12.4 Intravenous Vitamin C Supplementation Nov 2021

Question: Does IV Vitamin C supplementation result in improved clinical outcomes in critically ill patients?

Summary of evidence: There was 3 level 1studies (Zabet 2016, Zhang 2021, Servanskly 2021) and 12 level 2 studies (Nathens 2002, Razmkon 2011, Fowler 2014, Fowler 2019, Fujii 2020, Chang 2020, Hwang 2020, Iglesias 2020, Lv 2020, Mohamed 2020, Moskowitz 2020 and Wani 2020) that examined IV Vitamin C (ascorbic acid) supplementation either alone (Razmkon 2011, Fowler 2014, Zabet 2016, Fowler 2019, Lv 2020. Zhang 2021); in combination with hydrocortisone with or without thiamine (Fujii 2020, Chang 2020, Hwang 2020, Iglesias 2020, Mohamed 2020, Moskowitz 2020, Wani 2020 and Servansky 2021) or with α-tocopherol (Nathens 2002).

In the studies of Vitamin C alone, one study compared a daily dose of 24 gms/day (12 gms q12 hrs) to sterile water (Zhang 2021); one compared a low dose of 500 mg/day to high dose of 10 gms/day X 2 days followed by 4 gms/day for 3 days to Vitamin E (intramuscular) and placebo (Razmkon 2011); one compared a dose of 50 mg/kg/day to a higher dose of 200 mg/kg/day and 5% dextrose (Fowler 2014); one compared a dose of 200 mg/kg/day (50 mg/kg every 6 hrs) to dextrose (Fowler 2019); one compared 100 mg/kg/day (25 mg/kg/d Vit C every 6 hrs) to 5% dextrose (Zabet 2016), and one compared 3g of Vitamin C (BD) dissolved into 5% dextrose vs 5% dextrose as placebo.

In the combination studies, 6000 mg Vitamin C (1500 mg q6 hrs) was combined with 50 mg hydrocortisone q6 hrs and thiamin 200 mg q12 hrs (or 100 mg q 6hrs) (Chang 2020, Fujii 2020, Iglesias 2020, Mohamed 2020, Moskowitz 2020, Wani 2020, Sevransky 2021) or thiamin 200 mg q12 hrs only (Hwang 2020) and in one study 1000 mg Vitamin C was administered along with 1000 IU α-tocopherol q8hrs (Nathens 2002). While in majority of the studies, the control group received either normal saline, dextrose, hydrocortisone or nothing (usual care), two studies did not specify what the placebos were (Razmkon 2011, Sevransky 2021). The duration of the interventions varied across studies and is outlined in table 1.

Table showing daily doses of vitamin C

Study	**Vit C given in mg/day (using 70 kg weight) but did not account for duration**
Zhang 2021	24000
Razmkon 2011	Low dose: 500 High dose: 10,000 (day 1 and 4) to 4000 (day 5,6,7)
Fowler 2014	Low dose: 3500 High dose: 14,000
Fowler 2019	14,000
Zabet 2016, Hwang 2020	7,000
Chang 2020, Fujii 2020, Iglesias 2021, Lv 2020, Mohamed 2020, Moskowitz 2020, Wani 2020, Sevransky 2021	6000
Nathens 2002	3000

Mortality: When the data from all the studies were aggregated (12 studies reported on either 28 day or 30 day mortality, 3 studies reported on hospital mortality), vitamin C supplementation was associated with a trend towards a reduction in overall mortality (RR 0.87, 95% CI 0.75, 1.00, p=0.06, test for heterogeneity I^2=6%; figure 1). Vitamin C supplementation had no effect on ICU mortality (RR 0.96, 95% CI 0.76, 1.21, p=0.72, test for heterogeneity I^2=0; figure 2) or hospital mortality (RR 0.99, 95% CI 0.78, 1.25, p=0.94, test for heterogeneity I^2=0; figure 3). For the two studies that compared high dose to low dose vitamin C to placebo (Fowler 2014, Razmkon 2011), the mortality data from both intervention groups was combined in these analyses.

Mortality subgroup analyses (see figures in attached document)

1. **Sepsis vs. non sepsis trials:**
    a. **Overall mortality:** There was no difference in the effect of vitamin C supplementation in the trials of patients with sepsis (RR 0.87, 95% CI 0.74, 1.03, p=0.11, test for heterogeneity I^2=20%; figure 4) from the three non-sepsis trials when aggregated (RR 0.76, 95% 0.46, 1.27, p=0.30, test for heterogeneity I^2=0%; figure 4) as the test for subgroup differences between the sepsis and non sepsis studies was not significant, p=0.62; figure 4.

2. **High Dose Vit C (≥10,000 mg/day) vs. low dose Vit C (<10,000 mg/day)**

   For this analysis, the data from high vs. low dose Vit C groups from Fowler 2014 and Razmkon 2011 were reported separately under each subgroup.

   a. **Overall mortality:** High dose vitamin C supplementation (≥10,000 mg/day) was associated with a significant reduction in overall mortality (RR =0.70, 95% CI 0.52, 0.96, p=0.03, test for heterogeneity I^2=0%; figure 5) whereas low dose vitamin C (<10,000 mg/day) had no effect (RR 0.92, 95% CI 0.79, 1.07, p=0.26, test for heterogeneity I^2=0%; figure 5). There was a trend towards significant for the test for subgroup differences between high dose and low dose subgroups (p=0.14), with moderate heterogeneity (I^2=55.1%; figure 5).

3. **Monotherapy (Vit C alone) vs. Combination therapy (Vit C, Thiamine and Hydrocortisone)**

   Data from the Nathens 2002 study was not included in the combination therapy subgroup as it evaluated Vit C plus α-tocopherol.

   a. **Overall mortality:** Vitamin C supplementation given alone (monotherapy) was associated with a significant reduction in overall mortality (RR 0.64, 95% CI 0.49, 0.83, p=0.0006, test for heterogeneity I^2=0%; figure 6) while there was no effect on overall mortality in the studies of Vit C in combination with thiamine and hydrocortisone (RR 1.00, 95% CI 0.85, 1.18, p=0.99, test for heterogeneity I^2=0%; figure 6). Test for subgroup differences was significant, p=0.004 but there was high level of heterogeneity (I^2=87.9%; figure 6)

Infections: Only 3 studies reported on new infections (Nathens 2002, Chang 2020, Mohamed 2020) and there were no differences between the groups receiving vitamin C supplementation or placebo/none in either of these trials.

Length of Stay: All the studies reported on varying outcomes related to length of stay. Only few reported on the mean and standard deviation ICU length of stay (Zabet 2016, Mohamed 2020, Hwang 2020, Iglesias 2020 and Zhang 2021) and hospital length of stay (Mohamed 2020, Iglesias 2020, Wani 2020 and Zhang 2021**).** When these data were aggregated, vitamin C supplementation had no effect on ICU length of stay (WMD 0.41, 95% CI -1.32, 2.13, p=0.64, test for heterogeneity I^2=27%) or hospital length of stay (WMD 1.26, 95% CI -0.85, 3.37, p=0.24, test for heterogeneity I^2=21%) see figures 7 and 8. Razmkon et al 2011 reported a non-significantly higher hospital length of stay in the placebo group compared with the other groups (p = 0.08) but data was not shown. All other studies reported no significant differences in the length of stay outcomes between the groups.

Duration of ventilation: Fowler et al 2019 reported a trend towards an increase in mechanical ventilator free days in the vitamin C supplemented group vs. placebo (13.1 vs. 10.6; p=0.15). There were no significant differences in ventilator free days, duration of ventilation or ventilation and vasopressor free days between the groups in any of the other studies.

Duration of Vasopressor Use: The effects of vitamin C on vasopressor use were not statistically aggregated due to varying methods of reporting. Three studies reported a significant reduction in the time to alive and free of vasopressors (Iglesias 2020 p<0.001), duration of vasopressors (Wani 2020 p=0.01, Zabet 2016 p=0.007, Lv 2020 p=0.001) or mean dose of vasopressors (Zabet 2016, p=0.004) in the Vitamin C supplemented groups compared to placebo/control. Fowler (2019) reported a trend towards a reduction in vasopressor free days in the vitamin C supplemented groups. In the remaining trials, no significant differences between the groups observed or this outcome measure was not reported.

Organ dysfunction: Different methods of reporting the impact of vitamin C precluded the statistical aggregation of this important secondary outcome. Nevertheless, a significant reduction in SOFA scores was reported in the Vitamin C supplemented groups compared to placebo/control in four trials (Nathens 2002 p<0.04, Fowler 2014 p<0.05; Fujii 2020 p=0.02; Chang 2020 p=0.02) while four trials reported a trend towards a reduction in SOFA scores in the intervention groups (Iglesias 2020, p=0.10; Moskowitz 2020, p=0.12; Wani 2020, p=0.20; and Sevransky 2021, p=0.10:). There were no statistically significant differences in SOFA score changes in three trials (Fowler 2019, Hwang 2020, Mohamed 2020, Zhang 2021).

Safety: No RCT reported an increase in safety issues in the vitamin C group. Specifically, there were no reports of increased hemolysis, kidney stones or severe hypoglycemia.

Conclusions:
In Critically ill patients, IV vitamin C…

1. may be associated with lower overall mortality but has no effect on ICU or hospital mortality. The beneficial treatment effect may be greater with the use of high-dose vitamin C used alone (not in combination with thiamine or corticosteroids).
2. has no effect on ICU, hospital LOS or ventilation outcomes in critically ill patients.
3. may facilitate faster resolution of shock or less use of vasopressor but the heterogeneous nature of the data and conflicting results preclude firm conclusions.
4. may have a positive impact on the resolution of SOFA scores
5. appears to be safe.

Level 1 study: *if all of the following are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis.*
Level 2 study*: If any one of the above characteristics are unfulfilled.*

Table 1. Randomized studies evaluating vitamin C in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)	Infections # (%)†
1) Nathens 2002	General surgical/trauma ICU patients N=595 Single centre	C.Random: not sure ITT: no Blinding: no (7)	**IV ascorbic acid** (1000 mg in 100 mL D5W) every 8 hours **+ α-tocopherol** (1000 IU) every 8 hours via naso- or orogastric tube for duration of ICU stay, maximum 28 days vs. standard of care.	**Intervention vs. standard of care** **28 day** 4/301 (1%) vs. 7/294 (2%) **ICU** 3/301 (1%) vs. 9/294 (3%) **Hospital** 5/301 (2%) vs. 9/294 (3%)	**Intervention vs. standard of care** 36/301 (12%) vs. 44/294 (15%)
4) Razmkon 2011	Severe head injury patients N=100 Two centres	C.Random: no ITT: yes Blinding: double (8)	**IV low dose ascorbic acid (**500 mg/day) for 7 days **vs. IV high dose ascorbic acid** (10 gms on admission day and day 4 plus 4g/d X 3 remaining days) **vs. Vitamin E** (400 IU/day) intramuscularly X 7 days vs. placebo	**Low dose vs high dose vs. Vit E vs. placebo** **Hospital** 7/26 (26.9%) vs 7/23 (30.4%) vs. 4/24 (16.7%) vs. 8/27 (29.7%), p=NR **60 day** 8/26 (30.8%) vs. 7/23 (30.4%) vs. 5/24 (20.8%) vs. 8/27 (29.7%), p=NR **6 month** 9/26 (34.6%) vs. 7/23 (30.4%) vs. 6/24 (25%) vs. 8/27 (29.7%), p=NR	NR
2) Fowler 2014	Septic patients N=26 Single centre	C.Random: yes ITT: no Blinding: double (7)	**IV low dose ascorbic acid** (50 mg/kg/day) vs **IV high dose ascorbic acid** (200 mg/kg/day) vs placebo (5% dextrose in water).	**Low dose vs. high dose vs. placebo** **28-day** 3/8 (38.1%) vs. 4/8 (50.6%) vs. 5/8 (62.5)%, p=NR	NR

3) Zabet 2016	Surgical ICU patients with septic shock requiring vasopressors N=28 Single centre	C.Random: yes ITT: yes Blinding: double (12)	**IV ascorbic acid** (25 mg/kg q6h) for 72h vs IV placebo (5% dextrose)	**Intervention vs. placebo** **28 day** 2/14 (14%) vs. 9/14 (64%) =0.009	NR
5) Fowler 2019	ICU patients with sepsis and ARDS N=170 Multicentre, n=7	C. Random: yes; ITT: no Blinding: double (10)	**IV ascorbic acid** (50 mg/kg actual body weight, every 6 hrs for 96 hrs) vs. dextrose 5% in water alone (50 mg/kg actual body weight, every 6 hrs for 96 hrs)	**Intervention vs placebo** **28-day** 25/84 (29.8%) vs. 38/82 (46.3%); p=0.03	NR
6) Fujii 2020	ICU patients with shock N=216 Multicentre, n=10	C.Random: yes ITT: no Blinding: no (8)	**IV ascorbic acid (**1500 mg q6 hour), **hydrocortisone** (50mg q6hrs) **and thiamine** (200mg q12 hrs) **vs. IV hydrocortisone** (50mg q6hrs) **alone with thiamine** as per usual care. Given until resolution of shock or up to 10 days.	**Intervention vs. hydrocortisone & thamine** **ICU** 21/107(19.6%) vs. 19/104 (18.3%) p=0.80 **Hospital** 25/107 (23.4%) vs. 21/103 (20.4%) p= 0.60 **28 day** 22/106 **(**22.6 %) vs. 21/103 (20.4%) p=0.69 **90 day** 30/105 (28.6%) vs. 25/102 (24.5%), p=0.51	NR
7) Chang 2020	ICU patients with septic shock N=80 Single centre	C.Random: no ITT: yes Blinding: single (10)	**IV ascorbic acid (**1500 mg q6 hrs for 4 days), **hydrocortisone (**50 mg q6 hrs for 7 days**, and thiamine** (200 mg q12hrs for 4 days) or until ICU discharge for all vs. same volume of normal saline for 4 days or until ICU discharge	**Intervention vs. placebo** **28-day** 11/40 (27.5%) vs. 14/40 (35%); p=0.47	I**ntervention vs. placebo** **Number of new infections** 1/40 (2.5%) vs. 0/40 p=NS

8) Hwang 2020	Patients admitted from Emergency with septic shock. N=116 Multicentre, n=4	C.Random: yes ITT: no Blinding: double (11)	**IV ascorbic acid** (50 mg/kg) **and thiamine** (200 mg) infused over 60 minutes every 12 hrs for 48 hrs vs. same volume of normal saline	**Intervention vs. placebo** **ICU** 7/46 (15.2%) vs. 7/52 (13.5%), p=0.80 **Hospital** 13/53 (24.5%) vs.11/58 (19%); p=0.48 **28 day** 11/53 (20.8%) vs. 9/58 (15.5%), p=0.47 **90 day** 17/53 (32.1%) vs.16/58 (27.6), p=0.61	NR
9) Iglesias 2020	ICU patients with sepsis or septic shock. N=140 Multicentre, n=2	C.Random: yes ITT: no Blinding: double (9)	**IV ascorbic acid** (1500 mg q6hrs), **hydrocortisone** (50 mg q6hrs) **& thiamine** (200 mg q12hrs) vs. normal saline, both started within 10 hrs and given for 4 days	**Intervention vs. placebo** **ICU** 6/68 (9%) vs. 10/69 (14%), p=0.30 **Hospital** 11/68 (16%) vs. 13/69 (19.4%), p=0.60	NR
10) Lv 2020	ICU patients with sepsis n=117 Single-center	C.Random: No ITT: Yes Blinding: No (8)	IV 3.0 g vitamin C dissolved into 5% dextrose vs 5% dextrose as placebo (both given 100 ml/time, 2 times/day), started from ICU admission until ICU discharge	**Intervention vs. placebo** **28-day** 15/61 (24.6%) vs. 24/56 (42.9%), p=0.002	NR
11) Mohamed 2020	ICU patients with septic shock n=90 Single-center	C.Random: Yes ITT: No Blinding: no (6)	IV hydrocortisone (50 mg every 6 hours), vitamin C (AA) (1.5 g every 6 hours; infused over 60 minutes), and thiamine (200 mg every 12 hours) for 4 days, with the first doses of the drugs administered within 6 hours of onset of septic shock/ admission **vs** routine care	**Intervention vs. Standard of care** **All-cause mortality** 26/45 (57.8%) vs 25/45 (55.6%), p=NS	**Intervention vs. placebo** Multidrug resistant bacteria 25/45 (55.6%) vs 24/43 (55.5%)
12) Moskowitz 2020	ICU patients with septic shock. N=205, Multicentre, n=14	C.Random: yes ITT: no Blinding: double (10)	**IV ascorbic acid** (1500 mg), **hydrocortisone** (50 mg), & **thiamine** (100 mg) **vs**. normal saline, both started within 24 hrs q6	**Intervention vs. placebo** **ICU** 23/101 (22.7%) vs. 20/99 (20.2%), p=0.69 **Hospital**	NR

			hrs for 4 days or until ICU discharge	28/101 (27.7%) vs. 23/99 (23.2%), p=0.55 **30 day** 35/101 (34.7%) vs. 29/99 (29.3%), p=0.26	
13) Wani 2020	Critically ill patients with sepsis and septic shock N=100 Single centre	C.Random: yes ITT: yes Blinding: no (11)	**IV ascorbic acid (**1500 mg every 6 hrs for 4 days), **hydrocortisone** (50 mg every 6 hrs for 7 days) and **thiamine** (200 mg every 12 hrs for 4 days) or until hospital discharge for all **vs**. none. Started within 24 hrs.	**Intervention vs. none** **Hospital** 12/50 (24%) vs. 14/50 (28%); p=0.82 **30 day** 20/50 (40%) vs. 21/50 (42%), p=1.0	NR
14) Zhang 2021	Critically ill diagnosed with severe COVID-19 related pneumonia N=56 Multicentre, N=2	C.Random: yes ITT: yes Blinding: double (12)	**IV Ascorbic** acid (12 gms q 12 hrs) X 7 days **vs**. **sterile water**	**Intervention vs. placebo** **ICU** 6/27 (22.2%) vs, 11/29 (37.9%); p=0.20 **Hospital** 6/27 (22.2%) vs, 11/29 (37.9%); p=0.20 **28 day** 6/27 (22.2%) vs. 10/29 (34.5%), p=0.31 **ICU mortality** **(in subgroup SOFA ≥ 3)** 5/27(21.7%) vs. 11/29 (52.4%), p=0.04	NR
15) Sevransky 2021	Older adults with acute respiratory/ cardiovascular dysfunction expected to be in ICU N=501 Multicentre, N=43	C.Random: yes ITT: yes Blinding: double (13)	**IV ascorbic acid** (1500 mg), **hydrocortisone** (50 mg), & **thiamine** (100 mg) **vs**. matching placebos, q6 hrs for 4 days or until ICU discharge, both	**Intervention vs. placebo** **ICU** 52/252 (20.6%) vs. 49/249 (19.7%) difference (95%CI) 0.9 (-8.0, 6.1), p=0.79 **30 day (all cause)** 56/252 (22%) vs. 60/249 (24%); p=0.16 **180 day** 102/252 (40.5%) vs. 94/249 (37.8%) difference (95%CI) 2.7 (-11.3, 5.8); p=0.53	NR
16) Hussein 2021	Septic shock N=94	C.Random: No ITT: No	hydrocortisone 50 mg/6-h IV for 7 days or ICU discharge followed by a	**Intervention vs. hydrocortisone alone** **28-day**	NR

	Single centre	Blinding: No (XX)	taperover 3 days, vitamin C 1.5 g/6-h IV for 4 days or till ICU discharge, and thiamine 200 mg/12-h IV for 4 days or till ICU discharge **vs** hydrocortisone 50 mg/6-h IV for 7 days or till ICU discharge followed by ataper over 3 days,	17/47 (36.2) vs 21/47 (44.7); p=0.4005 **ICU mortality** 14/47 (29.7) vs 19/47 (40.4); p=0.2799	
17) Jamali Moghadam Siahkali 2021	COVID-19 with ARDS N=60 Single centre	C.Random: Unsure ITT: Yes Blinding: No (XX)	1.5 g vitamin C IV every 6 h for 5 days vs No Vitamin C	**Intervention vs. usual care** **Mortality (unspecifed)** 3/30 (10) vs 3/30 (10)	
Wacker 2021	Septick shock N=124 Multicentre, N=5	C.Random: Unsure ITT: No Blinding: Double (XX)	IV Vitamin C (10-mg/mL solution in normal saline) administered as a 1,000-mg bolus over 30 minutes followed by continuous infusion of 250 mg/h **vs** placebo of normal saline Up to 96h or vasopressor-free for 24 consecutive hours, whichever occurred sooner	**Intervention vs. normal saline** **28 day** 16/60 (26.7) vs 26/64 (40.6); p=0.10 **ICU** 14/60 (23.3) vs 20/64 (31.1); p=0.32	NR
Rosengrave 2022	Septic shock N=40 Single centre	C.Random: Yes ITT: Yes Blinding: Yes (XX)	IV Vitamin C in 5% dextrose - 25 mg/kg every 6h. Administered over 30 min. vs IV 5% dextrose Up to 96h, or until death or ICU DC	**Intervention vs. 5% dextrose** **30-d** 6/20 (30) vs 7/20 (35) **90-d** 8/20 (40) vs 7/20 (35) **Hospital** 7/20 (35) vs 7/20 (35)	NR

			if earlier		

Table 1. Randomized studies evaluating vitamin C in critically ill patients (continued)

Study	LOS days	Ventilator free days	Other Outcomes
1) Nathens 2002	**Intervention vs. standard of care** **ICU** Mean 5.3 vs. 6.4 **Hospital** Mean 14.6 vs. 15.1	**Intervention vs. standard of care** Mean 3.7 vs. 4.6	**Intervention vs. standard of care** Vasopressors not reported **AEs:** not reported. Multiple organ failure was significantly less likely to occurred in the intervention arm than control group (RR 0.43, 95% CI [0.19 – 0.96],p=0.04)
2) Razmkon 2011	**Hospital LOS** non significantly more prolonged in the placebo group compared with the other groups, which experienced a shorter (although not significantly) hospitalization (p = .08). Mean hospital LOS 15.2 ±4.3 days	NR	**Low dose vs. high dose vs. Vit E vs. placebo** **Glasgow Outcomes Scale (GOS):** At discharge and follow-up were significantly better for the vitamin E group patients (p =0.04) **Perilesional edema:** Only high-dose vitamin C stabilized or reduced the diameter of perilesional hypodense region in subsequent days in 68% of patients (p =0 .01). **AEs:** No adverse events reported
3) Fowler 2014	**Low dose vs. High dose vs. placebo** **ICU** 8.1 (1-19) vs. 9.1 (2-25) vs.11 (2-25) p=NR	**Low dose vs. High dose vs. placebo** 8.4 (0-22) vs. 4.8 (0-19) vs. 7.6 (0-23) p=NR	**Low dose vs. High dose vs. Placebo** **Days on Pressors:** 2.1(1-6) vs. 3.6 (2-8) vs. 3.9 (1-10); p:NR **SOFA score change day 0 to 4:** -0.020 vs. -0.043 vs. 0.003 High vs placebo p<0.01 High and low dose vs. non-zero slope (p<0.05) **AEs:** No adverse events reported
4) Zabet 2016	**Intervention vs. placebo** **ICU, in days** 21.45 +10.23 vs. 20.57 + 13.04, p=0.85	**Intervention vs. placebo** **In hrs** 36.63 + 16.11 vs. 46.78 + 10.11, p=0.5	**Intervention vs. placebo** **Mean dose of norepi (mcg/min) during 72h study period:** 7.44 + 3.65 vs. 13.79+6.48, p=0.004 **Duration or norepi administration** (mean hrs, SD): 49.64+25.67 vs. 71.57+1.60, p=0.007 **AEs:** No adverse events reported
5) Fowler 2019	**Intervention vs. placebo** **ICU 28 free days** 10.7 vs 7.7 days: p=0.03 **Hospital Free days** 22.6 vs. 15.5 days: p=0.04	**Intervention vs. placebo** 13.1 vs. 10.6 days: p= 0.15	**Intervention vs placebo** **mSOFA score from baseline to 96 hrs** decreased from 9.8 to 6.8 in the vitamin C group (3 points) from 10.3 to 6.8 in the placebo group (3.5 points) difference, –0.10; 95% CI, −1.23 to 1.03; p = 0.86

			Vasopressor use at 168 hrs (%)**:** 72% (median 22.2%) vs. 59% (median 10%); p=0.07. No differences at 48 or 96 hrs **AEs:** No adverse events were reported
6) Fujii 2020	**Intervention vs. Control** **28-day ICU-free days** 21.9 (0-25.8) vs. 22.1 (3.9-25.8); p=0.66 **Hospital** 12.3 (6.2-26) vs.12.3 (6.2-26.1), p= 0.75	**Intervention vs. Control** **28-day cumulative mechanical ventilation free days** 25.3 (5.2 -28) vs. 24.8 (9.5-28), p=0.73	**Intervention vs. control** **SOFA score change at day 3, (**median (IQR): -2 (-4 to 0) vs. -1 (-3 to 0), p = 0.02 **Acute Kidney Injury**: no differences in the number of stage 1, 2 or 3 of AKI, p= 0.80 **28-day RRT free-days**, median (IQR): no differences, p =0.71 **Time alive and vasopressor free,** median (IQR): no differences, p=0.83 **Duration of vasopressor (hours)** **Vitamins group** 46.4 (43.3) [No. required vasopressors and survived the index shock = 90] vs. **Control group** 48.0 (41.4) [No. required vasopressors and survived the index shock = 90] **AEs** 2 patients (2events, fluid overload and hyperglycemia) in the intervention group and 1 patient (1 event, gastrointestinal bleeding) in the control group. No serious adverse events or suspected unexpected serious adverse reactions were reported
7) Chang 2020	**Intervention vs. placebo** **ICU, in days** 7.5 (4-12.8) vs. 7.5 (4-11.8), p=0.98	**Intervention vs. placebo** **Mechanical Ventilation, hrs** 126.5 (63.5-239.3) vs. 94.5 (39.8-211), p=0.36	**Intervention vs. placebo** **SOFA score** change at 72 hrs (mean, SD) was higher in the intervention group (3.5 ± 3.3) vs. placebo (1.8 ± 3.0); p=0.02. **Vasopressor duration** was no different in the intervention group (median hrs and IQR 46; 23.8-102.5) vs. placebo (58.5; 28-104), p=0.70 **AEs:** **Hypernatremia** (>160 mmol/L) was significantly higher in in

			the intervention group vs, placebo (13 vs 3 patients, p=0.005). Also, the proportion of patients with GI bleeding (3 vs 2) and new infections (2 vs 0) were similar in the intervention and control group.
8) Hwang 2020	**Intervention vs. placebo** **ICU** 6.4 ± 5.6 (46) vs. 7.8 ± 7 (52); p=NR **ICU-free days** 9 (3-11) vs. 9 (0-11); p=0.42 **Hospital** 14 (11-21) vs. 13.5 (9-26), p=0.92	**Intervention vs. placebo** **Mechanical ventilation, days** 3.6 ± 7.2 (23) vs. 3.3 ± 6.2 (24); p =NR	**Intervention vs. placebo** **SOFA score change at 3 days,** median (IQR): 3 (-1 to 5) vs. 3 (0 to 4); p=0.96 **Time to alive and free of vasopressors (shock reversal),** mean hrs (SD): 44 (83) vs. 49 (84.5), p=0.83 **Vasopressor free days,** median IQR: 11 (5-12) vs. 11 (10-12); p=0.16 **AEs** No adverse events were reported in the treatment group (eTable 4 in Supplements). Two patients (3.5%) in the placebo group reported mild adverse events, including gastrointestinal symptoms.
9) Iglesias 2020	**Intervention vs. placebo** **ICU** 4.76 ± 4.3 vs. 4.66 ±3.45, p=0.88 **Hospital** 11.5±6.8 vs. 11±6.2, p=0.75	**Intervention vs. placebo** **Mechanical ventilation, days** 4.8 ± 4.9 vs. 5.65 ±4.3, p=0.27 **Ventilator free days** 22±6.2 vs. 22.4±4.3, p=0.63	**Intervention vs. placebo** **SOFA score change at 3 days,** mean (SD): 2.9±3.3 vs. 1.93±3.5, p=0.10 **Time to alive and free of vasopressors: mean hrs (SD):** 27±22 vs. 53±38, p<0.001 **Acute Kidney injury**, n (%): 54 (79%) vs. 52 (75%) **AEs:** none reported
10 Lv 2020	**Intervention vs. placebo** **ICU, days** 4.1 (3.2-8.3) vs 3.9 (3.1-7.5), p=0.811	**NR**	**Intervention vs. placebo** **SOFA score after 72h, median (IQR):** 4.2 (1.2-6.6) vs 2.1 (1.1-4.3), p=0.001 **Time on vasoactive drugs, hrs:** 25.6 (18.8-40.6) vs 43.8 (24.7-66.8), p=0.001 **Procalcitonin clearance after 72h, %:** 79.6 (66.5-85.6) vs 61.3 (50.9-66.2), p=0.001 **AEs:** not reported
11) Mohamed 2020	**Intervention vs. standard of care** **ICU, days** 12.44±14.2 vs 8.44±8.16, p=0.1	**NR**	**Intervention vs. standard of care** (n=45 vs 43) **Mean vasoactive inotropic score:** 7.77±12.12 vs 8.86±12.5, p=0.6 **Time to reversal of septic shock, h:** 34.58±22.63 vs

	Hosp, days 31.58±31.06 vs 20.9±15.01, p=0.043		45.42±24.4, p=0.03 **Change in SOFA score at 72h:** 2.23±2.4 vs 1.38±3.1, p=0.22 **SOFA at 72h:** 8.9±3.6 vs 9.3±3.8, p=0.7 **AEs:** No adverse events were recorded
12) Moskowitz 2020	**Intervention vs. placebo** **ICU free days** 22 (3-25) vs. 21 (4-25), p=0.69	**Intervention vs. placebo** **Ventilator free days** 6 (2-7) vs. 6 (0-7), p>0.99	**Intervention vs. placebo** **SOFA score change at 3 days, mean (SD):** 4.4±4.1 vs. 5.1±44.3, p=0.12 **AEs:** no unexpected serious AEs were reported. There were 12 (11.9%) and 7 (7.1%) patients in the intervention and control arm with hyperglycemia. Eleven and 7 patients in the intervention arm and control arm had hypernatremia, accordingly. Also, 13 patients in the intervention arm vs 12 in the control had new nosocomial infections.
13) Wani 2020	**Intervention vs. none** **Hospital, in days** 11.82 ± 7.36 vs. 10.7± 6.39, p=0.41	**Intervention vs. none** **Ventilator free days** 3.66 ±2.05 vs. 3.33± 2.62, p=NR	**Intervention vs. none** **SOFA Day 4 score:** 5.64±3.55 vs. 6.62±3.94, p=0.20 **Duration of vasopressor,** hrs**:** 75.72 ±30.29 vs. 96.13 ±40.5, p=0.01 **AEs:** none reported
14) Zhang 2021	**Intervention vs. placebo** **ICU, in days** 22.9 ± 14.8 vs. 17.8 ± 13.3; p=0.20 **Hospital, in days** 35.0 ± 17.0 vs. 32.8 ± 17.0, p =0.65	**Intervention vs. placebo** **Ventilator free days at day 28** 26.0 [9.0–28.0] vs. 22.0 [8.5–28.0]; p=0.57 **Mechanical ventilation days to day 28** 1.5 [0.0-19.0] vs. 6.0 [0.0–16.0]; p = 0.60	**Intervention vs. placebo** **Median SOFA Score change Day 1-7**: 0 [-2.75 to 1] vs. 0 [-1 to -3.5]; p=0.25 **Septic shock (n, %):** 9 (34.6) vs.8(28.6); p=0.77 **Acute kidney injury (n, %):** 3(12.0) vs. 6(22.2); p=0.50 **Acute cardiac injury** (n, %): 7(26.9) vs. 13(48.1);p=0.16 **Acute liver injury** (n, %): 12(48.0) vs. 13(48.1), p=1.00 **Coagulation disorders** (n, %): 9(34.6) vs. 7(25.9); p=0.56 **AEs:** Slight increase in bilirubin from day 1 to day 7 in the control group.
15) Sevransky 2021	**Intervention vs. placebo** **ICU, days** 4 (2-8) vs. 4 (2-8) difference (95% CI) 0.0 (−2.0,1.0); p=0.82	**Intervention vs. placebo** **Ventilator and Vasopressor free days** 25 (0-29) vs. 26 (0-28) difference (95% CI) −1 day (−4 to 2); p =0 .85	**Intervention vs. placebo** **SOFA score change to Day 4,** median, IQR 5 (3-7) vs. 5 (2-7); difference (95% CI) 0.0 (−1.0, 0.0); p=0.10 **Coma-/delirium-free days, median, IQR**

	Hospital, in days 10 (6-17) vs. 9 (5-17) difference (95% CI) 1.0 (−3.0, 2.0); p=0 .66		4 (2-5) vs. 4 (2-5); difference (95% CI) 0.0 (0.0 to 1.0); p= 0.45 **Kidney replacement therapy–free days, median, IQR** 30 (0-30) vs. 30 (0-30); difference (95% CI) 0.0 (0.0 to 0.0); p=0.58 **AEs:** There were 2 adverse events (hemorrhagic shock and worsening kidney function) in the intervention group assessed as potentially related to study participation. There were no reported serious adverse events in the study.
16) Hussein 2021	**Intervention vs. hydrocortisone alone** **ICU LOS** 8.319±4.071 (47) vs 9.787±4.206 (47); p=0.0889 **Hosp LOS** 9.447±4.226 (47) vs 11.17±5.036 (47); p=0.0756	**Intervention vs. hydrocortisone alone** **Mechanical ventilation days** **5.393**±3.521 (28) vs 5.379±3.755 (29); p=0.9888	**Intervention vs. hydrocortisone alone** **Duration on vasopressor:** 4 (3-7) vs 5 (4-8); p=0.100 **SOFA score at 48h:** 7.319±3.496 (47) vs 7.830±3.102 (47); p=0.4558 **SOFA score at 96h:** 4.725±3.486 (40) vs 5.698±3.726 (43); p=0.2239 **ICU readmission:** 2/47 (4.3) vs 8/47 (17.0); p=0.0447
17) Jamali Moghadam Siahkali 2021	**Intervention vs. usual care** **ICU LOS** 5.5 (5-10) vs 5 (5-7); p=0.381 (Note: unsure how many were admited to ICU) **Hosp LOS** 8.5 (7-12) vs 6.5 (4-12); p=0.028	**Intervention vs. usual care** **NR** (only 5/30 vs 4/30 were intubated)	**Intervention vs. usual care** **AEs:** none in borh groups
Wacker 2021	**Intervention vs. normal saline** **ICU LOS** 2.9 (1.8-7.5) (60) vs 2.6 (1.5-5.3) (64); p=0.47 **Hosp LOS** 8.9 (4.0-20.0) (60) vs 6.3 (3.8-12.5) (64); p=0.15	**Intervention vs. normal saline** **Duration of MV** 0 (0-60) (60) vs 5 (0-48) (64); p=0.45	**Intervention vs. normal saline** **Improvement in SOFA:** 3.5 (1-6) (n=58) vs 4 (1-6) (n=61); p=0.68 **Incidence of RRT during 96-h study period:** 10/60 (16.7) vs 2/60 (3.3); p=0.02 **AEs: 15 vs 12** **3 possible related to study drug:** nausea (vitamin C), bradycardia (placebo), loose stools (placebo)

Rosengrave 2022	**Intervention vs. 5% dextrose** **ICU LOS (survivor)** 3.8 (2.2-9.8) vs 7.1 (3.1-20); p=0.12 6.38±6.21 (16) vs 10.71±14.25 (14) **Hosp LOS (survivor)** 18 (11-35) vs 22 (10-52); p=0.65 19.46±13.58 (12) vs 28.71±27.13 (13)	**Intervention vs. 5% dextrose** NR	**Intervention vs. 5% dextrose** **Mean dose of vaopressor: 0**.99±0.55 vs 0.71±0.60 units/min; p=0.35 **Mean duration of vasopressor:** 48 (95% CI 35-62) vs 54 (95% CI 41-62); p=0.54 **96h SOFA:** 6.7±8.3 vs 5.5±7.0; p=0.64 **AEs:** 1 gastrointestinal bleed in placebo group

† refers to the # of patients with infections unless specified LOS: Length of stay ICU: intensive care unit C. Random: concealed randomization

ITT: intent to treat; NR: not reported; NS: not significant; hrs: hours; RR: Risk Ratio; WMD: weighted mean difference;

Figure 1. Overall Mortality (Fowler 2014 data and Razmkon 2011 data from both high and low dose groups combined)

Study or Subgroup	Vitamin C Events	Vitamin C Total	Control (placebo or none) Events	Control (placebo or none) Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Nathens 2002	4	301	7	294	1.4%	0.56 [0.17, 1.89]	2002
Razmkon 2011	14	49	8	27	3.7%	0.96 [0.46, 2.00]	2011
Fowler 2014	7	16	5	8	3.4%	0.70 [0.32, 1.52]	2014
Zabet 2016	2	14	9	14	1.1%	0.22 [0.06, 0.85]	2016
Fowler 2019	25	84	38	82	11.5%	0.64 [0.43, 0.96]	2019
Chang 2020	11	40	14	40	4.6%	0.79 [0.41, 1.52]	2020
Fujii 2020	22	106	21	103	6.8%	1.02 [0.60, 1.73]	2020
Hwang 2020	11	53	9	58	3.1%	1.34 [0.60, 2.97]	2020
Moskowitz 2020	35	101	29	99	11.3%	1.18 [0.79, 1.78]	2020
Lv 2020	15	61	24	56	6.8%	0.57 [0.34, 0.98]	2020
Mohamed 2020	26	45	25	45	13.9%	1.04 [0.72, 1.49]	2020
Wani 2020	20	50	21	50	8.6%	0.95 [0.59, 1.52]	2020
Iglesias 2020	11	68	13	69	3.7%	0.86 [0.41, 1.78]	2020
Sevransky 2021	56	252	60	249	17.3%	0.92 [0.67, 1.27]	2021
Zhang 2021	6	27	10	29	2.7%	0.64 [0.27, 1.53]	2021
Total (95% CI)		1267		1223	100.0%	0.87 [0.75, 1.00]	
Total events	265		293				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 14.83$, $df = 14$ ($P = 0.39$); $I^2 = 6\%$

Test for overall effect: $Z = 1.90$ ($P = 0.06$)

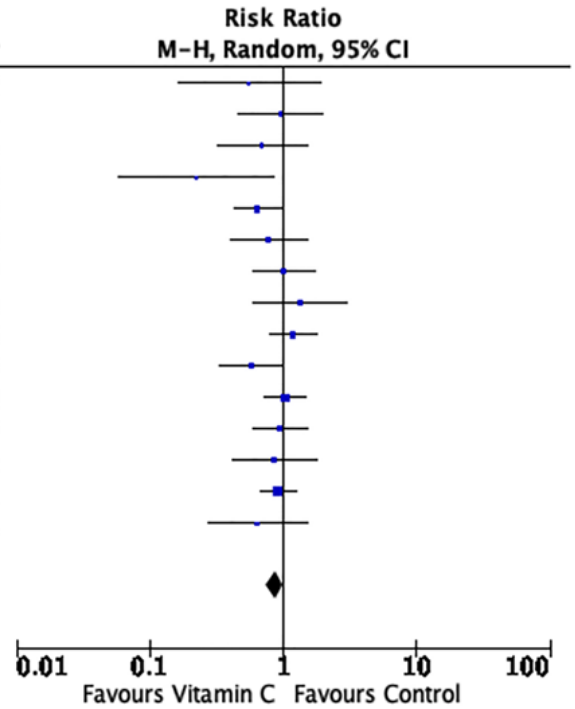


Figure 2. ICU Mortality

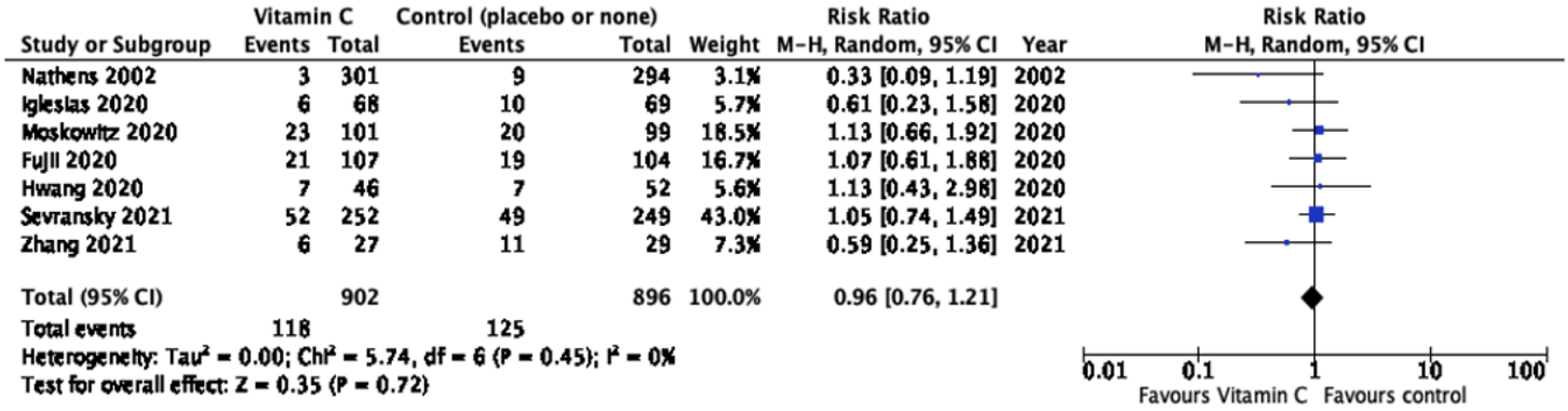


Figure 3. Hospital Mortality (Razmkon 2011 data from both high and low dose groups combined)

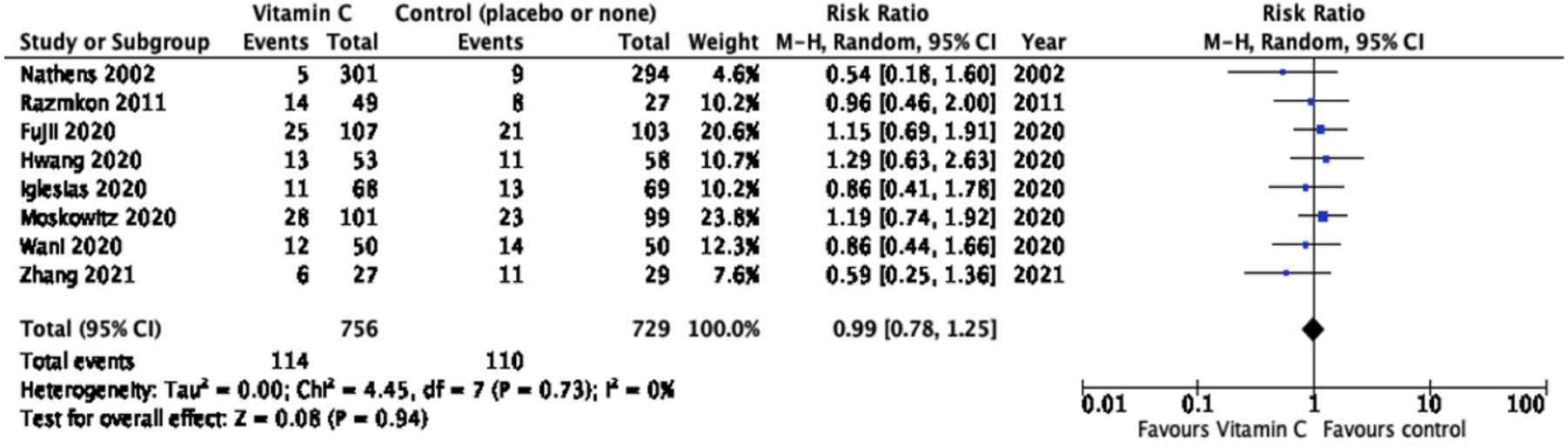


Figure 4. Overall Mortality: Sepsis. vs. non sepsis

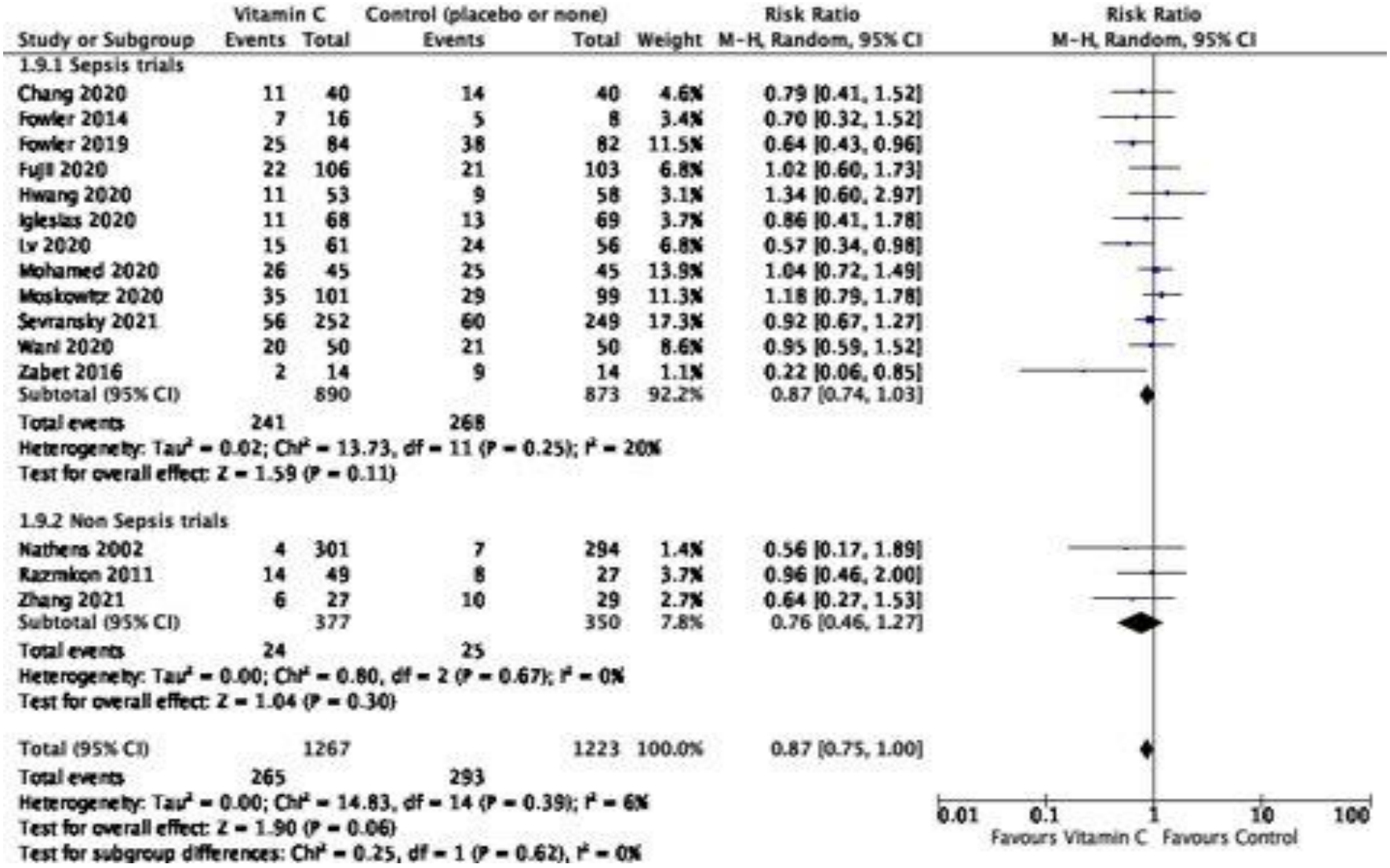


Figure 5. Overall Mortality: High dose Vitamin C (≥ 10,000 mg/day) vs. Low dose (<10,000 mg/day)

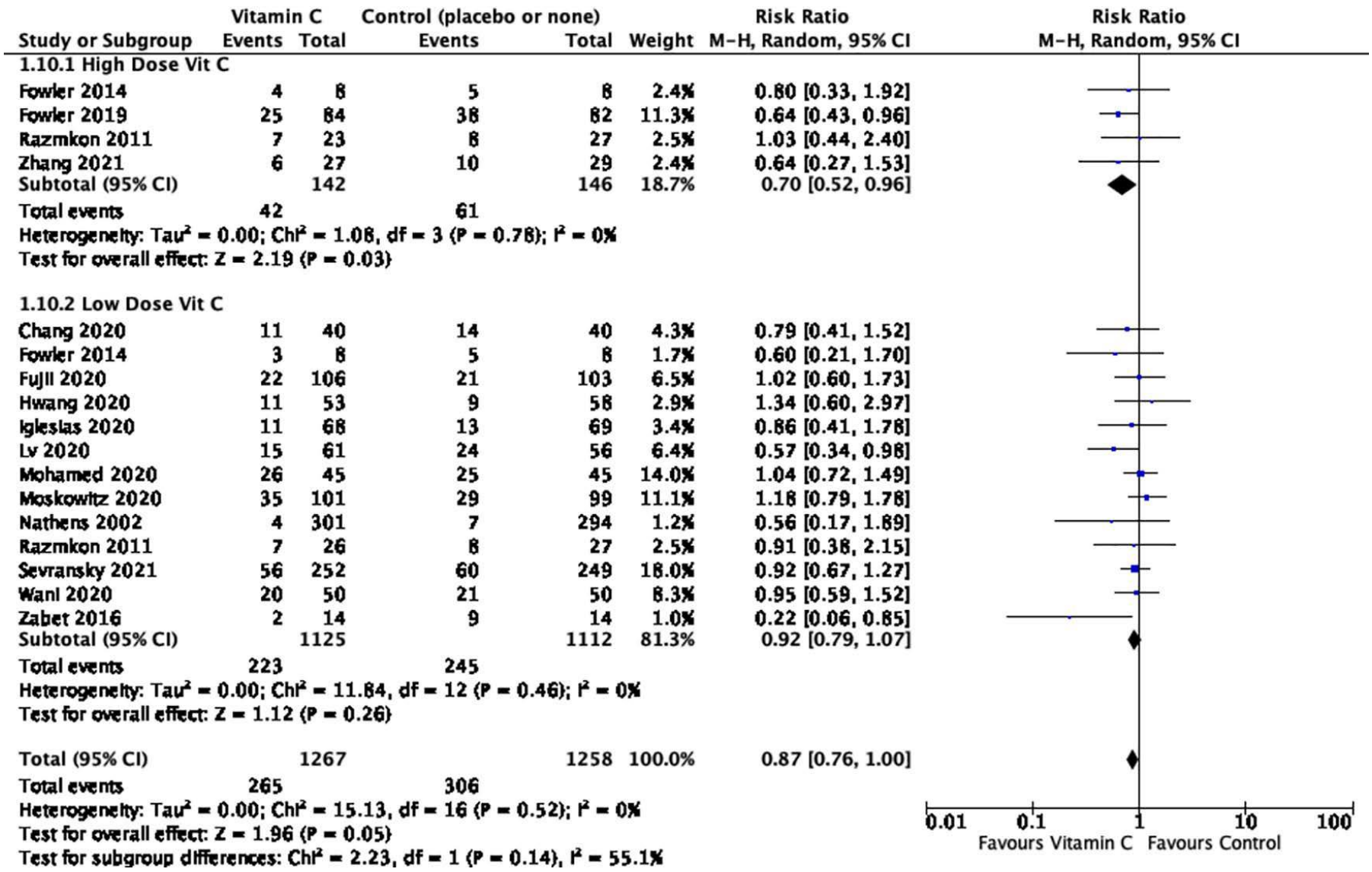


Figure 6. Overall mortality: Monotherapy (Vit C alone) vs. Combination therapy (Vit C, Thiamine and Hydrocortisone)

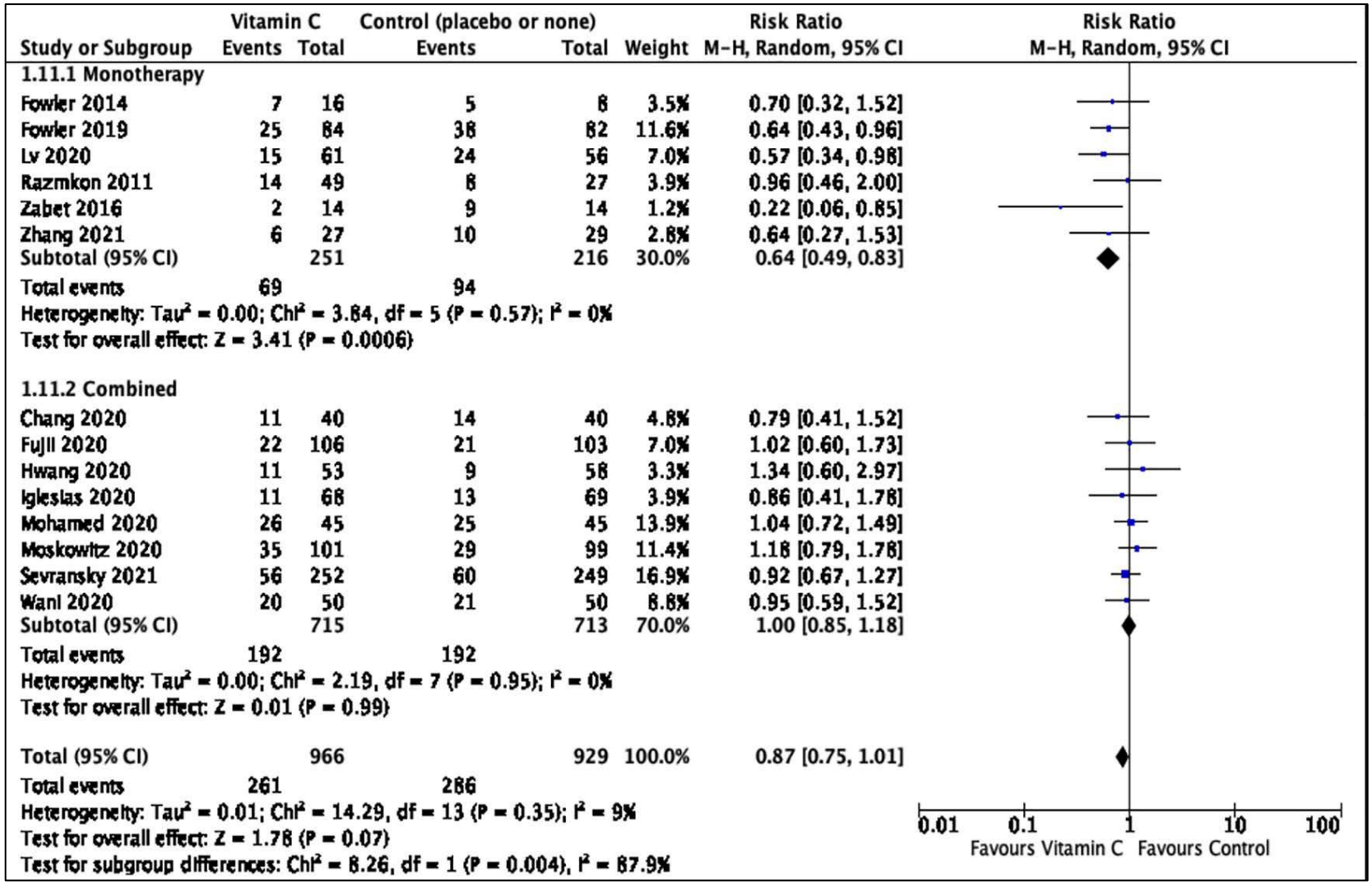


Figure 7. ICU Length of Stay, days

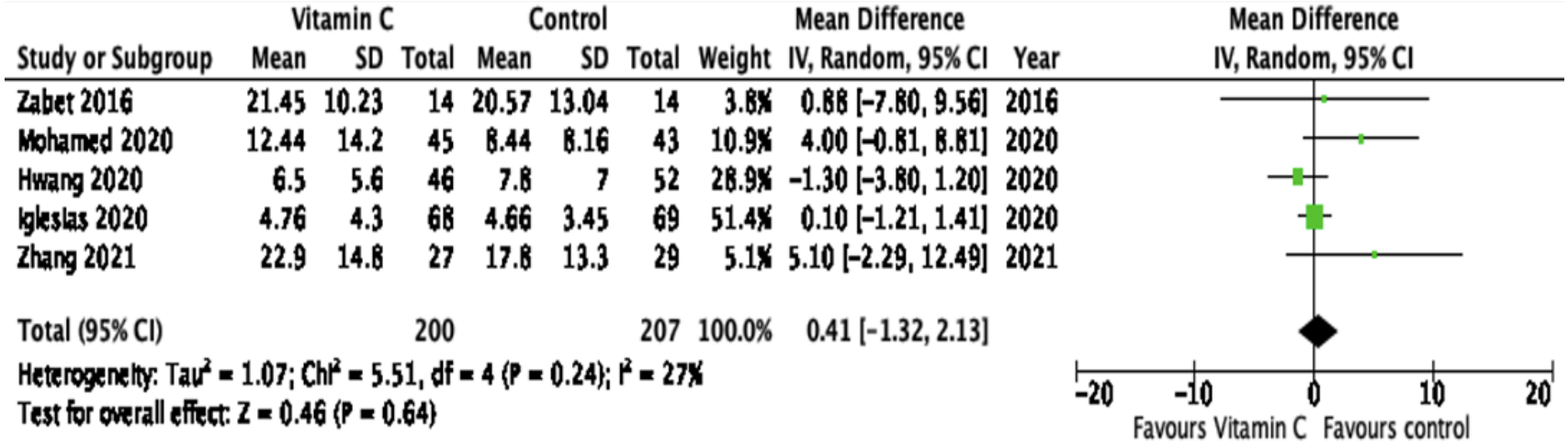
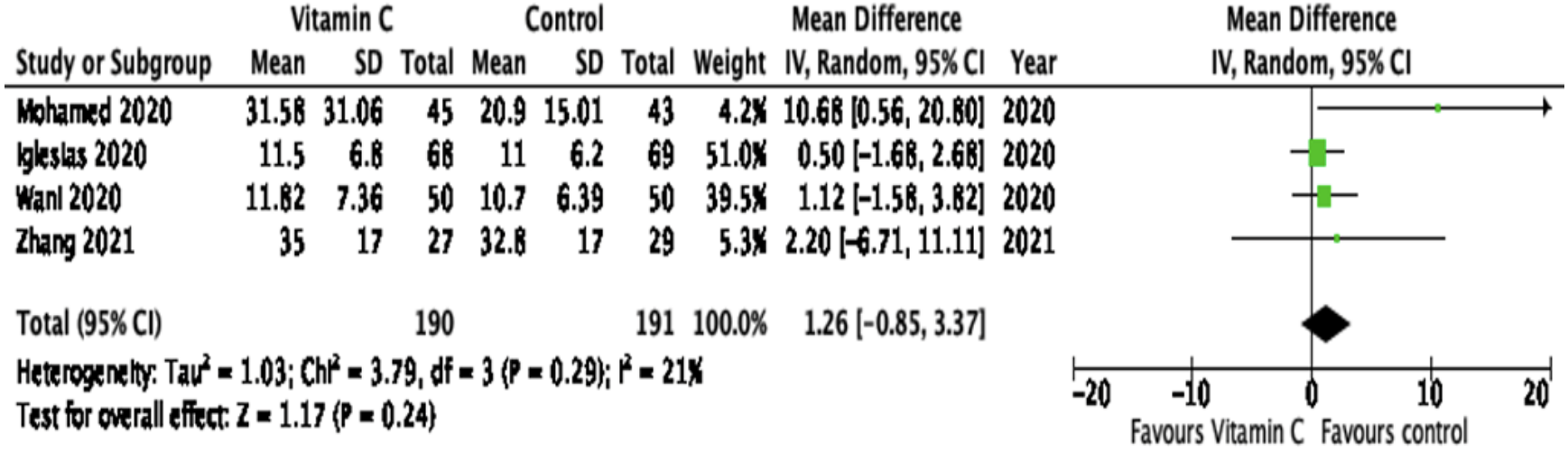


Figure 8. Hospital Length of Stay, days



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27	Ferrón-Celma I, Mansilla A, Hassan L, et al. Effect of vitamin C administration on neutrophil apoptosis in septic patients after abdominal surgery. J Surg Res. 2009;153(2):224-230. doi:10.1016/j.jss.2008.04.024	No clinical outcome
28	Hudson EP, Collie JT, Fujii T, Luethi N, Udy AA, Doherty S, Eastwood G, Yanase F, Naorungroj T, Bitker L, Abdelhamid YA, Greaves RF, Deane AM, Bellomo R. Pharmacokinetic data support 6-hourly dosing of intravenous vitamin C to critically ill patients with septic shock. Crit Care Resusc. 2019 Dec;21(4):236-42. PMID: 31778629..	No clinical outcome
29	Zhang C, Li JM, Hu JL, Zhou X. The effects of large doses of vitamin C and vitamin E on nerve injury, neurotrophic and oxidative stress in patients with acute craniocerebral injury. J Acute Dis 2018;7:69-73	No clinical outcome. VIt E was given concomitantly
30	de Grooth HJ, Manubulu-Choo WP, Zandvliet AS, Spoelstra-de Man AME, Girbes AR, Swart EL, Oudemans-van Straaten HM. Vitamin C Pharmacokinetics in Critically Ill Patients: A Randomized Trial of Four IV Regimens. Chest. 2018 Jun;153(6):1368-1377. doi: 10.1016/j.chest.2018.02.025. Epub 2018 Mar 6. PMID: 29522710.	No nutrition support involved or clinically important end point
31	Duffy MJ, O'Kane CM, Stevenson M, et al. A randomized clinical trial of ascorbic acid in open abdominal aortic aneurysm repair. Intensive Care Med Exp. 2015;3(1):50. doi:10.1186/s40635-015-0050-5	Not critically ill patients
32	Emadi N, Nemati MH, Ghorbani M, et al. The Effect of High-Dose Vitamin C on Biochemical Markers of Myocardial Injury in Coronary Artery Bypass Surgery. *Brazilian J Cardiovasc Surg*. 2019;34(5):517-524. doi:https://dx.doi.org/10.21470/1678-9741-2018-0312	Not critically ill patients
33	Yanase F, Bitker L, Hessels L, Osawa E, Naorungroj T, Cutuli SL, Young PJ, Ritzema J, Hill G, Latimer-Bell C, Hunt A, Eastwood GM, Hilton A, Bellomo R. A Pilot, Double-Blind, Randomized, Controlled Trial of High-Dose Intravenous Vitamin C for Vasoplegia After Cardiac Surgery. J Cardiothorac Vasc Anesth. 2020 Feb;34(2):409-416. doi: 10.1053/j.jvca.2019.08.034. Epub 2019 Aug 24. PMID: 31526557.	Not critically ill patients (4% control group mortality)
34	Du WD, Yuan ZR, Sun J, et al. Therapeutic efficacy of high-dose vitamin C on acute pancreatitis and its potential mechanisms. World J Gastroenterol. 2003;9(11):2565-2569. doi:10.3748/wjg.v9.i11.2565	Not ICU patients
35	Crimi E, Liguori A, Condorelli M, et al. The beneficial effects of antioxidant supplementation in enteral feeding in critically ill patients: a prospective, randomized, double-blind, placebo-controlled trial. Anesth Analg. 2004;99(3):857-863. doi:10.1213/01.ANE.0000133144.60584.F6	Not IV. VIt E was given concomitantly

36	Raghu K, Ramalingam K. Safety and Efficacy of Vitamin C, Vitamin B1, and Hydrocortisone in clinical outcome of septic shock receiving standard care: A quasi experimental randomized open label two arm parallel group study. Eur J Mol Clin Med. 2021;8(2):873-891.	Not RCT
37	Nabil Habib T, Ahmed I (2017) Early Adjuvant Intravenous Vitamin C Treatment in Septic Shock may Resolve the Vasopressor Dependence. Int J Microbiol Adv Immunol. 05(1), 77-81. doi: http://dx.doi.org/10.19070/2329-9967-1700015	Pseudorandomized trial
38	Tanaka H, Matsuda T, Miyagantani Y, Yukioka T, Matsuda H, Shimazaki S. Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration: a randomized, prospective study. Arch Surg. 2000 Mar;135(3):326-31.	Pseudorandomized trial
39	Balakrishnan M, Gandhi H, Shah K, et al. Hydrocortisone, Vitamin C and thiamine for the treatment of sepsis and septic shock following cardiac surgery. Indian J Anaesth. 2018;62(12):934-939. doi:10.4103/ija.IJA_361_18	The number of mortality / number randomized in each group is not reported (Author did not respond to email)
40	Bansal D, Bhalla A, Bhasin DK, et al. Safety and efficacy of vitamin-based antioxidant therapy in patients with severe acute pancreatitis: a randomized controlled trial. Saudi J Gastroenterol. 2011;17(3):174-179. doi:10.4103/1319-3767.80379	VIt A and E was given concomitantly
41	Abdoulhossein D, Taheri I, Saba MA, Akbari H, Shafagh S, Zataollah A. Effect of vitamin C and vitamin E on lung contusion: A randomized clinical trial study. Ann Med Surg (Lond). 2018;36:152-157. Published 2018 Nov 9. doi:10.1016/j.amsu.2018.10.026	VIt E was given concomitantly
42	Reddy PR, Samavedam S, Aluru N, Yelle S, Rajyalakshmi B. Metabolic Resuscitation Using Hydrocortisone, Ascorbic Acid, and Thiamine: Do Individual Components Influence Reversal of Shock Independently?. Indian J Crit Care Med. 2020;24(8):649-652. doi:10.5005/jp-journals-10071-23515	No clinical outcome
43	Majidi N, Rabbani F, Gholami S, et al. The Effect of Vitamin C on Pathological Parameters and Survival Duration of Critically Ill Coronavirus Disease 2019 Patients: A Randomized Clinical Trial. Front Immunol. 2021;12:717816. Published 2021 Dec 15. doi:10.3389/fimmu.2021.717816	Not IV