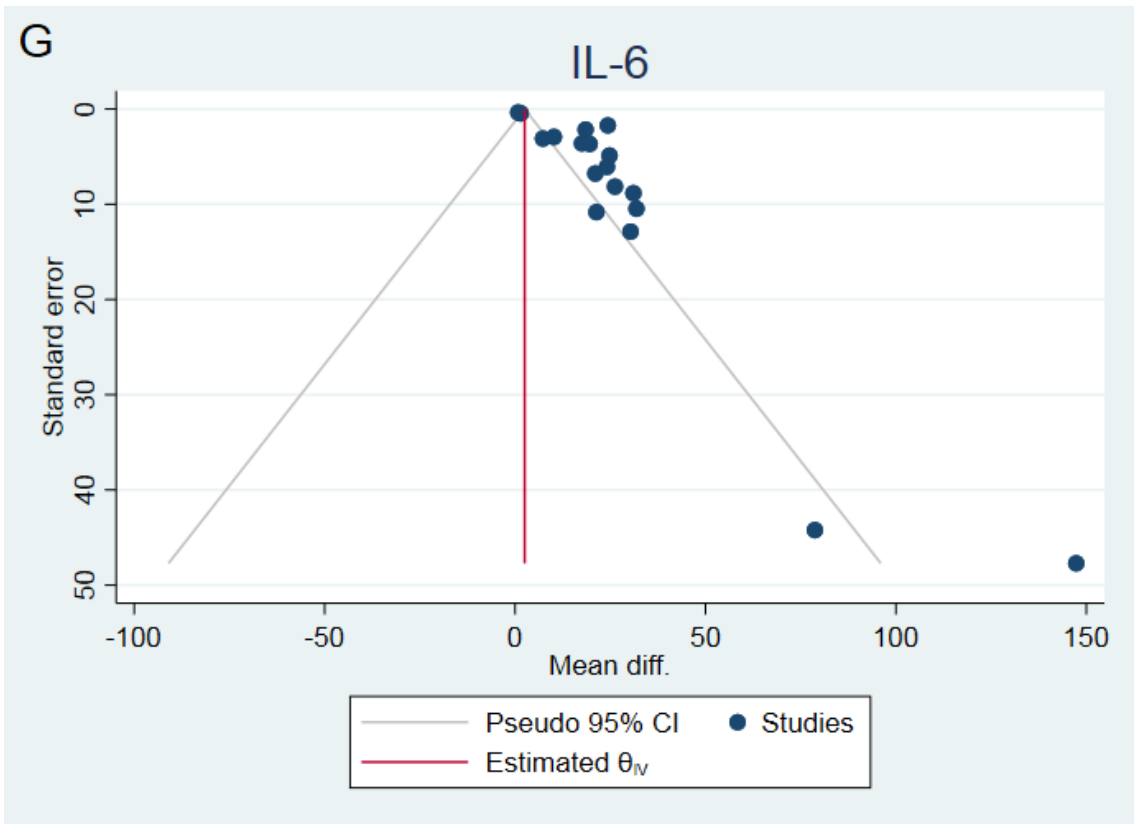


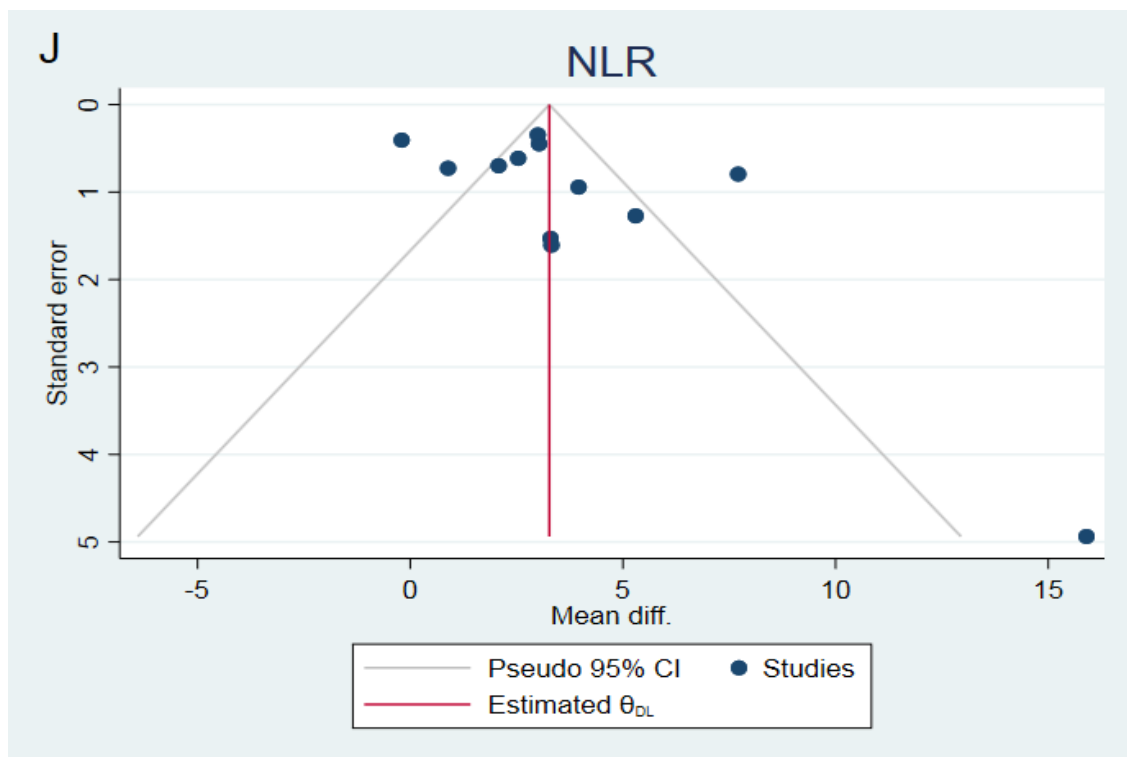
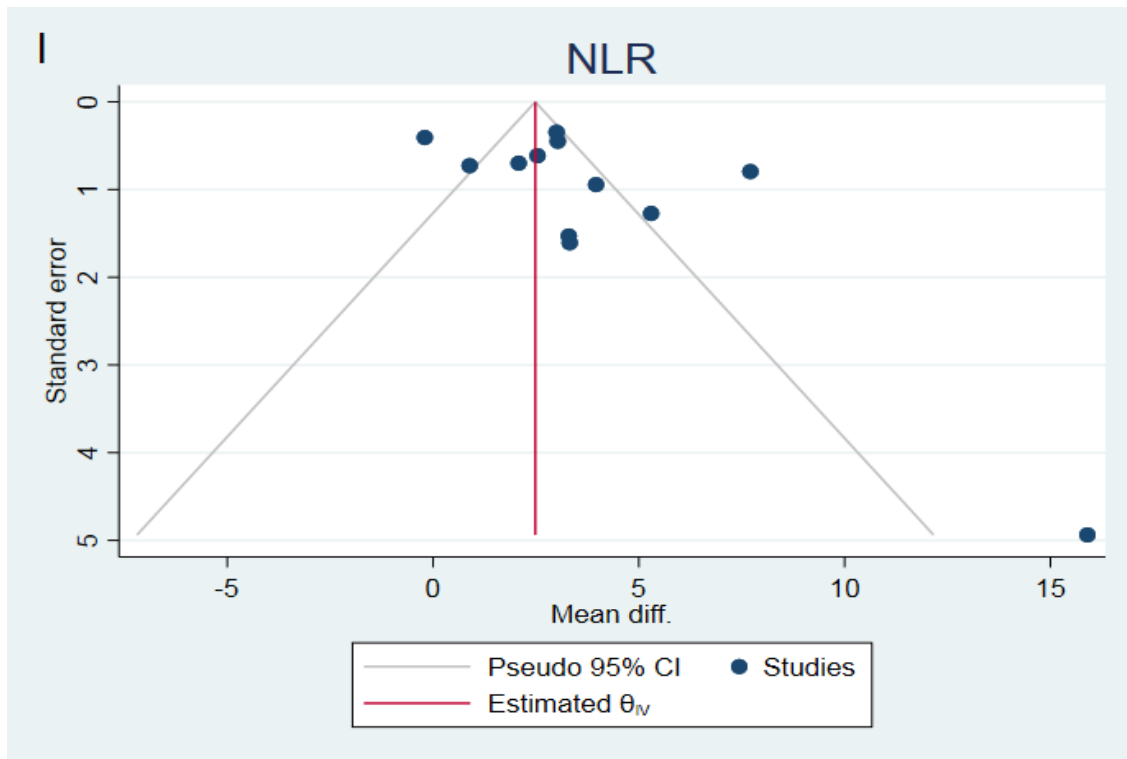
**Supplement-4:** Forest plot (A-E) showing subgroup analysis of inflammatory parameters (CRP, ESR, PCT, ferritin and NLR) by sample size in mortality studies.











**Supplement-5:** Funnel plots for inflammatory parameters in severity studies. (A, B) Funnel plot and adjusted funnel plot for CRP. (C, D) Funnel plot and adjusted funnel plot for ESR. (E, F) Funnel plot and adjusted funnel plot for PCT. (G, H) Funnel plot and adjusted funnel plot for IL-6. (I, J) Funnel plot and adjusted funnel plot for NLR.

**A. CRP**

. meta trimfill, funnel

Effect-size label: Std. Mean Difference  
Effect size: \_meta\_es  
Std. Err.: \_meta\_se

Nonparametric trim-and-fill analysis of publication bias  
Linear estimator, imputing on the left

Iteration                                      Number of studies =      44  
  Model: Random-effects                      observed =              44  
  Method: DerSimonian-Laird                 imputed =              0

Pooling  
  Model: Random-effects  
  Method: DerSimonian-Laird

theta: Overall Std. Mean Difference

Studies	theta	[95% Conf. Interval]	
Observed	1.145	0.970	1.319
Observed + Imputed	1.145	0.970	1.319

**B. ESR**

. meta trimfill, funnel

Effect-size label: Mean Diff.  
Effect size: \_meta\_es  
Std. Err.: \_meta\_se

Nonparametric trim-and-fill analysis of publication bias  
Linear estimator, imputing on the left

Iteration                                      Number of studies =      22  
  Model: Random-effects                      observed =              17  
  Method: DerSimonian-Laird                 imputed =              5

Pooling  
  Model: Random-effects  
  Method: DerSimonian-Laird

Studies	Mean Diff.	[95% Conf. Interval]	
Observed	12.077	8.045	16.110
Observed + Imputed	8.419	4.167	12.672





## **E. NLR**

. meta trimfill, funnel

Effect-size label: Mean Diff.

Effect size: `_meta_es`

Std. Err.: `_meta_se`

Nonparametric trim-and-fill analysis of publication bias  
Linear estimator, imputing on the left

Iteration	Number of studies =	12
Model: Random-effects	observed =	12
Method: DerSimonian-Laird	imputed =	0

Pooling

Model: Random-effects

Method: DerSimonian-Laird

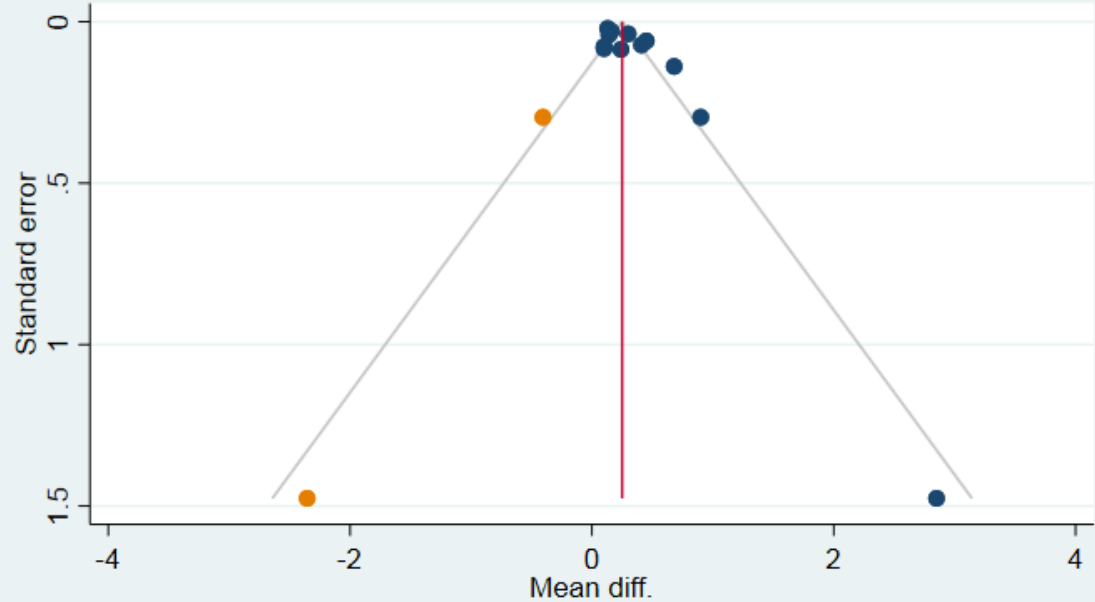
Studies	Mean Diff.	[95% Conf. Interval]	
Observed	3.271	1.992	4.550
Observed + Imputed	3.271	1.992	4.550

**Supplement-6:** (A) Trim and fill method for CRP. (B) Trim and fill method for ESR. (C) Trim and fill method for PCT. (D) Trim and fill method for IL-6. (E) Trim and fill method for NLR.



C

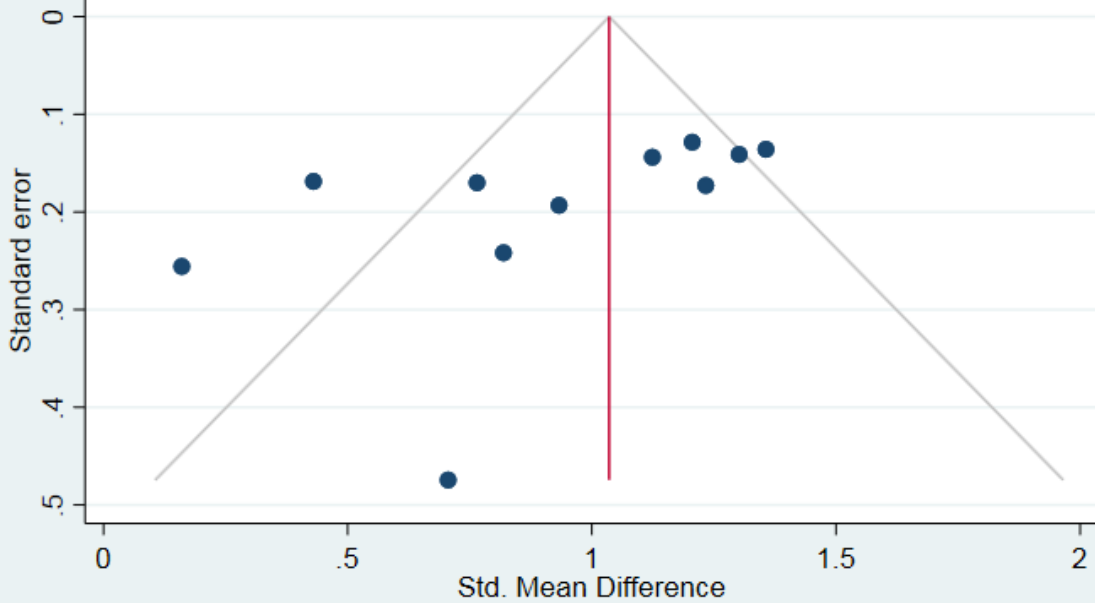
### PCT



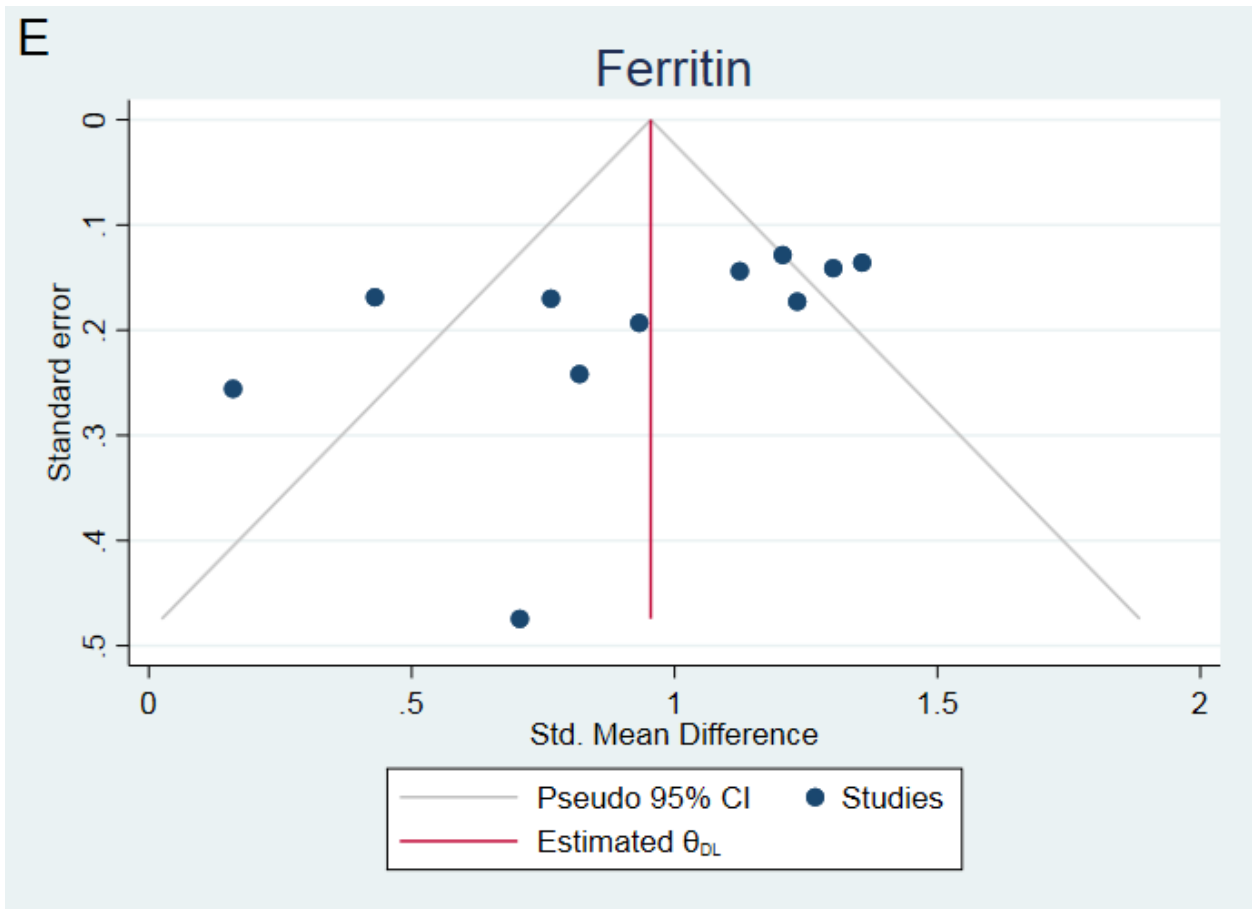
- Pseudo 95% CI
- Estimated  $\theta_{DL}$
- Observed studies
- Imputed studies

D

### Ferritin



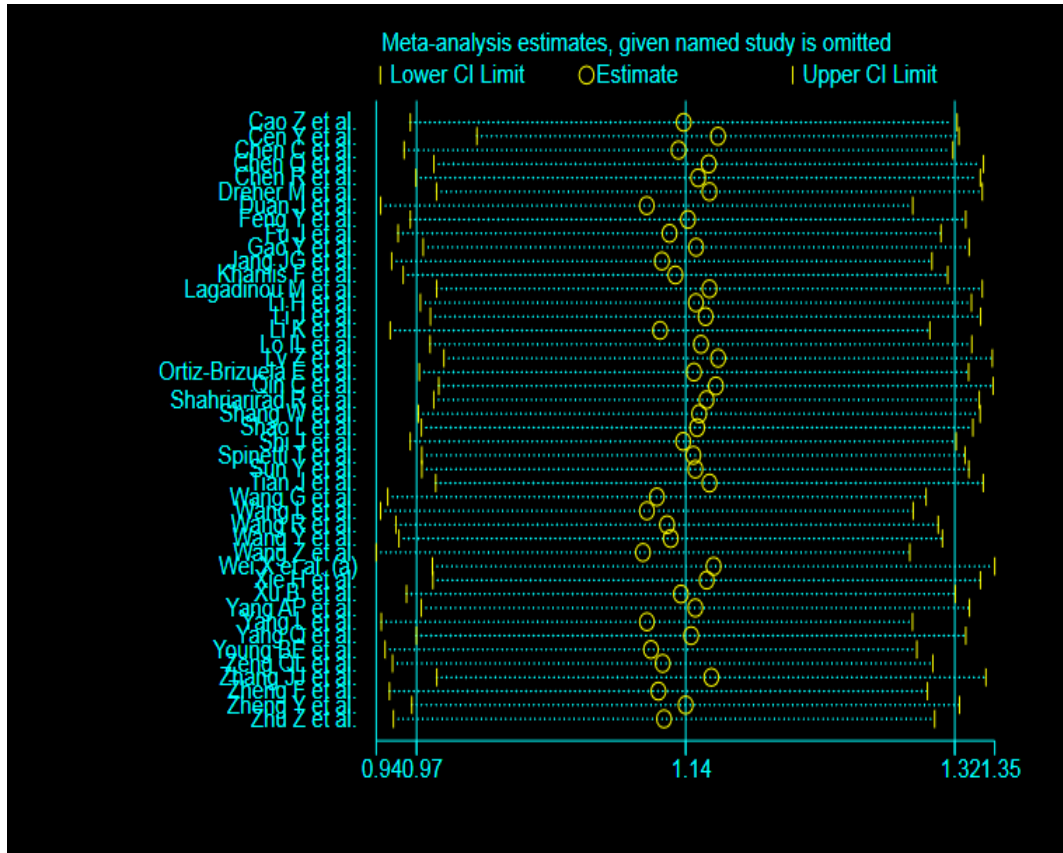
- Pseudo 95% CI
- Estimated  $\theta_{IV}$
- Studies



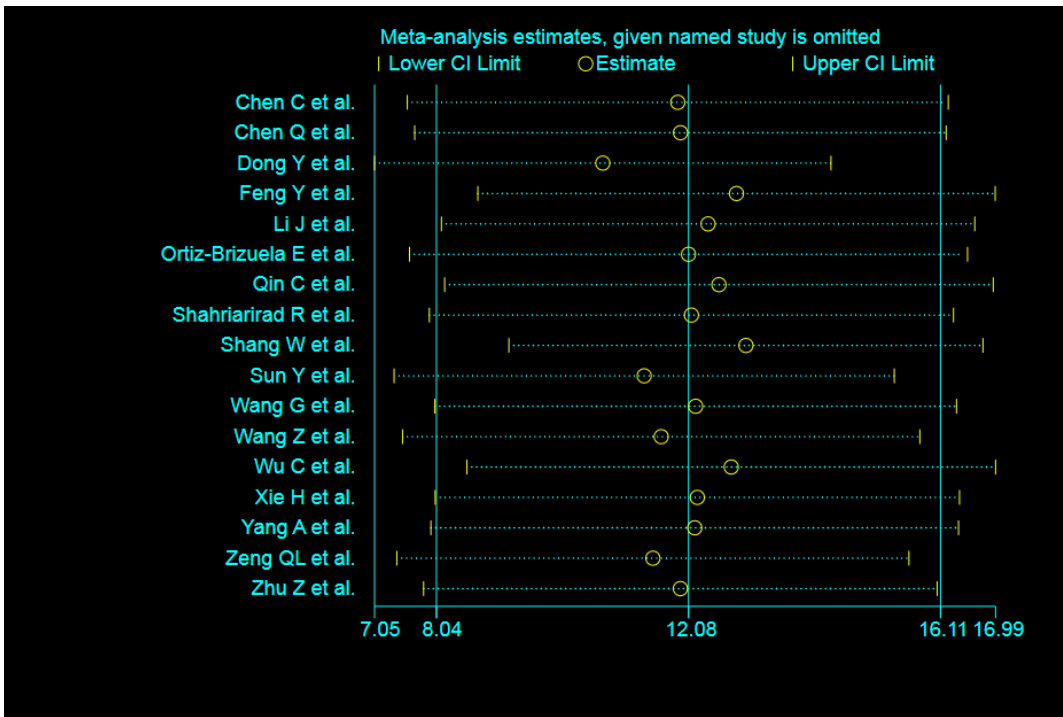
**Supplement-7:** Funnel plots for inflammatory parameters in mortality studies. (A) Funnel plot for CRP. (B, C) Funnel plot and adjusted funnel plot for PCT. (D, E) Funnel plot and adjusted funnel plot for ferritin.



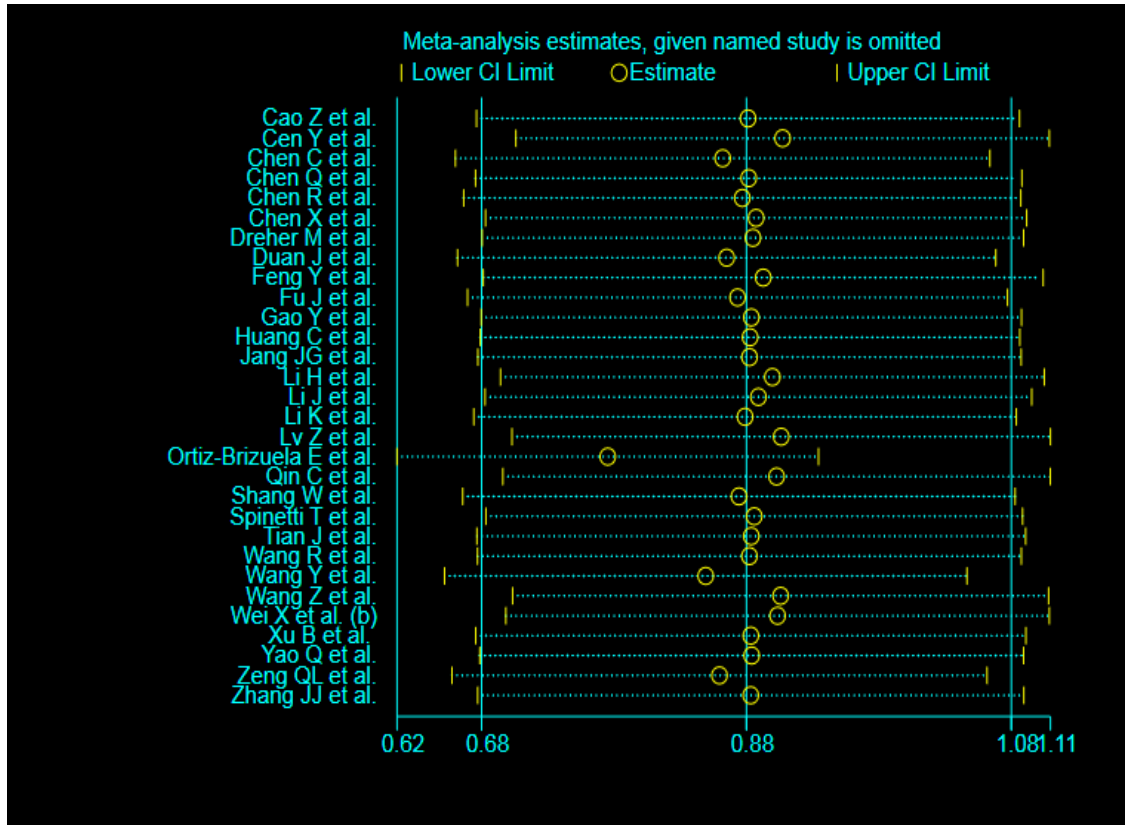
**A. CRP**



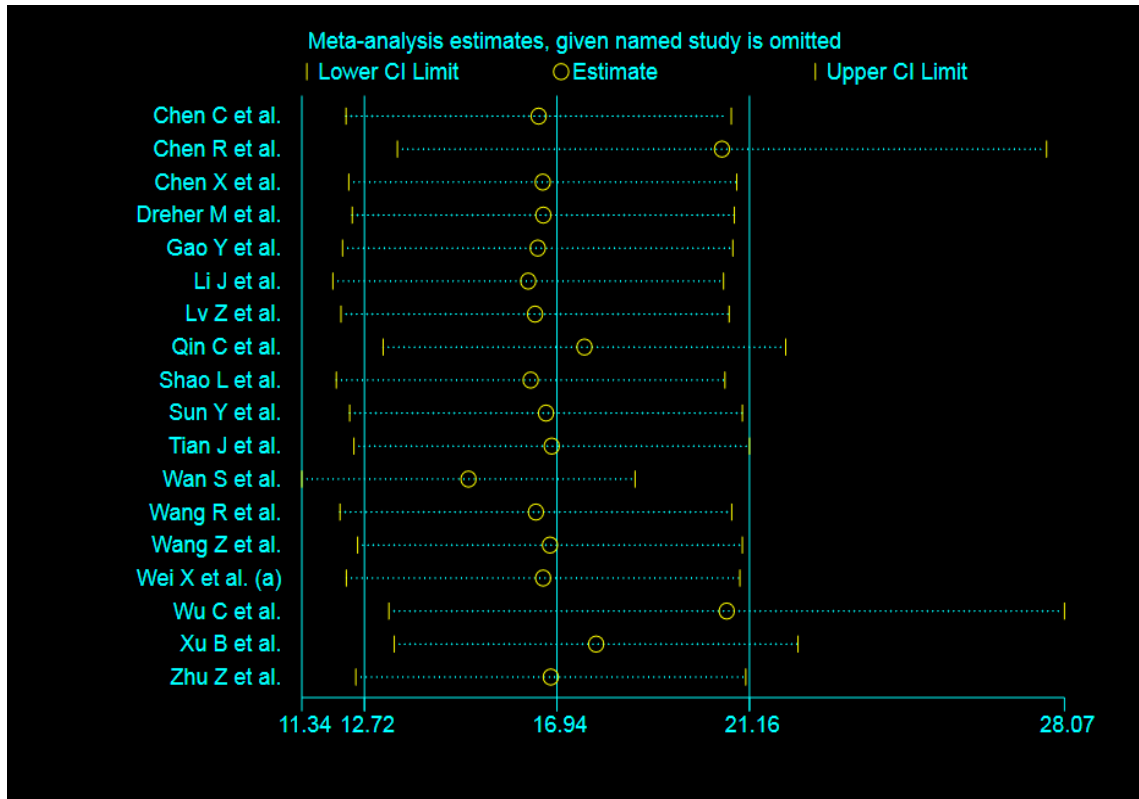
**B. ESR**



C. PCT

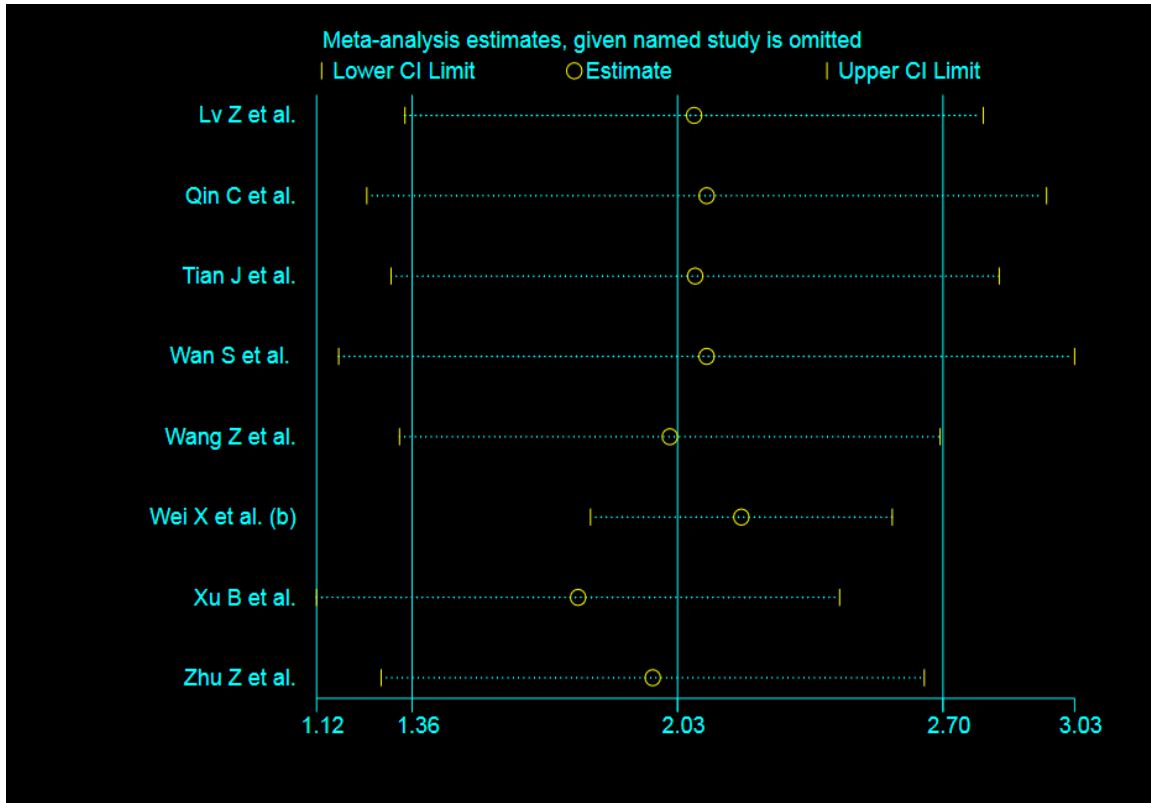


D. IL-6

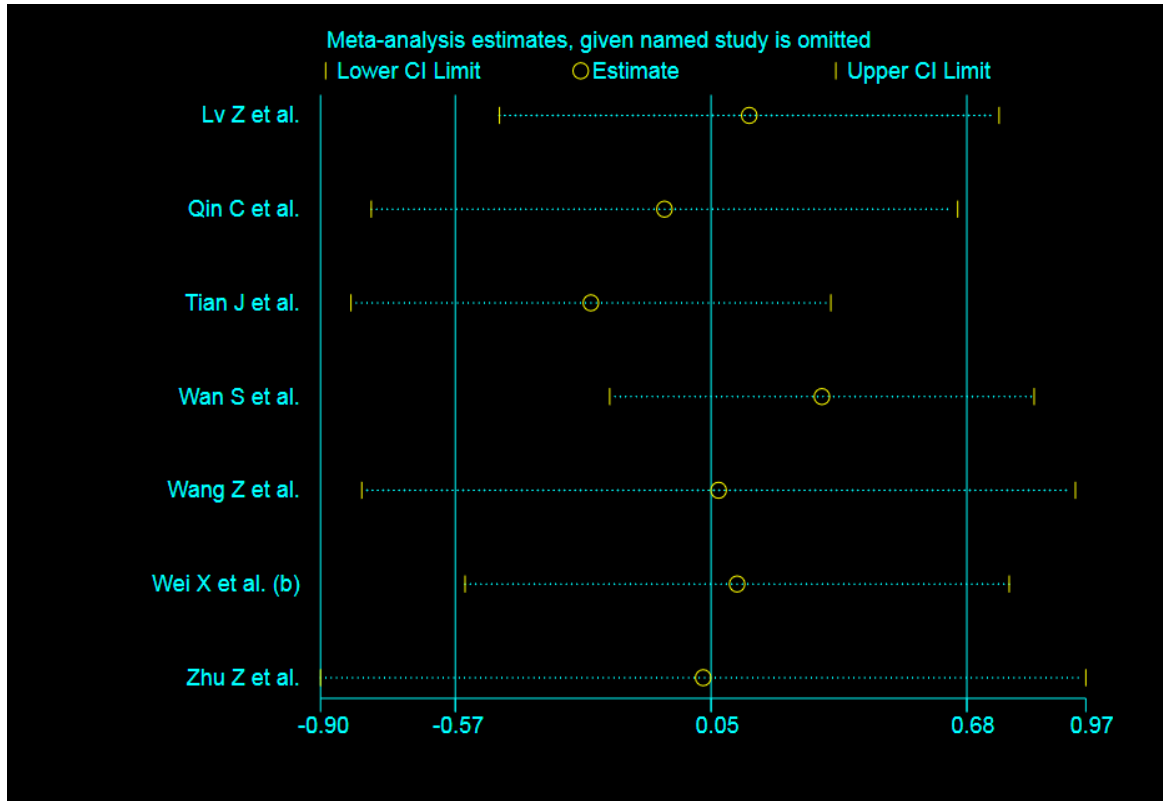




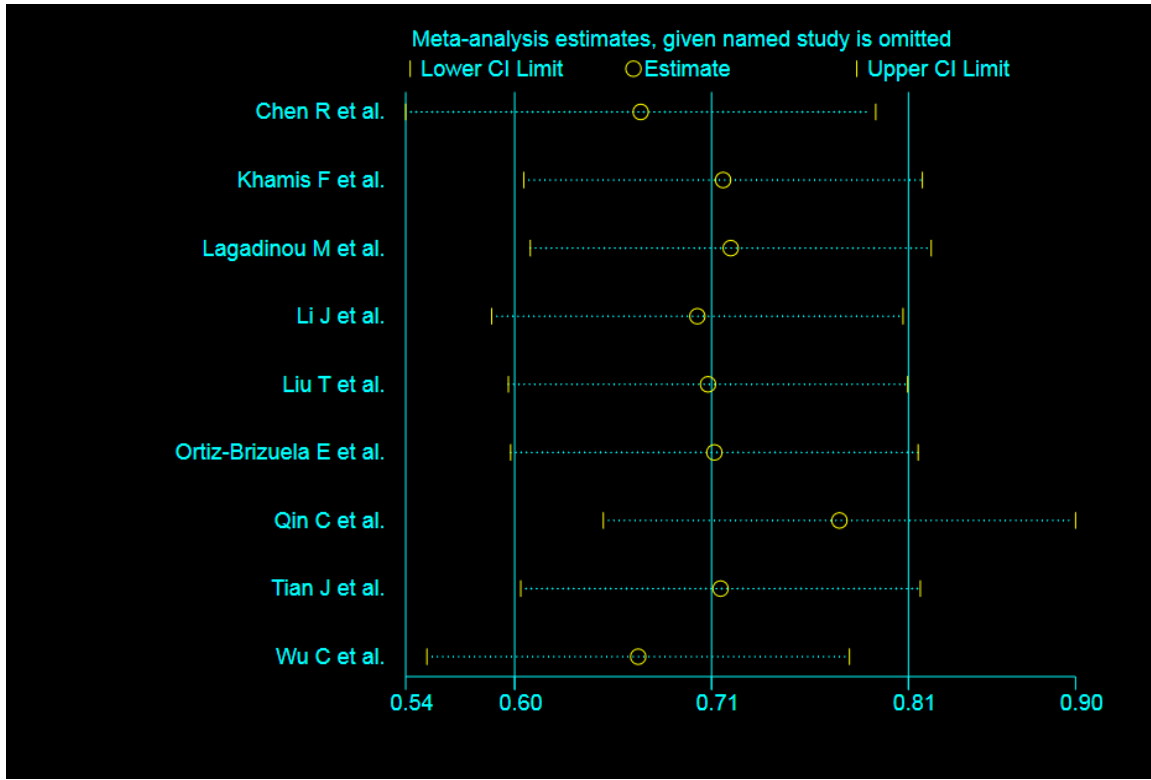
E. IL-10



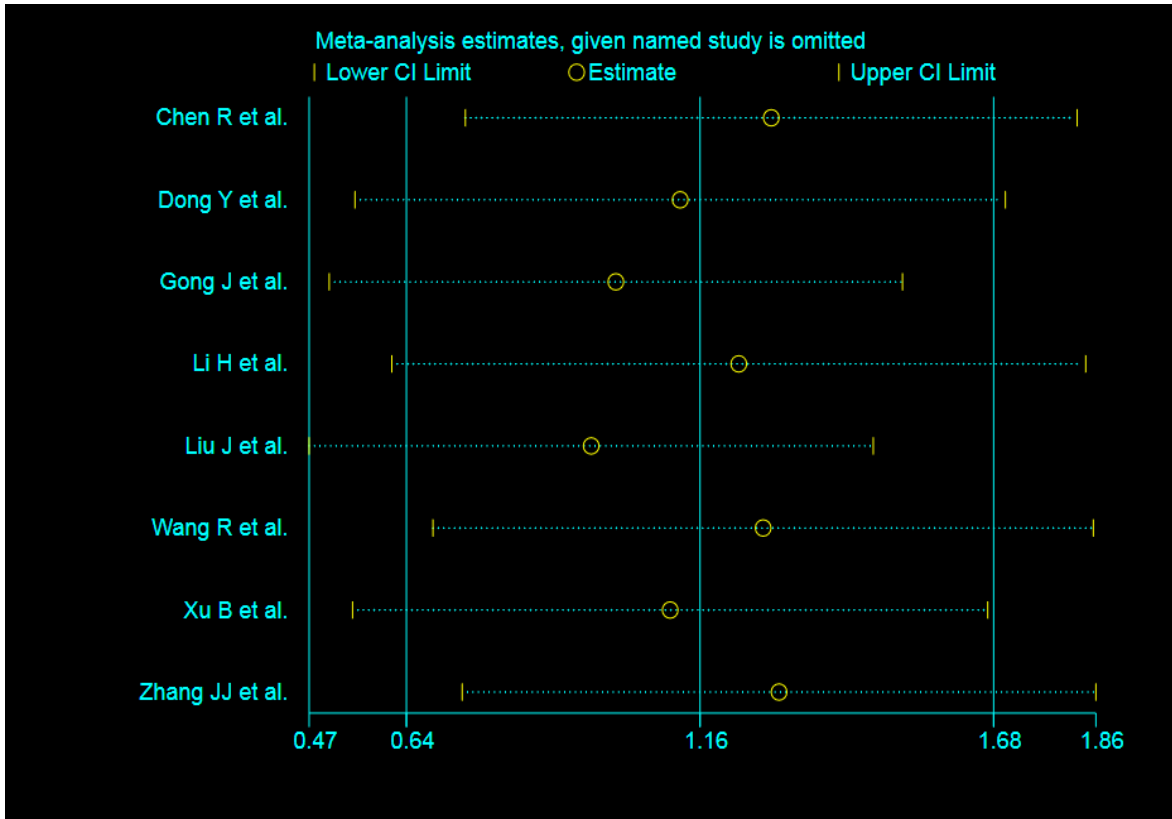
F. TNF- $\alpha$



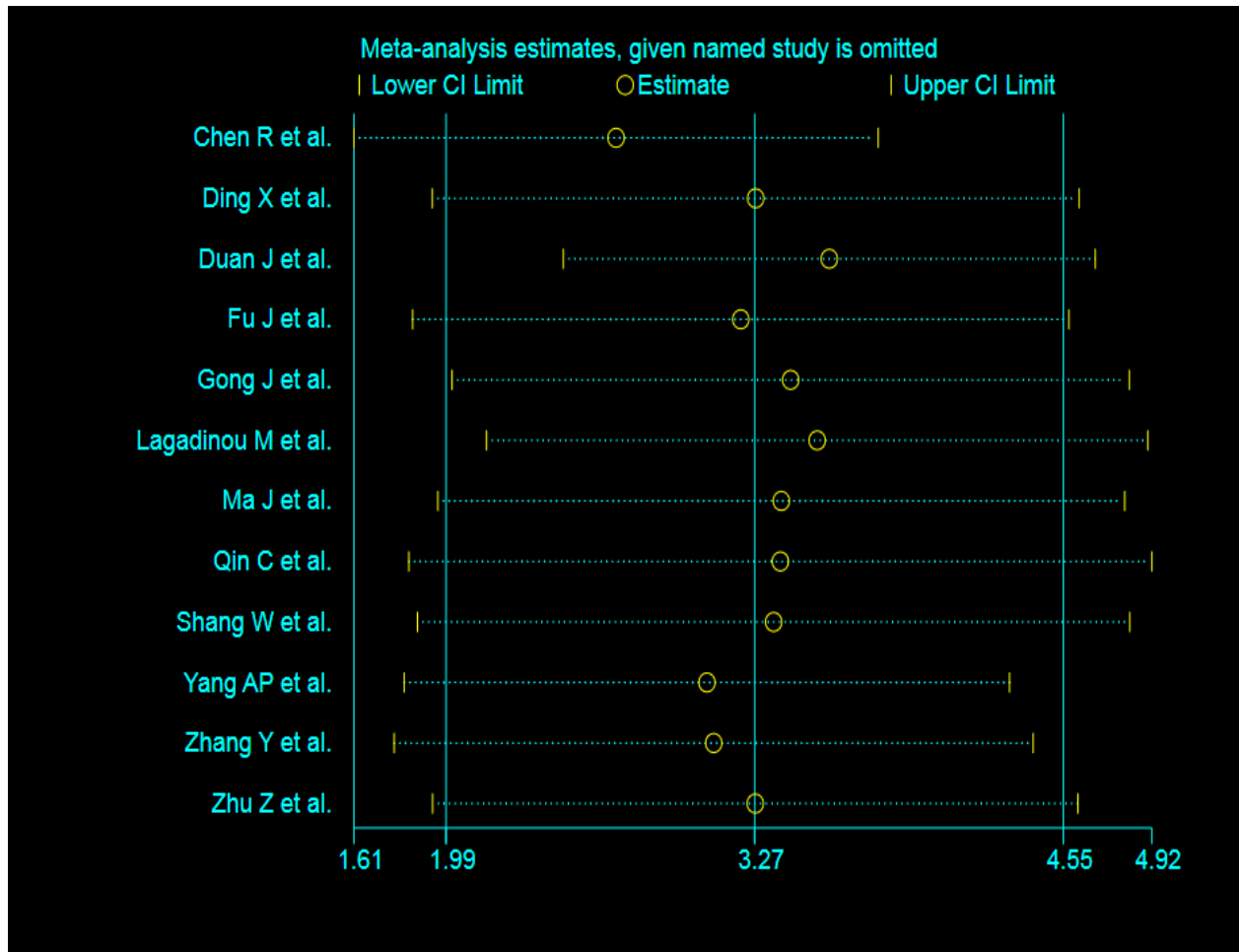
### G. Ferritin



### H. SAA

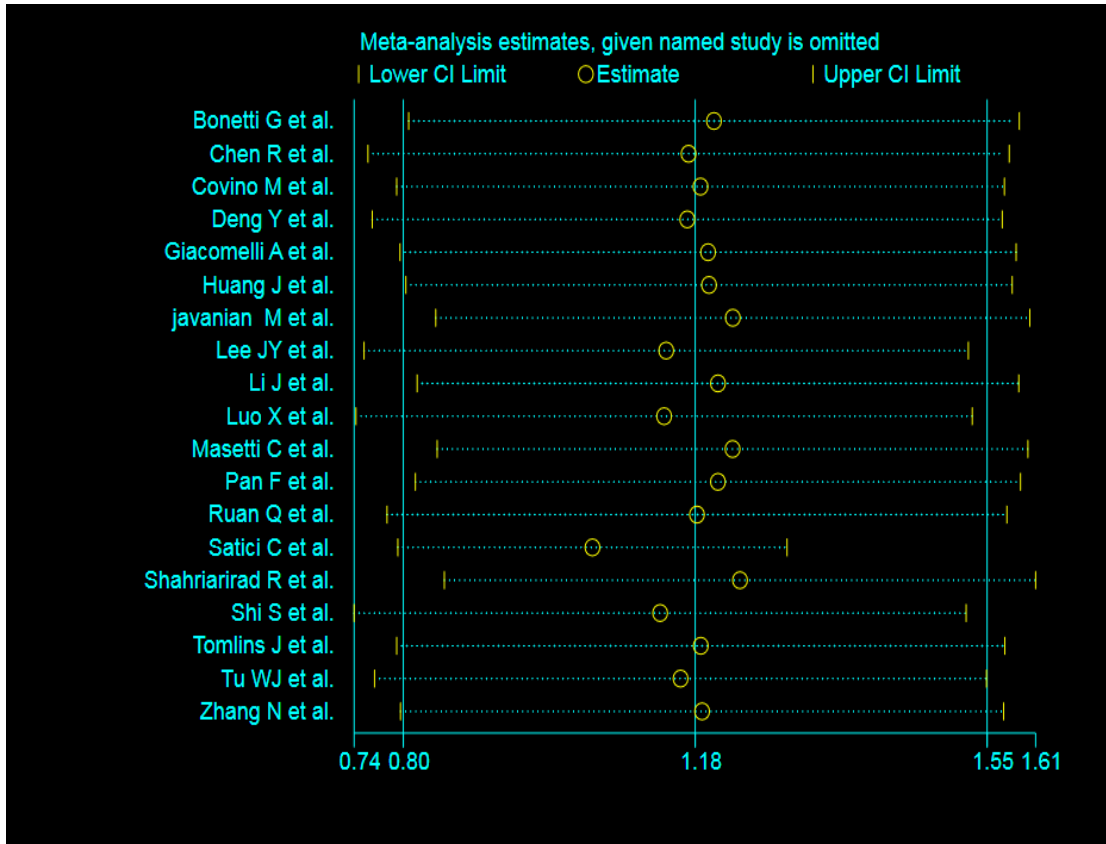


**I NLR**

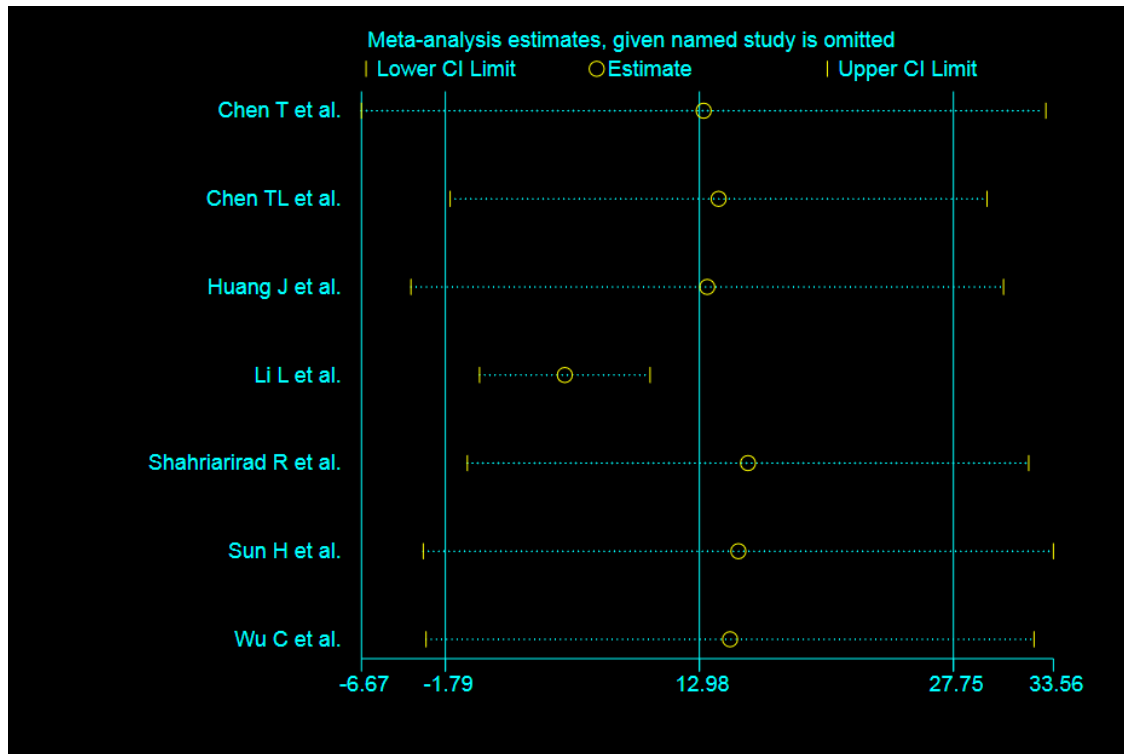


**Supplement-9:** Sensitivity analysis (A-I). Sensitivity analysis between severe and non-severe groups for levels of CRP (A), ESR (B), PCT (C), IL-6 (D), IL-10 (E), TNF- $\alpha$  (F), ferritin (G), SAA (H) and NLR (I).

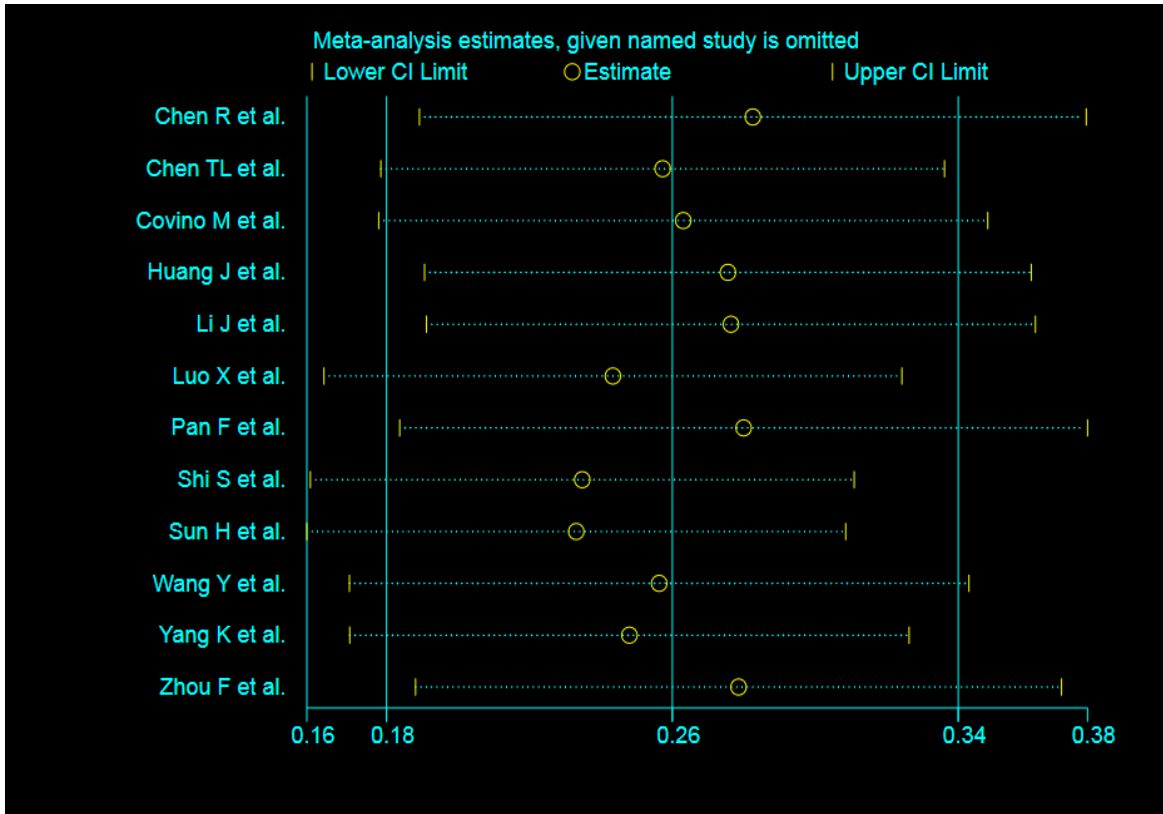
**A. CRP**



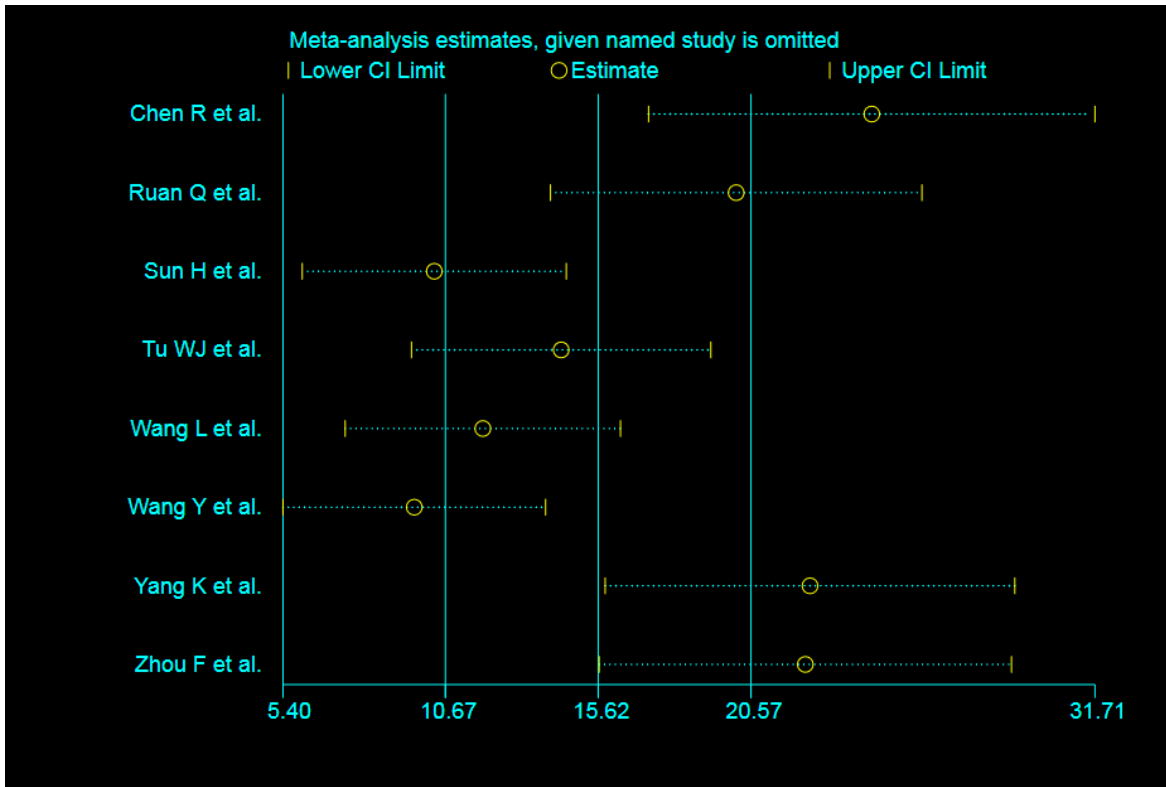
**B. ESR**



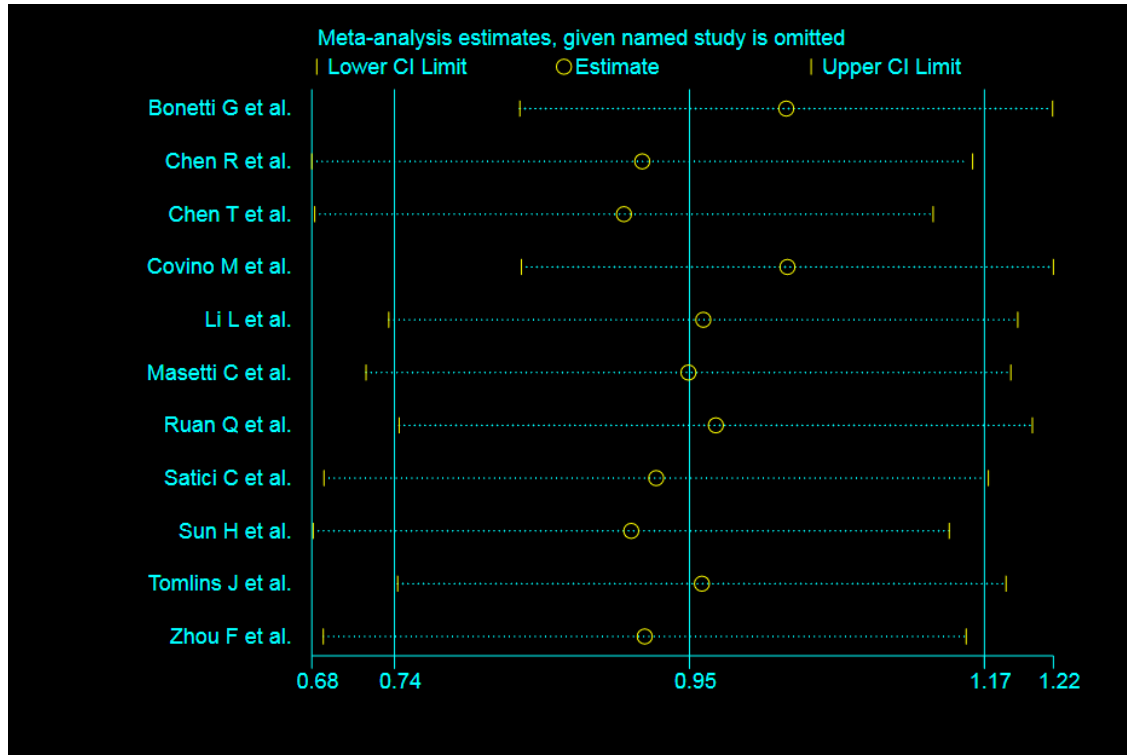
C. PCT



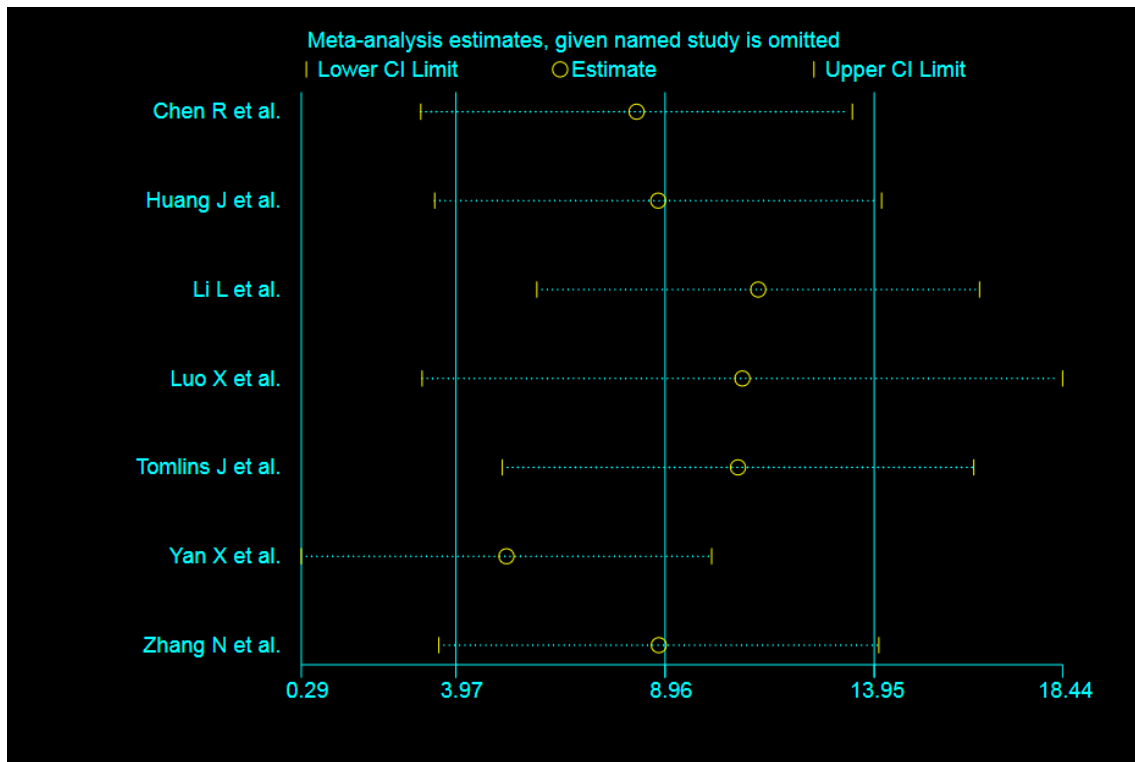
D. IL-6



**E. Ferritin**



**F. NLR**



**Supplement-10:** Sensitivity analysis (A-F). Sensitivity analysis between survivor and non-survivor groups for levels of CRP (A), ESR (B), PCT (C), IL-6 (D), ferritin (E) and NLR (F).

### Search strategies in databases:

Search engines	Keywords	Records
PubMed	("COVID-19" OR "2019-nCoV" OR "SARS-COV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "COVID-19 patients" OR "novel coronavirus 2019" OR "coronavirus disease-2019") AND ("erythrocyte sedimentation rate" OR "C-reactive protein" OR "ferritin" OR "procalcitonin" OR "interleukin-6" OR "interleukin-10" OR "interleukin-2R" OR "tumor necrosis factor- $\alpha$ " OR "serum amyloid A" OR "neutrophil-to-lymphocyte ratio" OR "inflammatory markers" OR "inflammatory parameters")	598
Europe PMC	("COVID-19" OR "2019-nCoV" OR "SARS-COV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "COVID-19 patients" OR "novel coronavirus 2019" OR "coronavirus disease-2019") AND ("erythrocyte sedimentation rate" OR "C-reactive protein" OR "ferritin" OR "procalcitonin" OR "interleukin-6" OR "interleukin-10" OR "interleukin-2R" OR "tumor necrosis factor- $\alpha$ " OR "serum amyloid A" OR "neutrophil-to-lymphocyte ratio" OR "inflammatory markers" OR "inflammatory parameters")	4010
Google Scholar	("COVID-19" OR "2019-nCoV" OR "SARS-COV-2" OR "novel coronavirus disease" OR "COVID-19 patients" OR "novel coronavirus 2019" OR "coronavirus disease-2019") AND ("inflammatory markers" OR "inflammatory parameters")	1000



# PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1, 2
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2, 3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3, 4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4, 5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5, 6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6, 7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	6, 7





# PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6, 7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6, 7
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8, Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-13
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17, 18
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097