Supplementary file S3. Additional analysis

Vitamin C in critically ill patients: An Updated Systematic Review and Meta-analysis

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1. Overall hospital mortality

1.1. Among RCTs

a. Based on patient group:

Neither among patients in sepsis/septic shock (OR, 0.98; 95% CI, 0.76-1.26; n= 1297; I^2 = 0%; p=0.86) nor among surgical patients (OR, 1.08; 95% CI, 0.63- 1.86; n= 860; I^2 = 4%) significant differences for hospital mortality was observed comparing vitamin C and placebo or SOC groups (**Figure S1**).

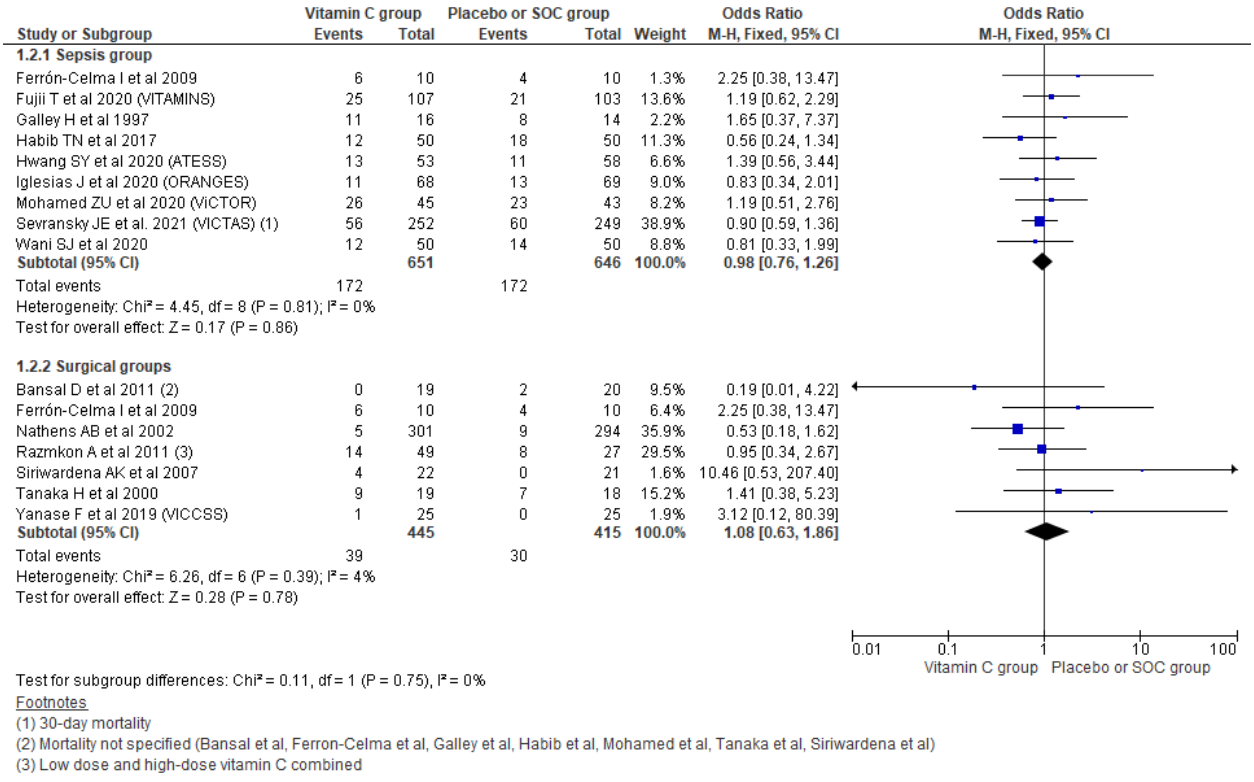

Figure S1. Forest plot showing hospital mortality outcome across surgical and sepsis group among RCTs

b. Based on blinding

Running analysis for hospital mortality taking RCTs based on blinding of trials also could not show significant differences between two groups. For double blinded trials, odds for mortality was showed to be slightly higher among vitamin C group (OR, 1.04; 95% CI, 0.76-1.43; n= 938; I^2 = 0%; p=0.80) while for single blinded/open odds was slightly reduced (OR 0.92, 95% CI 0.65 to 1.29; n= 1199; I^2 = 0%; p=0.61) comparing with placebo or SOC group; but it could not reach statistical significance (**Figure S2**).

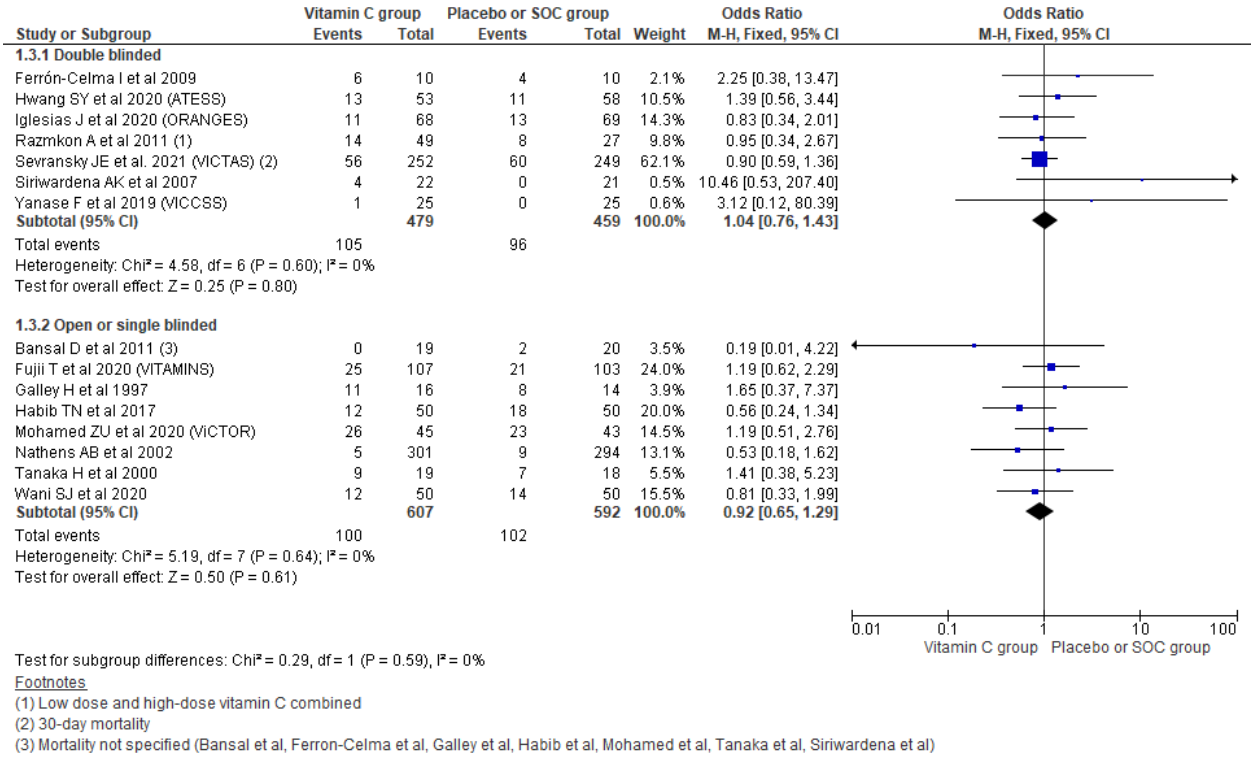

Figure S2. Forest plot showing hospital mortality outcome across double blinded and single blinded/open RCTs

c. Based on concomitant other anti-oxidants use

Analysis comparing placebo/ SOC with vitamin C only (OR, 0.93; 95% CI, 0.49-1.76; n= 207; I^2 = 5%; p=0.82) and placebo/ SOC with other concomitant anti-oxidants use with vitamin C (OR,

0.99; 95% CI, 0.77- 1.27; n= 1930; I^2 = 0%; p=0.94) also could not show significant differences in hospital mortality (**Figure S3**).

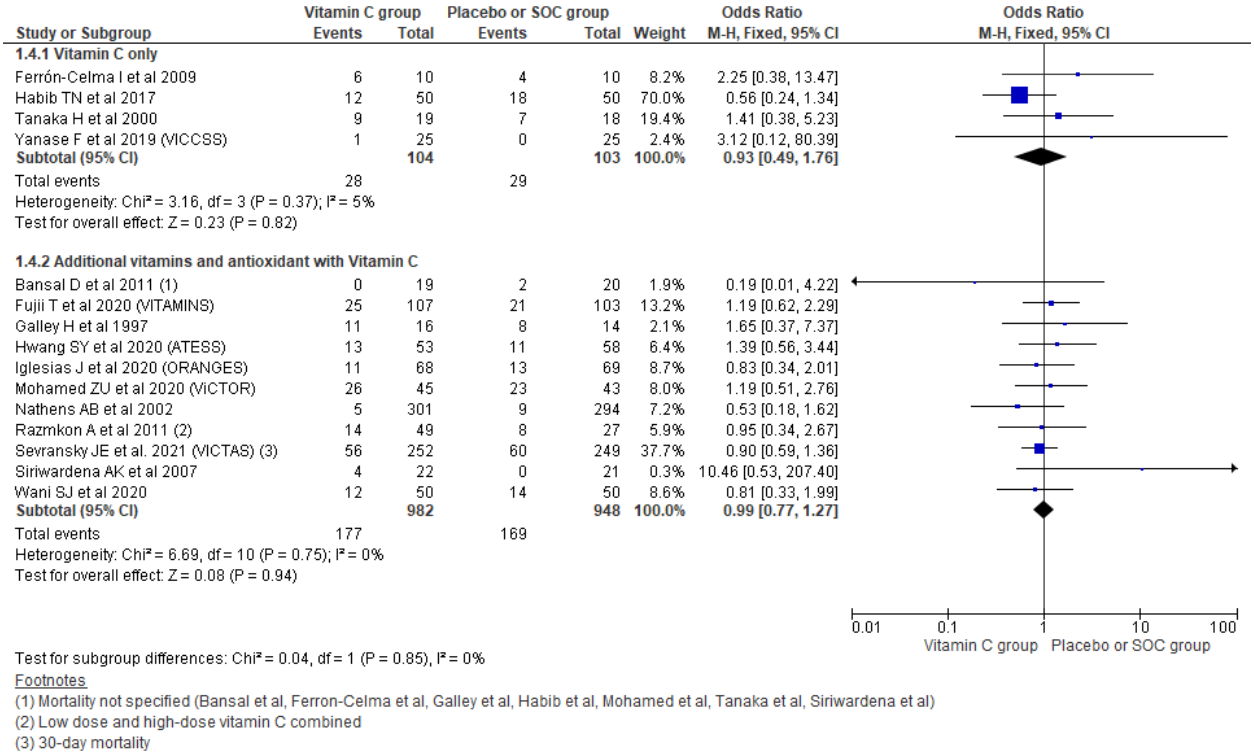

Figure S3. Forest plot showing hospital mortality outcome across use of vitamin C only or other anti-oxidants with vitamin C as treatment group across RCTs

1.2. Among observational studies

a. Based on patient group:

In sepsis/septic shock group mortality could not reach significant differences (OR, 0.73; 95% CI, 0.46-1.15; n= 340351; I^2 = 86%; p=0.17) while among surgical patients (OR, 0.69; 95% CI, 0.56-0.85; n= 5143; I^2 = 4%; p=0.0005) significant reduction in hospital mortality was observed comparing vitamin C and placebo/ SOC groups (**Figure S4**).

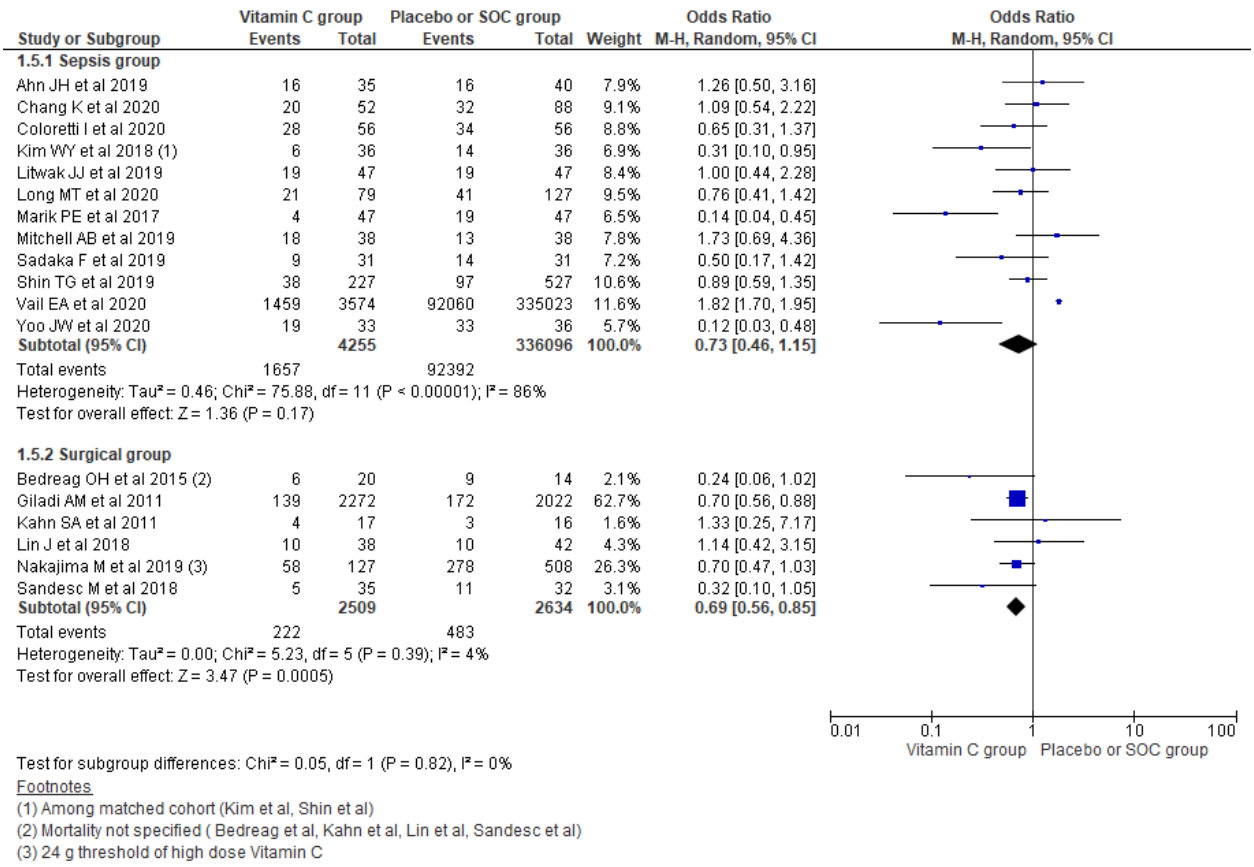

Figure S4. Forest plot showing hospital mortality outcome across surgical and sepsis group among observational studies

b. Based on concomitant other anti-oxidants use

Analysis comparing placebo/ SOC with vitamin C only could not reach significant differences in mortality (OR, 0.86; 95% CI, 0.64-1.16; n= 963; I^2 = 0%; p=0.32); while comparing placebo/ SOC with other concomitant anti-oxidants use with vitamin C showed significant reduction in hospital mortality (OR, 0.60; 95% CI, 0.38-0.95; n= 344531; I^2 = 91%; p<0.0001) (**Figure S5**).

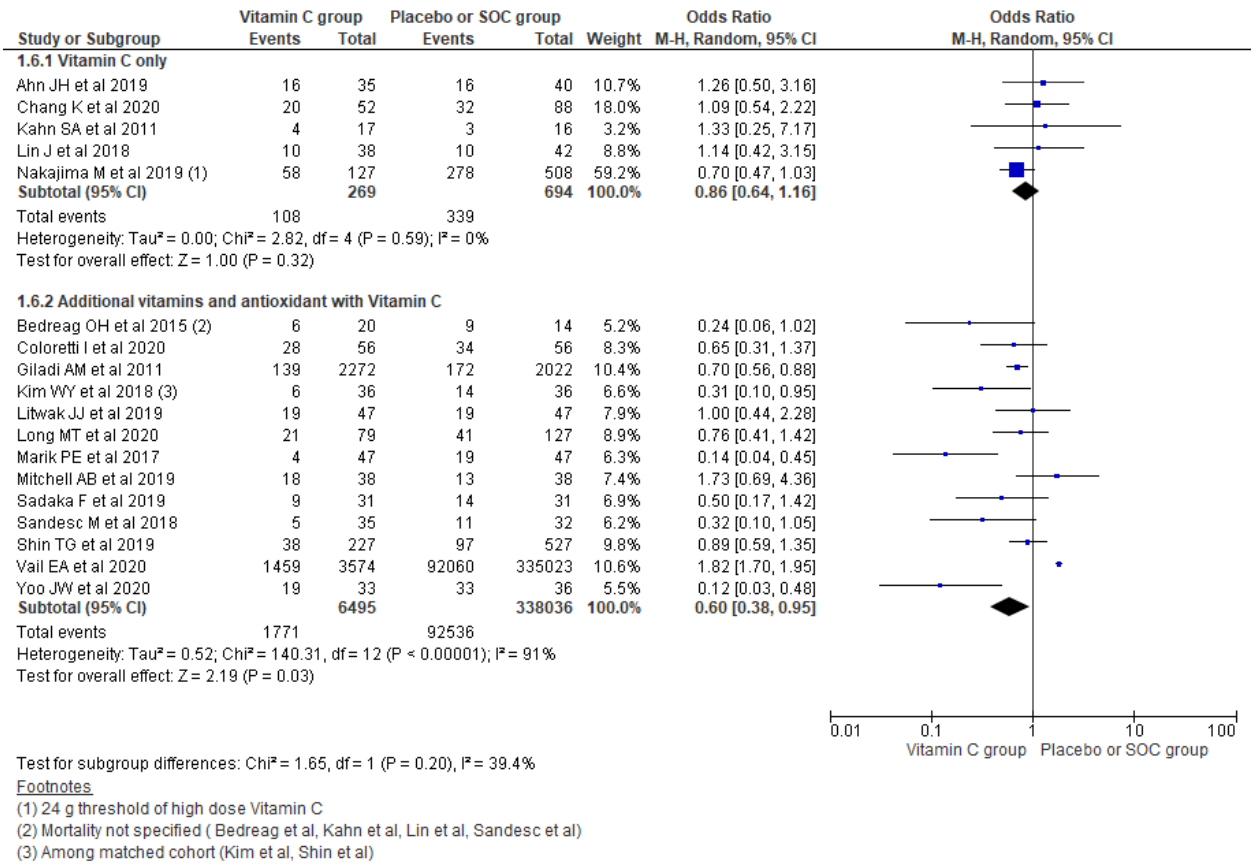

Figure S5. Forest plot showing hospital mortality outcome across use of vitamin C only or other anti-oxidants with vitamin C as treatment group across observational studies

2. 28/30-day mortality

Pooling data for 28/30-days mortality using random effect model also showed similar findings as in fixed effect model with no significant group differences in overall 28/30-days mortality (OR, 0.86; 95% CI, 0.69-1.07; n= 3405; I^2 = 28%; p=0.18); among RCTs (OR, 0.77; 95% CI, 0.57-1.05; n= 2131; I^2 = 37%; p=0.10); observational studies (OR, 1.00; 95% CI, 0.75-1.33; n= 1274; I^2 = 4%; p=0.98) (**Figure S6**).

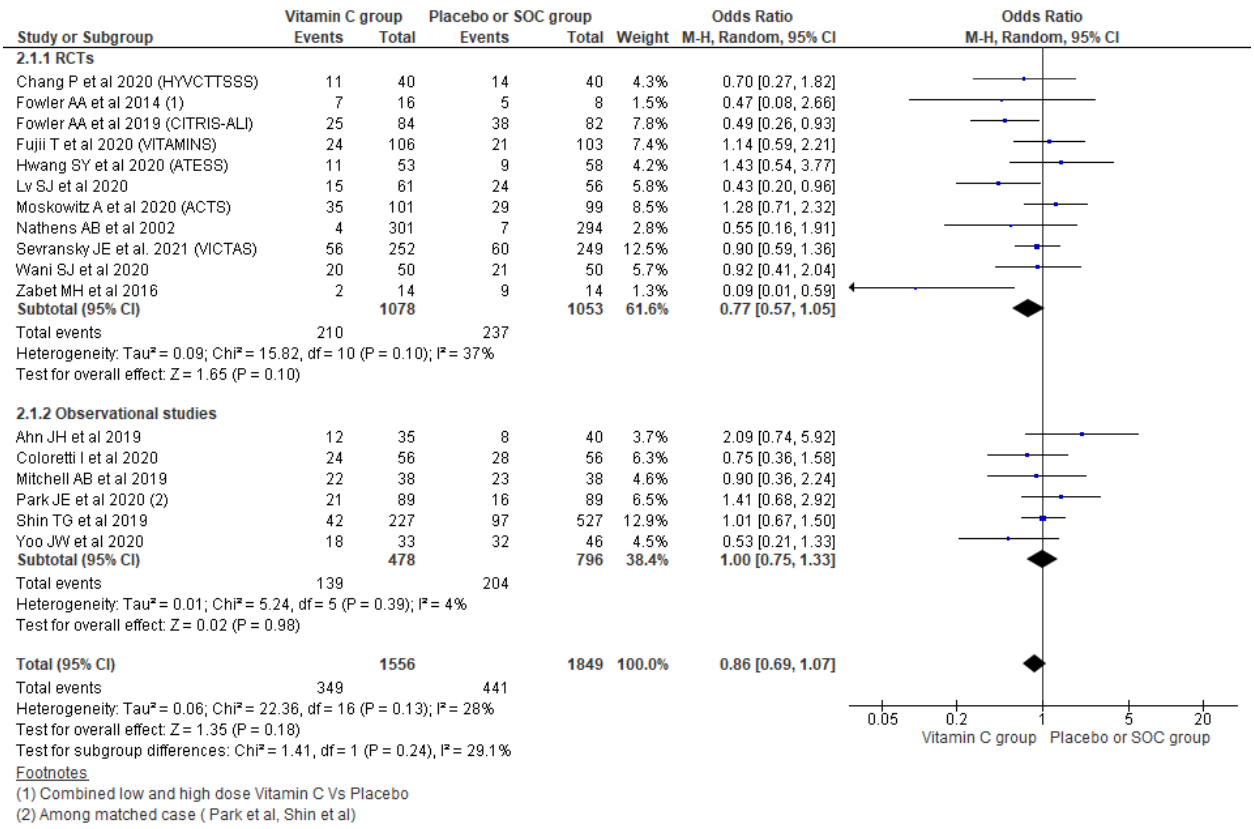

Figure S6. Forest plot showing 28/30-days mortality outcome using random effect model

3. ICU mortality

Pooling data from 14 studies reporting ICU mortality showed OR of 0.83 for overall ICU mortality (95% CI, 0.61-1.13; n= 2448; I^2 = 38%; p=0.24), though it could not reach statistical significance. Similarly, further subgroup analysis taking type of study under consideration showed similar result with RCTs (OR, 1.02; 95% CI, 0.75-1.38; n= 1716; I^2 = 0%; p=0.91) and observational studies (OR, 0.69; 95% CI, 0.41-1.17; n= 732; I^2 = 55%; p=0.17) (**Figure S7**).

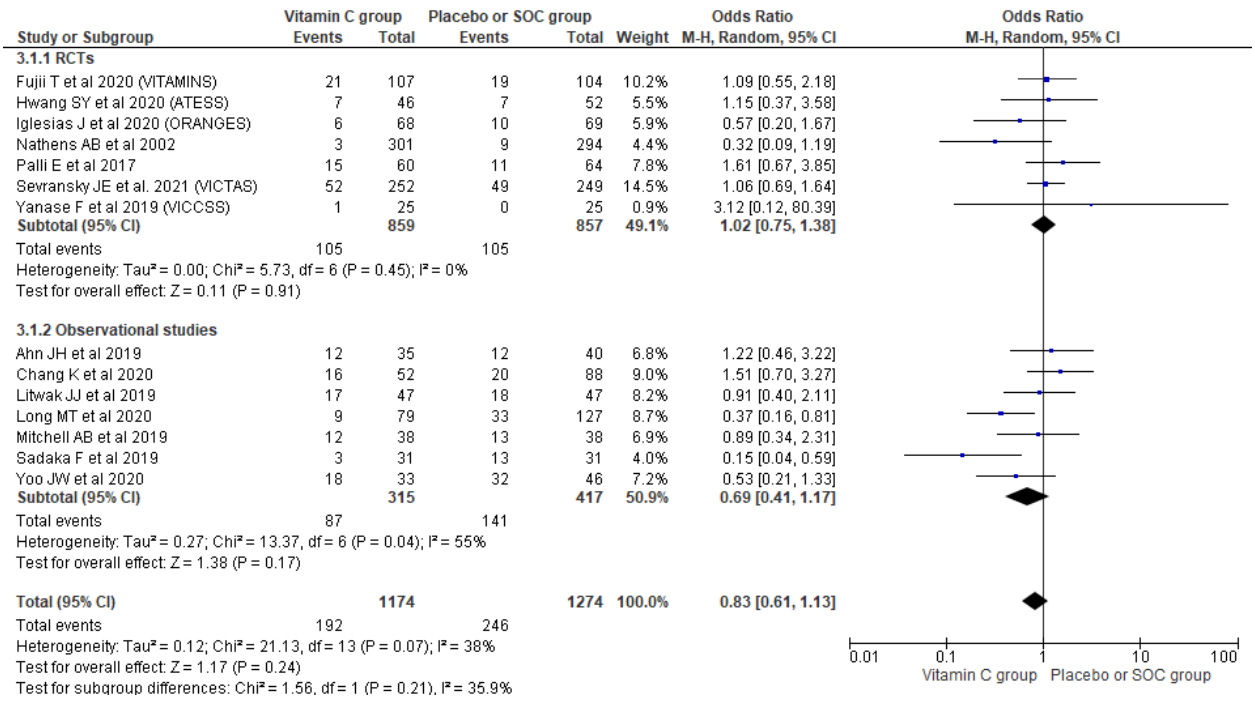

Figure S7. Forest plot showing ICU mortality outcome using random effect model

4. Overall length of hospital stay (LoHS)

4.1. Among RCTs

a. Based on patient group:

Among patients in sepsis/septic shock there was no significant differences in length of hospital stay between two groups (MD, 0.63; 95% CI, -0.41 to 1.68; n= 1141; I^2 = 0%; p=0.23) however among critically ill surgical patients average 1.7 days reduction in LoHS was observed among vitamin C group comparing with placebo/SOC (MD, -1.70; 95% CI, -2.89 to -0.51; n= 663; I^2 = 52%; p=0.005) (**Figure S8**).

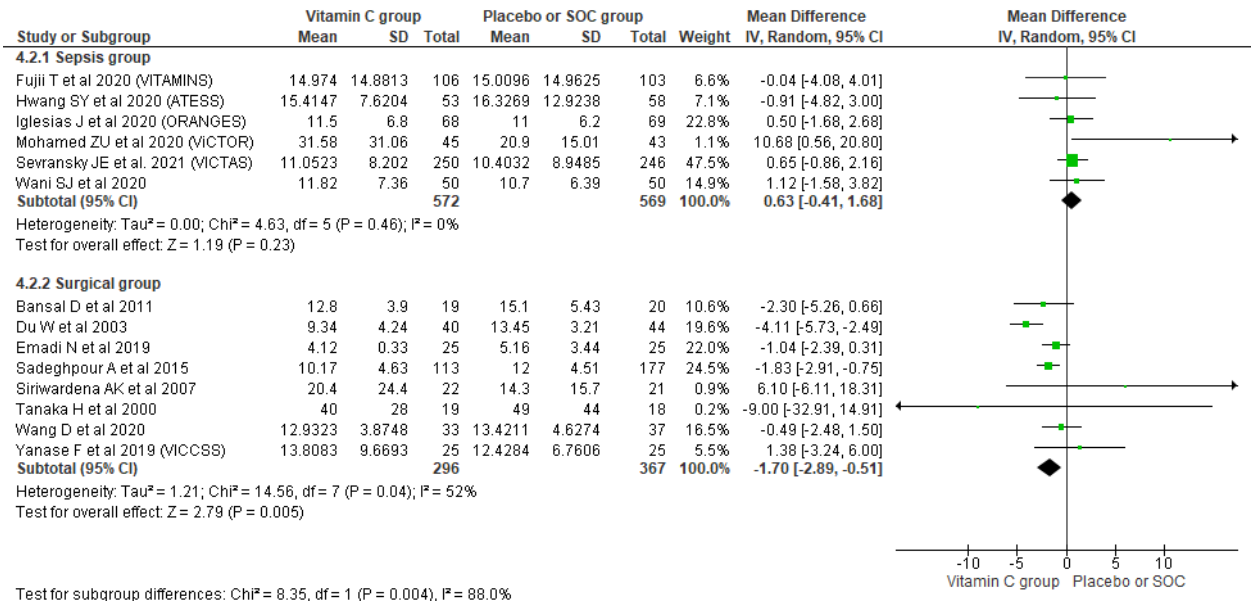

Figure S8. Forest plot showing LoHS outcome across surgical and sepsis group among RCTs

b. Based on blinding

Running analysis for LoHS taking RCTs based on blinding of trials showed some reduction in length of hospital stay of vitamin C group among both double blinded trials (MD, -0.54; 95% CI, -1.43 to 0.36; n= 1247; I^2 = 34%; p=0.24) and single blinded/open RCTs reduction in LoHS among vitamin C group (MD, -0.78; 95% CI, -3.77 to 2.20; n= 557; I^2 = 73%; p=0.61) comparing with placebo or SOC group but could not reach statistical significance (**Figure S9**).

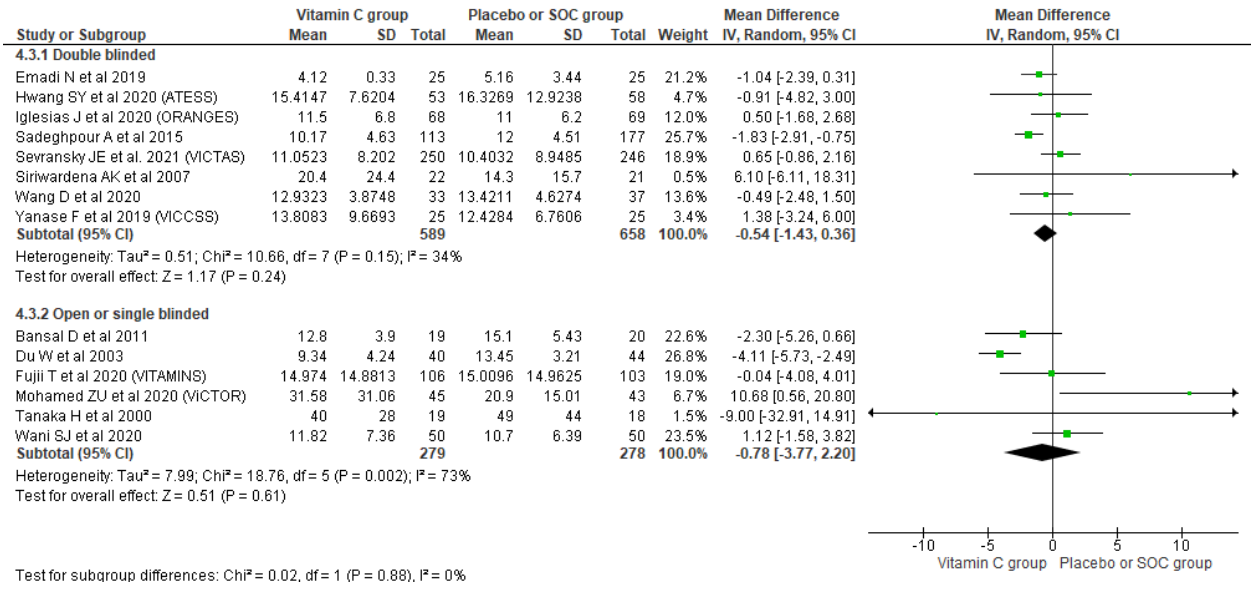

Figure S9. Forest plot showing LoHS outcome across double blinded and single blinded/open RCTs

c. Based on concomitant other anti-oxidants use

Analysis comparing vitamin C only with placebo/ SOC showed on an average 1.7 days reduction in LoHS among vitamin C group (MD, -1.70; 95% CI, -3.02 to -0.37; n= 581; I^2 = 61%; p=0.01) while such reduction is not seen in other concomitant anti-oxidants use with vitamin C (MD, 0.31; 95% CI, -0.91 to 1.53; n= 1223; I^2 = 21%; p=0.62) also could not show significant differences in hospital mortality (**Figure S10**).

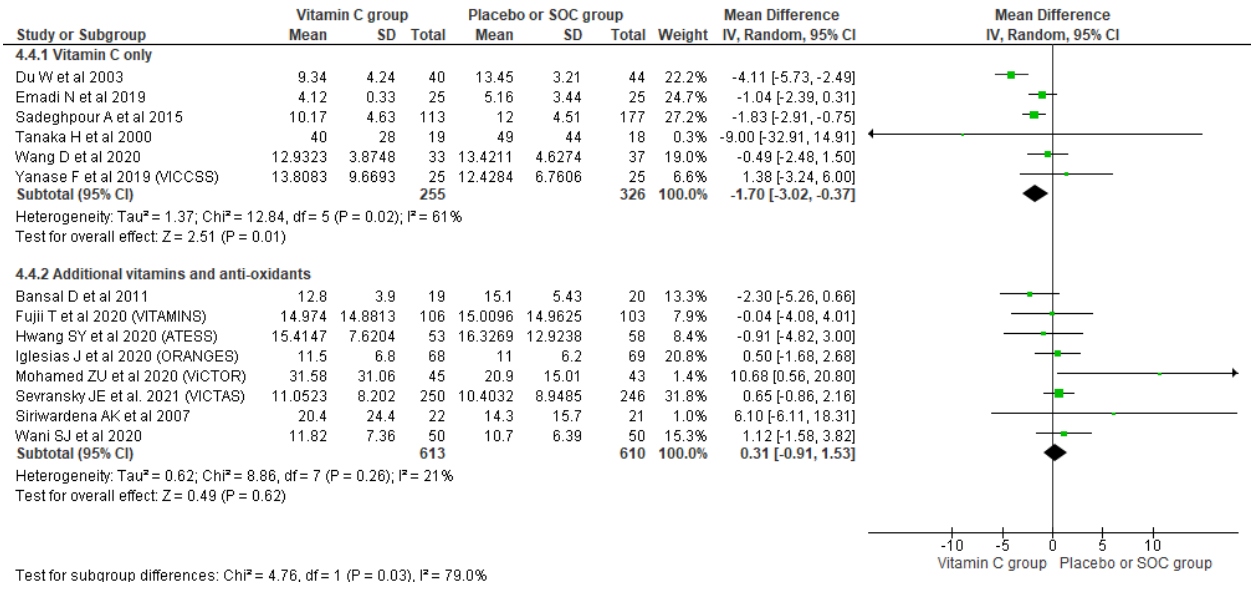

Figure S10. Forest plot showing hospital mortality outcome across use of vitamin C only or other anti-oxidants with vitamin C as treatment group across RCTs

4.2. Among observational studies

a. Based on patient group:

In both sepsis/septic shock group (MD, 1.34; 95% CI, -0.43 to 3.10; n = 246631; I2 = 64%; p=0.14) and surgical group (MD, -5.25; 95% CI, -14.19 to 3.69; n = 4526; I^2 = 97%; p=0.25) reduction in LoHS could not reach statistical significance comparing vitamin C with placebo/ SOC groups (**Figure S11**).

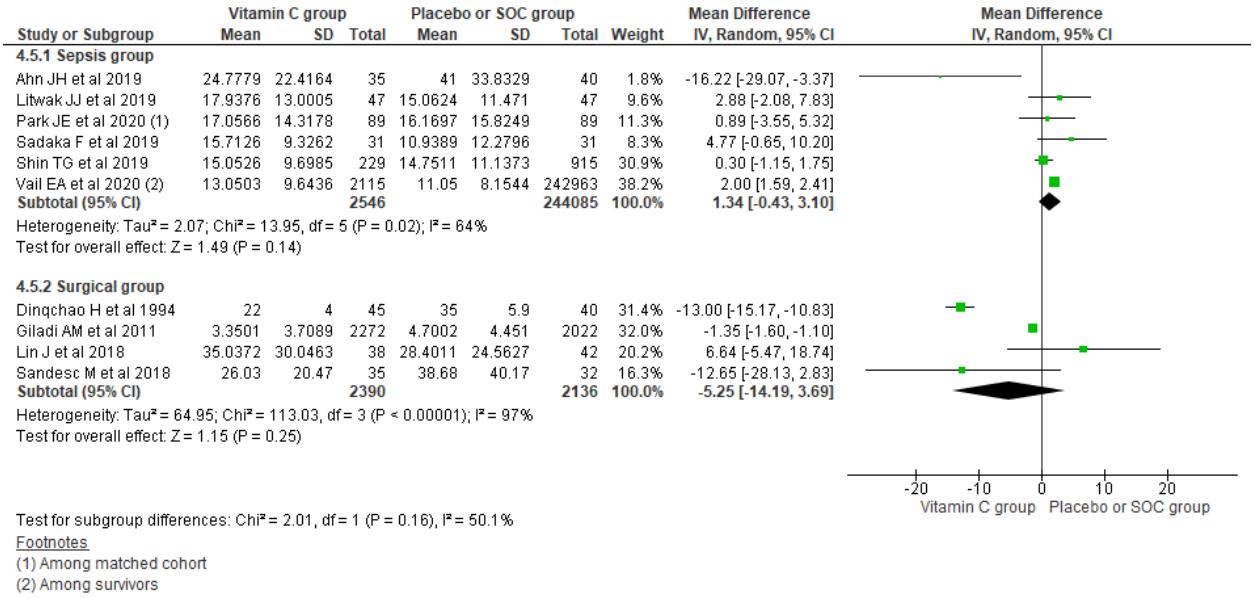

Figure S11. Forest plot showing hospital mortality outcome across surgical and sepsis group among observational studies

b. Based on concomitant other anti-oxidants use

Running analysis considering concomitant use of other anti-oxidants with vitamin C among observational studies also could not show significant differences in length of hospital stay comparing placebo/ SOC with vitamin C only (MD, -8.12; 95% CI, -19.97 to 3.74; n = 240; I^2 = 80%; p=0.18) or concomitant use of other anti-oxidants with vitamin C (MD, 0.83; 95% CI, -1.31 to 2.97; n= 250917; I^2 = 97%; p=0.45) (**Figure S12**).

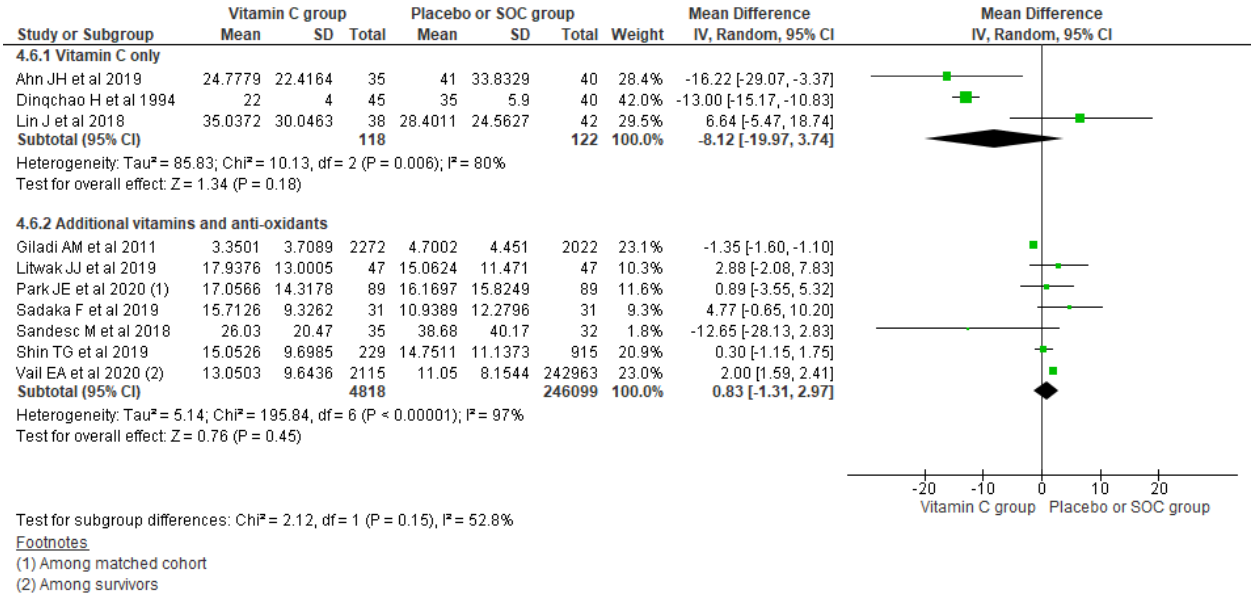

Figure S12. Forest plot showing hospital mortality outcome across use of vitamin C only or other anti-oxidants with vitamin C as treatment group across observational studies

5. New AKI

Pooling new onset AKI outcome using random effect model also showed no significant difference in new AKI outcome (OR, 1.22; 95% CI, 0.94 to 1.58; n= 5330; I^2 = 0%; p=0.14). Similarly, based on type of study also could not show significant changes with fixed effect model result among observational studies (OR, 1.66; 95% CI, 0.78 to 3.54; n= 4482; I^2 = 37%; p=0.35) and RCTs (OR, 1.17; 95% CI, 0.85 to 1.61; n= 848; I^2 = 0%; p=0.35) (**Figure S13**).

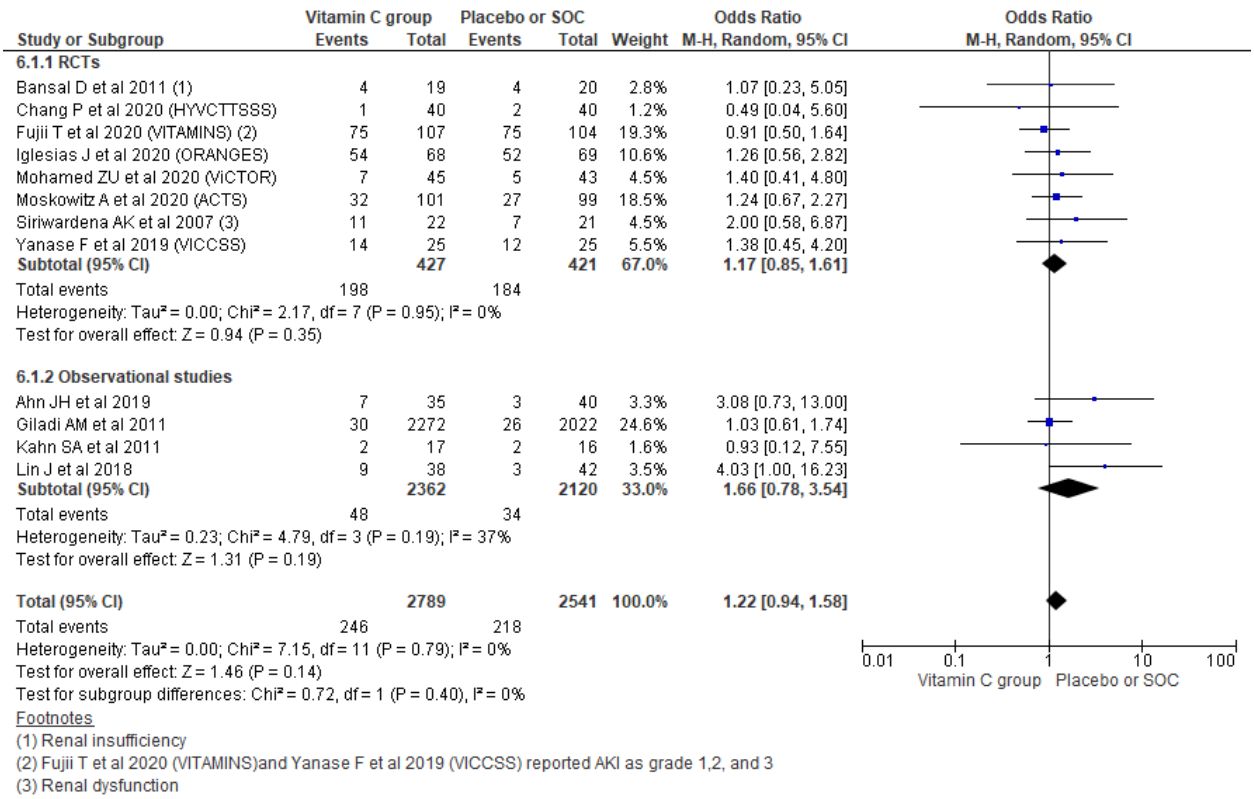

Figure S13. Forest plot showing new AKI outcome using random effect model