9.2a Composition of Parenteral Nutrition: Glutamine Supplementation

Question: Compared to standard parenteral nutrition (PN), does glutamine-supplemented PN result in improved clinical outcomes in critically ill patients?

Summary of Evidence: There were 33 studies on IV glutamine supplementation included that were done in ICU patients ranging from pancreatitis, trauma, burns to sepsis. While in majority of the studies the intervention and control groups received parenteral nutrition/amino acids progressing to enteral nutrition, in three studies patients only received enteral nutrition (Palmese 2006, Ozgultekin 2008, and Eroglu 2009). In one study, the dosage of glutamine was questionably lower than the other studies (0.002 gm/kg/day, Yang 2007), while another only reported on data from a subgroup (Goeters 2002), hence these were not included in the meta-analyses. Additionally, we explored the effect of glutamine in trials where IV glutamine was given to patients who primarily were given EN vs. where the IV glutamine was given in the context of PN. Finally, we explored the treatment effect observed in multi-center trials compared to single center trials.[1]

Overall Mortality: Of the 30 studies that reported mortality, when the data from the 28 studies were aggregated, IV glutamine supplementation was associated with a trend towards a reduction in overall mortality (RR 0.87, 95% CI 0.75, 1.01, p =0.06, heterogeneity I^2=0%; figure 1) in patients on EN or PN. The following subgroup analyses were done:

> **EN vs PN:** In the studies in which patients received IV glutamine plus PN, glutamine supplementation was associated with a trend in the reduction in overall mortality (RR 0.86, 95% CI 0.73, 1.01, p=0.07, heterogeneity I^2=0%; figure 1). When the studies in which patients received IV glutamine and enteral nutrition (Palmese 2006, Luo 2008, Ozgultekin 2008, Eroglu 2009, Wischmeyer 2001) were aggregated, glutamine supplementation had no effect on overall mortality (RR 0.89, 95% CI 0.58, 1.38, p=0.61, heterogeneity I^2=0%; figure 1). The test for subgroup differences was not significant (p=0.88).
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> **Single vs Multi Centre:** In the 22 studies that were completed at a single centre, IV glutamine supplementation was associated with a significant reduction in overall mortality (RR 0.74, 95% CI 0.60, 0.92, p=0.006, heterogeneity I^2=0%; figure 2). In the 6 multi-centre studies, IV glutamine supplementation had no effect (RR 1.00, 95% CI 0.81, 1.23, p=0.98, heterogeneity I^2=0%; figure 2). Therefore, the signal towards reduced overall mortality in the glutamine supplemented group may be driven by the single centre studies. There was a trend in subgroup differences (p=0.05).

[1] We have explored the effects of free glutamine vs. dipeptides and isonitrogenous vs. non isonitrogenous feeding on outcomes but no differences were found and we have not included these data in this report. Data available upon request.

Hospital Mortality: In the 16 studies that reported hospital mortality, a significant reduction in hospital mortality was seen when the data were aggregated (RR 0.69, 95% CI 0.52, 0.90, p=0.007, heterogeneity I^2=0%; figure 3). The following subgroup analyses were done:

EN vs. PN: IV glutamine supplementation in the PN based studies was associated with a significant reduction in hospital mortality (RR 0.70. 95% CI 0.53, 0.92, p=0.01, test for heterogeneity I^2=0%; figure 3). Only one of the two EN based trials had any deaths and there was no effect on mortality (RR 0.29, 95% CI 0.04, 2.27, p=0.24, figure 3). The test for subgroup differences was not significant (p=0.41).

Single vs Multi Centre: In the 13 studies that were completed at a single centre, IV glutamine supplementation was associated with a significant reduction in hospital mortality (RR 0.65, 95% CI 0.48, 0.89, p=0.006, heterogeneity I^2=0%; figure 4). In the 3 multi-centre studies, IV glutamine supplementation had no effect (RR 0.85, 95% CI 0.46, 1.55, P=0.59, heterogeneity I^2=0%; figure 4). Therefore, the signal towards reduced hospital mortality in the glutamine supplemented group may be driven by the single centre studies. The test for subgroup differences was not significant (p=0.45).

Infections: When the 17 studies which reported infectious complications were aggregated, glutamine supplementation was associated with a trend towards a reduction in infectious complications (RR 0.89, 95% CI 0.79, 1.01, p=0.08, heterogeneity I^2 = 27%; figure 5). The following subgroup analyses were explored:

EN vs. PN: For the subgroup of studies in which patients received IV glutamine plus PN, glutamine supplementation had no effect on infectious complications (RR 0.91, 95% CI 0.79, 1.04, p=0.18, heterogeneity I^2 = 33%; figure 5). However, for the subgroup of studies in which patients received IV glutamine and were on enteral nutrition (Palmese 2006, Eroglu 2009. Wischmeyer 2001), glutamine supplementation was associated with a trend towards a reduction in infectious complications (RR 0.75, 95% CI 0.53, 1.06, p=0.11, heterogeneity I^2=0%; figure 5). The test for subgroup differences was not significant (p=0.32).

Single vs Multi Centre: In the 12 studies that were completed at a single centre, IV glutamine supplementation was associated with a significant reduction in infections (RR 0.81, 95% CI 0.68, 0.96, p=0.01, heterogeneity I^2=10%; figure 6). In the 5 multi-centre studies, IV glutamine supplementation had no effect (RR 0.99, 95% CI 0.84, 1.17, p=0.92, heterogeneity I^2=34%; figure 6). Therefore, the signal towards reduced hospital mortality in the glutamine supplemented group may be driven by the single centre studies. The test for subgroup differences was consistent with a trend (p=0.09).

Pneumonia: When the 8 studies which reported pneumonia were aggregated, overall glutamine supplementation showed a trend towards a reduction (RR 0.83, 95% CI 0.64, 1.08, p=0.17, heterogeneity I^2=0%; figure 7). The following subgroup analyses were explored:

EN vs. PN: Glutamine supplementation had no effect on pneumonia in PN fed patients (RR 0.86, 95% CI 0.66, 1.11, p=0.25, heterogeneity I^2=0%; figure 7) or EN fed patients (RR 0.44, 95% CI 0.11, 1.67, p=0.23, heterogeneity I^2=0%; figure 7). The test for subgroup differences was not significant (p=0.33).

Single vs Multi Centre: IV glutamine supplementation had no effect on pneumonia in the single centre trials (RR 0.83, 95% CI 0.57, 1.22, p=0.34, heterogeneity I^2=0%; figure 8) or multicentre trials (RR 0.81, 95% CI 0.50, 1.29, p=0.37, heterogeneity I^2=39%; figure 8). The test for subgroup differences was not significant (p=0.92).

ICU LOS: Fifteen studies reported ICU length of stay as a mean ± standard deviation and when the studies were aggregated, glutamine supplementation was associated with a significant reduction in ICU LOS (WMD -2.10, 95% CI -4.10,-0.11, p=0.04, heterogeneity I^2=91%; figure 9). The following subgroup analyses were explored:

EN vs. PN: Glutamine supplementation was associated with a trend towards a reduction in ICU LOS for the subgroup of studies in which patients received IV glutamine plus PN (WMD -2.60, 95% CI -5.59, 0.39, p=0.09, heterogeneity I^2=88%; figure 9) but had no effect in patients on EN (WMD -0.47, 95% CI -1.84, 0.90, p=0.50, heterogeneity I^2= 68%; figure 9). The test for subgroup differences was not significant (p=0.21).

Single vs Multi Centre: There were 12 single centre studies that reported ICU LOS and when statistically aggregated, they showed a significant reduction in ICU LOS (WMD -2.60, 95% CI -4.65, -0.54, p=0.01, heterogeneity I^2=91%; figure 10). Only 1 multicentre study reported on ICU LOS as mean ± standard deviation (Zeigler 2013) and suggested a trend towards increased ICU LOS (WMD 3.90, -0.10, 7.90, p=0.06; figure 10). The test for subgroup differences was significant (p=0.005).

Hospital LOS: When the 12 studies that reported hospital length of stay as a mean ± standard deviation were aggregated, glutamine supplementation was associated with a significant reduction in hospital LOS (WMD -2.72, 95% CI -4.31, -1.13, p=0.0008, heterogeneity I^2 = 62%; figure 11). The following subgroup analyses were explored:

EN vs. PN: Only one of the 6 studies in which patients only received enteral nutrition reported on hospital LOS and showed no effect of glutamine supplementation (RR 0.00, 95% CI -7.36, 7.36, p=1.0; figure 11). IV glutamine supplementation was associated with a significant reduction in hospital LOS when the data from the PN based studies were aggregated (RR -2.83, 95% CI -4.47, -1.18, p=0.0008, test for heterogeneity I^2=65%; figure 11). Test for subgroup differences was not significant (p=0.46).
Single vs Multi Centre: There were 11 single centre studies that reported hospital LOS and when statistically aggregated, they showed a significant reduction in hospital LOS (WMD -2.95, 95% CI -4.54, -1.37, p=0.0003, heterogeneity I^2=63%; figure 12). Only 1 multicentre study reported on hospital LOS as mean ± standard deviation (Zeigler 2013) and glutamine supplementation had no effect on hospital LOS (WMD 3.90, -3.98, 11.78, p=0.33; figure 12). The test for subgroup differences was p=0.09.

Mechanical Ventilation: When the data from the 11 studies that reported on mechanical ventilation were aggregated, glutamine supplementation was associated with a significant reduction in the duration (WMD -2.16, 95% CI -3.89, -0.43, p=0.01, test for heterogeneity 1^2 = 86%; figure 13). The following subgroup analyses were explored:

EN vs. PN: IV glutamine supplementation was associated with trend towards a reduction in mechanical ventilation duration in the studies in which patients were fed via PN (WMD -3.10, 95% CI -6.32, 0.11, p=0.06, test for heterogeneity I^2 =86%; figure 13). IV glutamine supplementation had no effect on mechanical ventilation in the studies of EN fed patients (WMD -0.46, 95% CI -1.94, 1.03, p=0.55, test for heterogeneity I^2 =76%; figure 13). There was a trend towards a difference between the subgroups (p=0.14).

Single vs Multi Centre: None of the 11 studies that reported on mechanical ventilation were multicentre, hence a subgroup analysis was not done.

Quality of Life: Powell Tuck et al asked patients about their perceived morbidity and quality of life at entry in the trial and when PN stopped. Though all modalities improved within each group (p<0.0001), there was no statistical difference between groups. Andrews et al completed the SF-12 physical and mental composite scale score and the EQ-5D instrument at 3 and 6 months with survivors and found no significant different between scores.

Conclusions:

1) IV glutamine supplementation may be associated with a reduction in overall mortality, infectious complications, ICU and hospital length of stay but the observed treatment effect is observed exclusively in small, single center studies.
2)There is no difference between IV glutamine supplementation given as free glutamine vs dipeptides or isonitrogenous vs. non isonitrogenous feeding.
3) IV glutamine supplementation has no effect on quality of life in the critically ill.

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 glutamine (PN) in critically ill patients

Study	Population	Methods (score)	Intervention Dose of Lglutamine gm/kg/day	Mortality # (%)† Experimental vs. Control	Infections # (%)‡ Experimental vs. Control	Length of stay (days) Experimental vs. Control	Length of Ventilation (days) Experimental vs. Control
1) Griffiths 1997 & 2002	Single-centre, mixed ICU patients N=84	C.Random: yes ITT: yes Blinding: double (11)	PN and 0.26 IV L-glutamine vs. PN Isocaloric, isonitrogenous	**Hospital** 18/42(43) vs. 25/42(60)	28/42 (67) vs. 26/42 (62)	**ICU** 10.5 (6-19)* vs. 10.5 (6-24)*	NR
2) Powell-Tuck 1999	Single-centre, mixed ICU/hospital patients N=168	C.Random: yes ITT: yes Blinding: double (8)	0.26 IV free glutamine mixed into PN vs. PN, isocaloric, non-isonitrogenous.	**Hospital** 14/83(17) vs. 20/85(24)	NR	**Hospital** 43.4 ± 34.1 (83) vs. 48.9 ± 38.4 (85)	NR
3) Wischmeyer 2001	Single-centre, critically ill burns N=31	Random: not sure ITT: no Blinding double (8)	0.57 IV L-glutamine and EN or EN+PN vs. AAcids + PN or EN or EN+PN Non isonitrogenous, isocaloric	**Hospital** 1/12 (8) vs. 4/14 (29)	7/12 (58) vs. 9/14 (64)	**Hospital** 40 ± 10 (12) vs. 40 ± 9 (14)	NR
4) Goeters 2002*	Single-centre, surgical ICU patients N=68	C.Random: not sure ITT: no Blinding: no	0.2 IV L-alanyl-L-glutamine + PN or EN or EN+PN vs PN or EN or EN+PN. Non-isonitrogenous.	**ICU** 7/33 (21)* vs.10/35 (29)* **30-day** 7/33 (21)* vs. 11/35 (31)* **6-month** 11/33 (33)* vs. 21/35 (60)*	NR	**ICU (avg)** 21.3 ± 13.5 (33)* vs. 20.8 ± 9.1 (35)* **Hospital (avg)** 46 ± 49.1 (33)* vs. 39.4 ± 31.1 (35)*	NR

5) Carrol 2004	Single center, N=19	C. Random: no ITT: yes Blinding: no (9)	PN with IV gln (L-glutamine 0.4 g/kg/d) vs standard PN. Isocaloric, non-isonitrogenous.	**Hospital** 0/7 vs. 0/7 **ICU** 0/7 vs. 0/7	NR	NR	NR
6) Fuentes-Oroczo 2004	Single-centre, secondary peritonitis requiring TPN N=33	C.Random: yes ITT: yes Blinding: double (11)	PN with added 0.27 L-alanyl-L-glutamine vs. PN, isocaloric, isonitrogenous	**Hospital** 2/17 (12) vs.3/16 (19)	4/17 (23) vs. 12/16 (75)	**ICU** 7.2 ± 9.2 (17) vs. 7.3 ± 4.5 (16) **Hospital** 16.5 ± 8.9 (17) vs. 16.7 ± 7 (16)	4.88 ± 8.2 (17) vs. 4.47 ± 4.4 (16)
7) Zhou 2004	Single-centre Severe burns N=30	C.Random: yes ITT: yes Blinding: double (11)	0.35 IV glutamine (given as 0.5 g/kg/d L-alanyl-L-glutamine) + PN vs. PN, isocaloric, isonitrogenous.	NR	3/15 (20) vs. 4/15 (26)	**Hospital** 42 ± 7.0 (15) vs. **46 ± 6.6 (15)**	NR
8) Xian-Li 2004	Single-centre, severe acute pancreatitis N=69	C.Random: yes ITT: no Blinding: no (5)	0.4 IV L-alanyl-L-glutamine + PN vs. PN. Nonisonitrogenous	**Hospital** 0/20 (0) vs. 3/21 (14)	**# Complications** 4/20 vs. 11/21	**Hospital** 25.3 ± 7.6 (20) vs. 28.6 ± 6.9 (21)	NR
9) Dechelotte 2006	Multi-centre, Multiple trauma, surgery,sepsis, pancreatitis from 16 ICUs N=114	C.Random: NR ITT: yes Blinding: double (N/A)	0.35 IV glutamine (given as 0.5 g/kg/d L-alanyl-L-glutamine) + PN vs. PN + L-alanine and L-proline. isocaloric, isonitrogenous.	**Hospital** 2/58 (3) vs. 2/56 (3) **6-month** 16/58 (28) vs. 9/56 (16)	**All** 23/58 (40) vs. 32/56 (58) **Pneumonia** 10/58 (17) vs. 19/56 (34)	**ICU** 12.5 (1-430) vs. 11.5 (3-121) **Hospital** 30 (1-560) vs. 26 (4-407)	NR
10) Palmese 2006	Single-centre, mixed ICU N=84	C.Random: yes ITT: yes Blinding: outcomes assessors (10)	0.14 IV free glutamine + EN with FOS vs. EN without FOS. Unable to tell if isonitrogenous with glutamine.	**ICU** 6/42 (14) vs. 8/42 (19)	**All** 13/42 (31) vs. 21/42 (50) **Pneumonia** 2/42 (5) vs. 6/42 (14)	**ICU** 12 ± 4.6 (42) vs. 13 ± 3.4 (42)	6 ±1.7 (42) vs. 5 ±2.5 (42)

11) Tian 2006	Single-centre, MODS N=40	C.Random: not sure ITT: yes Blinding: no (6)	PN + 0.27 IV glutamine (given as 0.4 g/kg/d L-alanyl-L-glutamine) vs PN. Nonisonitrogenous.	**Unspecified** 2/20 (10) vs.5/20 (25)	NR	NR	NR
12) Sahin 2007	Single-centre, acute pancreatitis N=40	C.Random: not sure ITT: yes Blinding: not sure (9)	0.3 L-alanyl-L-glutamine PN vs. PN, Non-isonitrogenous.	**Hospital** 2/20 (10) vs.6/20 (30)	NR	**Hospital** 14.2 ± 4.4 (20) vs. 16.4 ± 3.9 (20)	NR
13) Yang 2007α	Single-centre, Brain injury Neurosurgical ICU N=46	C.Random: not sure ITT: yes Blinding: no (6)	0.002 IV glutamine dipeptide + PN vs. PN. Unable to tell if isonitrogenous.	**Hospital** 5/23 (22) vs.9/23 (39)	NR	**ICU** 10 ± 3.5 (23) vs. 18 ± 5.6 (23)	NR
14) Zhang 2007	Single centre Emergency and neurosurgical ICU, pts requiring PN for >7 days N=44	C.Random: not sure ITT: yes Blinding: no (6)	EN and PN + IV glutamine (Chinese article, unable to tell) 0.4 g/kg/day vs EN and PN alone. Unable to tell if isonitrogenous	NR	NR	**ICU** 11.73 ±6.57 (22) vs. 13.39 ±5.08 (22)	5.27±1.78 (22) vs. 7.18 ±2.76 (22)
15) Cai 2008	Single-centre, elderly, severe sepsis N=110	C.Random: not sure ITT: yes Blinding: no (10)	PN or PN & EN with 0.19 IV L-alanyl-L-glutamine (10 g/d) Patients received vs PN or EN + PN non-isonitrogenous	**28-day** 17/55 (31) vs. 20/55 (36)	NR	**ICU** 22.1 ± 4.9 (55) vs. 23.8 ± 5.1 (55)	15.6±5.7 (55) vs. 17.2±5.9 (55)
16) Duska 2008 ∂	Single-centre, trauma N=30	C.Random: not sure ITT: yes Blinding: HCPs (8)	EN or EN & PN + 0.3 IV L-alanyl-Lglutamine vs. EN or EN+PN w normal saline + non-isonitrogenous	**ICU** 2/10 (20) vs.0/10 (0)	NR	**ICU** 23 (median) vs. 24 (median)	NR

17) Estivariz 2008	Single-centre, pancreatic and non pancreatic surgery N=63	C.Random: not sure ITT: no** Blinding: double (9)	0.5 L-alanyl-L-glutamine containing PN vs. Glutamine-free PN. isocaloric, isonitrogenous	**Hospital** 1/32 (3) vs. 6/31 (19)	**Pneumonia** 13/30 (43) vs. 16/29 (55)	**ICU** 12 ± 2 (32) vs. 23 ± 6 (31) **Hospital** 20 ± 2 (32) vs. 30 ± 6 (31)	9±2 (15) vs.21±5 (12)
18) Fuentes-Oroczo 2008	Single-centre, Acute pancreatitis requiring admission N=44	C.Random: not sure ITT: yes Blinding: double (12)	0.4 g/kg/d L-alanyl-L-glutamine in PN vs. PN isocaloric, isonitrogenous	**ICU** 2/22 (9) vs. 5/22 (23)	9/22 (41) vs. 16/22 (73)	**ICU** 11 ± 11.7 (22) vs. 11.14 ± 7.41 (22) **Hospital** 30.18 ± 10.42 (22) vs. 26.59 ± 13.3 (22)	NR
19) Luo 2008* **	Single-centre, medical surgical N=44	C.Random: not sure ITT: no Blinding: double (9)	0.50 g/kg/d IV L-alanyl-L-glutamine + EN vs.. IV 15% Clinisol (placebo) +EN isocaloric, isonitrogenous	**Hospital** 0/11 (0) vs.0/9 (0)	NR	**ICU** 7.6 ± 0.7 (14) vs. 6.9 ± 0.9 (9)	5±1 (14) vs. 6±1 (9)
20) Perez-Barcena 2008	Single-centre, mixed ICU N=30	C.Random: not sure ITT: yes Blinding: outcomes assessors (10)	0.35 IV gln (given as 0.5 g/kg/d L-alanyl-L-glutamine) + PN vs. PN isocaloric, isonitrogenous	**Hospital** 3/15 (20) vs. 0/15 (0)	11/15 (73) vs. 13/15 (87)	**ICU** 22.9 ± 20.6 (15) vs. 20.5 ± 16.0 (15) **Hospital** 35.5 ± 33.6 (15) vs. 42.9 ± 28.8 (15)	14±10 (15) vs. 14±10 (15)
21) Ozgultekin 2008	Single-centre, CHI & GCS pts, ventilated, sedated, mean APACHE II 18-19 N=60	C.Random: not sure ITT: no Blinding: none (4)	EN + 0.2-0.4g/kg/d IV gln (given as 20 g L-alanyl-L-glutamine) vs. EN. Nonisonitrogenous	**30-day** 12/20 (60) vs. 12/20 (60)	NR	**ICU** 11.8 ± 5.9 (20) vs. 17.3 ± 16.4 (20)	10.1±4.4 (20) vs. 14.4 ±14 (20)

22) Yang 2008	Single-centre, severe pancreatitis N=61	C.Random: not sure ITT: no Blinding: single (4)	PN + IV L-alanyl-L-glutamine (dose unknown) vs PN + saline (Chinese article, unable to get further info)	**Hospital** 1/25 (4) vs. 3/25 (12)	NR	**Hospital** 13.48 ± 1.42 (25) vs. 15.18 ± 1.14 (25)	NR
23) Eroglu 2009	Single-centre, severe trauma, ISS>20 N=40	C.Random: yes ITT: yes Blinding: double (12)	EN + 0.5 g/kg/d IV L-alanyl-L-glutamine vs EN, saline. Nonisonitrogenous, nonisocaloric.	**ICU** 1/20 (5) vs. 1/20 (5)	**Overall** 8/20 (40) vs. 10/20 (50) **VAP** 1/20 (5) vs. 1/20 (5)	**ICU** 14 ± 2 (20) vs. 15 ± 2 (20)	8±3 (20) vs. 9±3 (20)
24) Perez-Barcena 2010	Single-centre, trauma pt ISS >12, requires PN based on ASPEN N=43	C.Random: not sure ITT: yes Blinding:Outcomes assessors (6)	PN, 0.35 g/kg/d IV glutamine (given as 0.5 g/kg/d L-alanyl-L-glutamine) vs PN. Isocaloric, isonitrogenous	**ICU** 4/23 (17) vs.2/20 (10) **Hospital** 4/23 (0) vs. 3/20 (5)	**Pneumonia** 11/23 (48) vs. 8/20 (40)	**ICU** 21 (17-25) vs. 21 (14-47) **Hospital** 31 (19-42) vs. 40 (24-80)	15.2±8.2 (23) vs. 18.9±11.1 (20)
25) Andrews 2011	Multi-centre, critically ill adults, 25% medical pts, from 10 centres N=502	C. Random: yes ITT: yes Blinding: double (13)	PN containing 0.2-0.4 g/kg/day (20.2 g/day x 7 days) vs.PN isocaloric, isonitrogenous (unknown gln form)	**ICU** 88/250 (35) vs. 80/252 (32) **6-month** 115/250 (46) vs. 106/252 (42)	134/250 (54) vs. 131/252 (52)	**ICU** 15 (7.9-28.4) vs. 13.4(8.2-23.9) **Hospital** 32.5 (14.7-55.6) vs. 28.2 (15.1-52.4)	NR
26) Cekman 2011	Single-centre, mixed surgical ICU, ISS ≥ 10, APACHE II >10 N=30	C.Random: yes ITT: yes Blinding: double (10)	PN containing 0.5 g/kg/d L-alanyl-L-glutamine vs PN (nonisonitrogenous)	**ICU (presumed)** 3/15 (20) vs. 6/15 (40)	NR	**ICU** 19.2 ± 12 (15) vs. 27.4 ± 12 (15)	NR

27) Grau 2011	Multi-centre, mechanically ventilated, APACHE II >12, need TPN N=127	C.Random: not sure ITT: yes Blinding: double (11)	PN, 0.5 g/kg/d L-alanyl-L-glutamine IV glutamine vs PN. Isonitrogenous, isocaloric.	**ICU** 9/59 (15) vs. 13/68 (19) **6-month** 16/59 (27) vs. 23/68 (34)	**All** 24/59 (41) vs. 31/68 (46) **Surgical** 13/59 (22) vs. 17/68 (25) **Pneu (#/1000 vent days)** 13.5 vs. 27.2 **# infect/pt** 1.5 vs. 2.4	**ICU** 12 (7-22) vs. 12 (7-24) **Hospital** 35 (23-56) vs. 31 (20-58)	NR
28) Wernerman 2011	Multi-centre, mixed ICU, APACHE II ≥10 N=413	C.Random: yes ITT: yes Blinding: double (11)	EN or PN, 0.28 g/kg/day IV glutamine (given as L-alanyl-L-glutamine) vs EN or PN, normal saline IV. Nonisocaloric, nonisonitrogenous	**ICU** 8/205 (4) vs. 11/208 (5) **28-day** 14/205 (7) vs. 20/208 (10)	NR	NR	NR
29) Grintescu 2014	Single center, trauma pts N=97	C. Random: yes ITT: no Blinding: no (7)	EN + PN, L-alanyl-L-glutamine dipeptide (0.5 g/kg/day) vs EN + PN w standard amino acid solution (0.5 g/kg/day as Aminoven 10%; Fresenius Kabi). Isonitrogenous, isocaloric.	**ICU** 4/48 (8) vs. 4/49 (8)	**All** 10/41 (24) vs. 14/41 (34)	**NR**	NR
30) Koksal 2014* **	Single centre, Septic, malnourished ICU patients N=60	C.Random: yes ITT: other Blinding: single (outcomes) (9)	30 g/day parenteral glutamine (dipeptides) + EN vs EN, no placebo, no supplemental glutamine	NR	NR	NR	13±12.2 (30) vs. 14.3±5.4 (30)

31) Perez-Barcena 2014	Multi-center, trauma ICU N=142	C. Random: yes ITT: yes Blinding: double (13)	EN or PN, L-alanyl-L-glutamine dipeptide (0.5 g/kg/d = 0.35 g of L-glutamine/kg /d) vs EN or PN w placebo. Non-isonitrogenous, non-isocaloric.	**Hospital** 4/71 (6) vs. 5/71 (7) **ICU** 3/71 (4) vs. 3/71 (4)	**Any** 45/71 (63) vs. 44/71 (62) **Respiratory** 37/71 (52) vs. 33/71 (47) **Pneumonia** 23/71 (32) vs. 21/71 (30)	**ICU** 14 (8-28) vs. 14 (7-24) **Hospital** 29 (17-47) vs. 27 (16-46)	9.0 (3-18) vs. 9.5 (5-18.5)
32) Ziegler 2016	Multi-center, N=150	C. Random: yes ITT: yes Blinding: double (12)	PN containing 0.5 gm/kg/day L-alanyl-L-glutamine vs. PN, isocaloric. Isonitrogenous.	**Hospital** 11/75 (15) vs. 13/75 (17)	**Any** 33/75 (44) vs. 24/75 (32) **Pneumonia** 10/75 (13) vs. 12/75 (16)	**ICU** 17.5 ± 14.6 (75) vs. 13.6 ± 10 (75) **Hospital** 33.6 ± 28 (75) vs. 29.7 ± 20.7 (75)	NR
33) Liu 2016	Single centre, acute pancreatitis requiring PN N=47	C. Random: not sure ITT: yes Blinding: no (4)	PN containing glutamine (dose not reported) vs. Standard PN Unclear if isonitrogenous, isocaloric or not	1/24 (4.2%) vs.4/23 (17.4%)	**Pneumonia** 3/24 (12.5%) vs. 5/23 (21.7%)	**ICU** 11.5 ± 2.0 (24) vs. 15.2 ± 2.0 (23) **Hospital** 20 ± 2.4 (24) vs. 23 ± 2.03 (23)	NR

C.Random: Concealed randomization median (range)
ITT: Intent to treat
NR: Not reported
EN: Enteral nutrition; TPN Total parenteral nutrition
± ( ) : Mean ± Standard deviation (number)
† Hospital mortality unless stated otherwise
‡ Number of patients with infections unless stated otherwise
* Data from a sub group, hence not included in meta-analysis
** Data for mortality is ITT, infections is non-ITT.
*** Data from EN glutamine group not shown here, appears in EN glutamine section
α Unable to confirm the low dose from authors (0.002 gm/kg/day) hence data not included in the meta-analyses
∂ Data from growth hormone group not shown here

Ozgultekin 2008: data presented here only pertains to glutamine supplemented group and standard group, refer to section 9.1 Branched Chain Amino Acids (BCAA) for data pertaining to BCAA vs standard.

Table 2. QOL Outcomes

Study	QOL Outcomes
2) Powell Tuck 1999	**Perceived morbidity/quality of life scores – patients were asked to score mood, sleep, energy, appetite, pain and mobilisation on a 10 point scale** **Measured at entry into trial and when PN stopped** All modalities improved (p<0.0001 for each) but no statistical difference between groups.
25) Andrews 2011	**Gln** / **Gln+Se** / **Se** / **Neither** **SF-12 PCS at 3 months** 35.2 ± 9.8 (49) / 33.3 ± 11.1 (50) / 33.9 ± 9.8 (52) / 36.6 ± 11.6 (59) **SF-12 PCS at 6 months** 35.9 ± 9.3 (45) / 35.9 ± 10.9 (43) / 36.3 ± 10.0 (46) / 39.9 ± 10.5 (53) **SF-12 MCS at 3 months** 420 ± 11.8 (49) / 40.3 ± 12.0 (50) / 41.9 ± 11.9 (52) / 42.2 ± 12.2 (59) **SF-12 MCS at 6 months** 43.4 ± 11.9 (45) / 44.8 ± 11.9 (43) / 44.1 ± 11.6 (46) / 43.3 ± 12.1 (53) **EQ-5D at 3 months** 0.47 ± 0.41 (52) / 0.51 ± 0.35 (52) / 0.49 ± 0.35 (55) / 0.56 ± 0.34 (61 **EQ-5D at 6 months** 0.53 ± 0.35 (49) / 0.60 ± 0.30 (51) / 0.53 ± 0.33 (47) / 0.63 ± 0.28 (55)

Figure 1. Overall Mortality (EN vs PN)

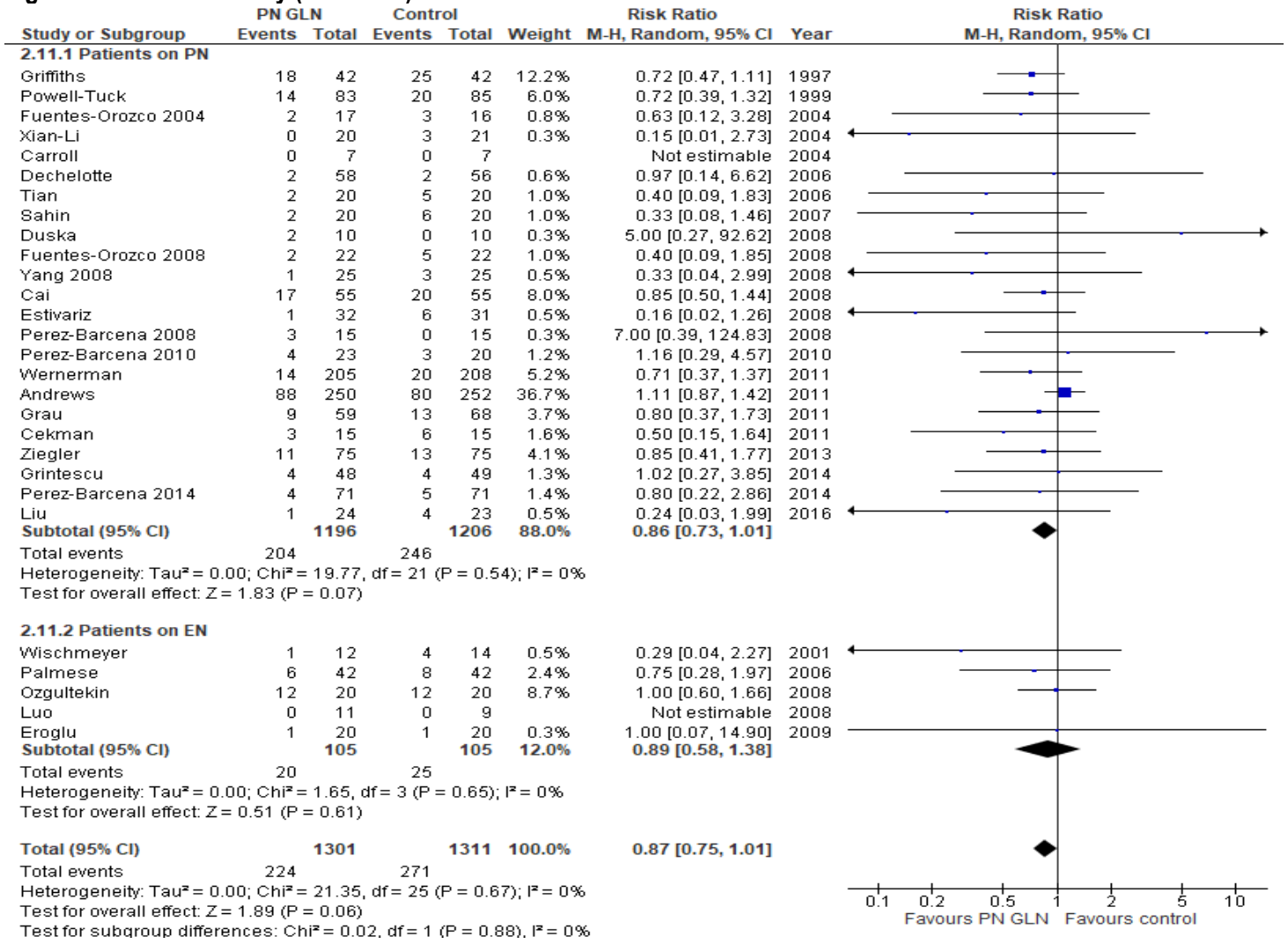


Figure 2. Overall Mortality (Single vs Multi Centre)

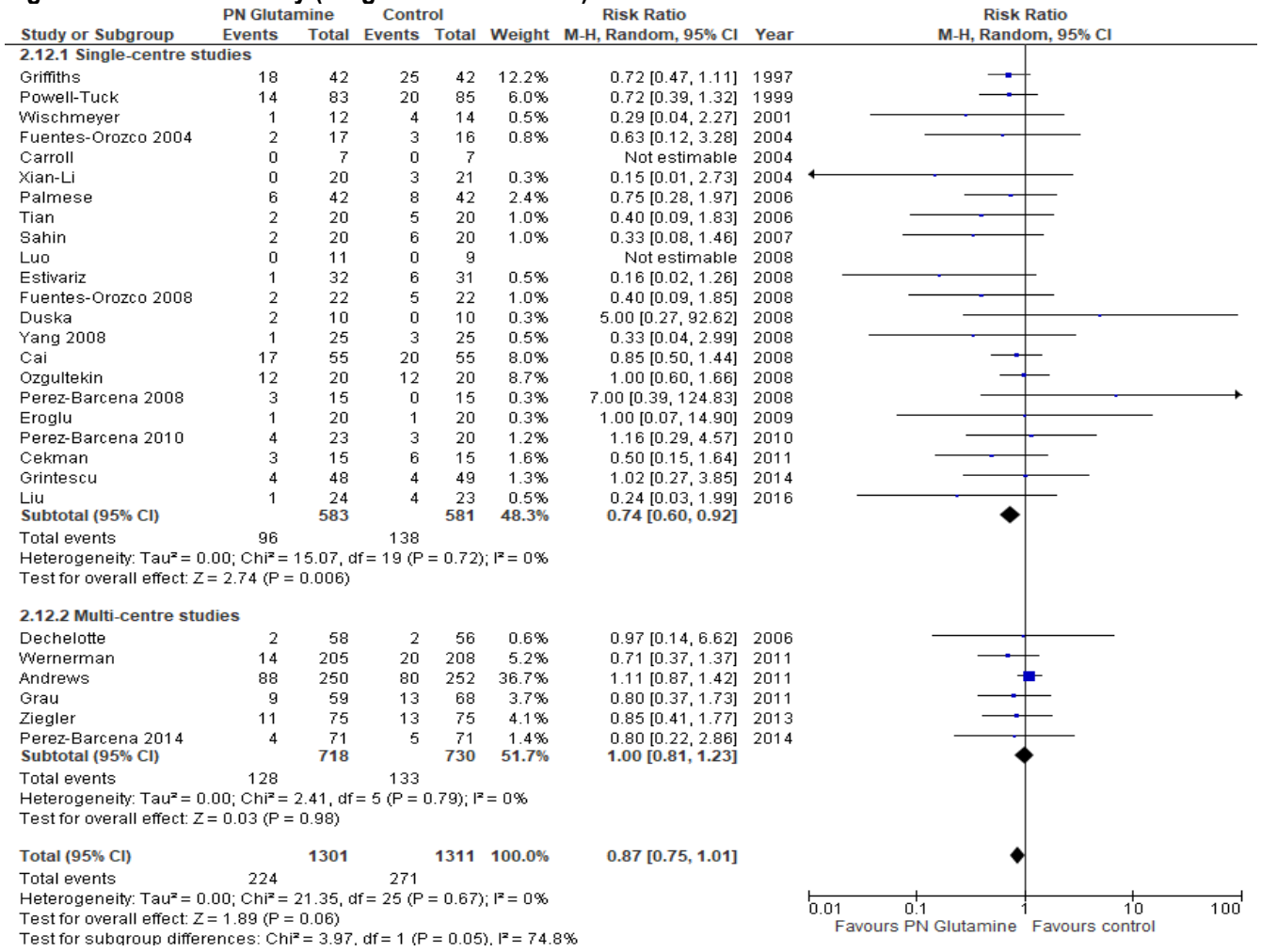


Figure 3. Hospital Mortality (EN vs. PN)

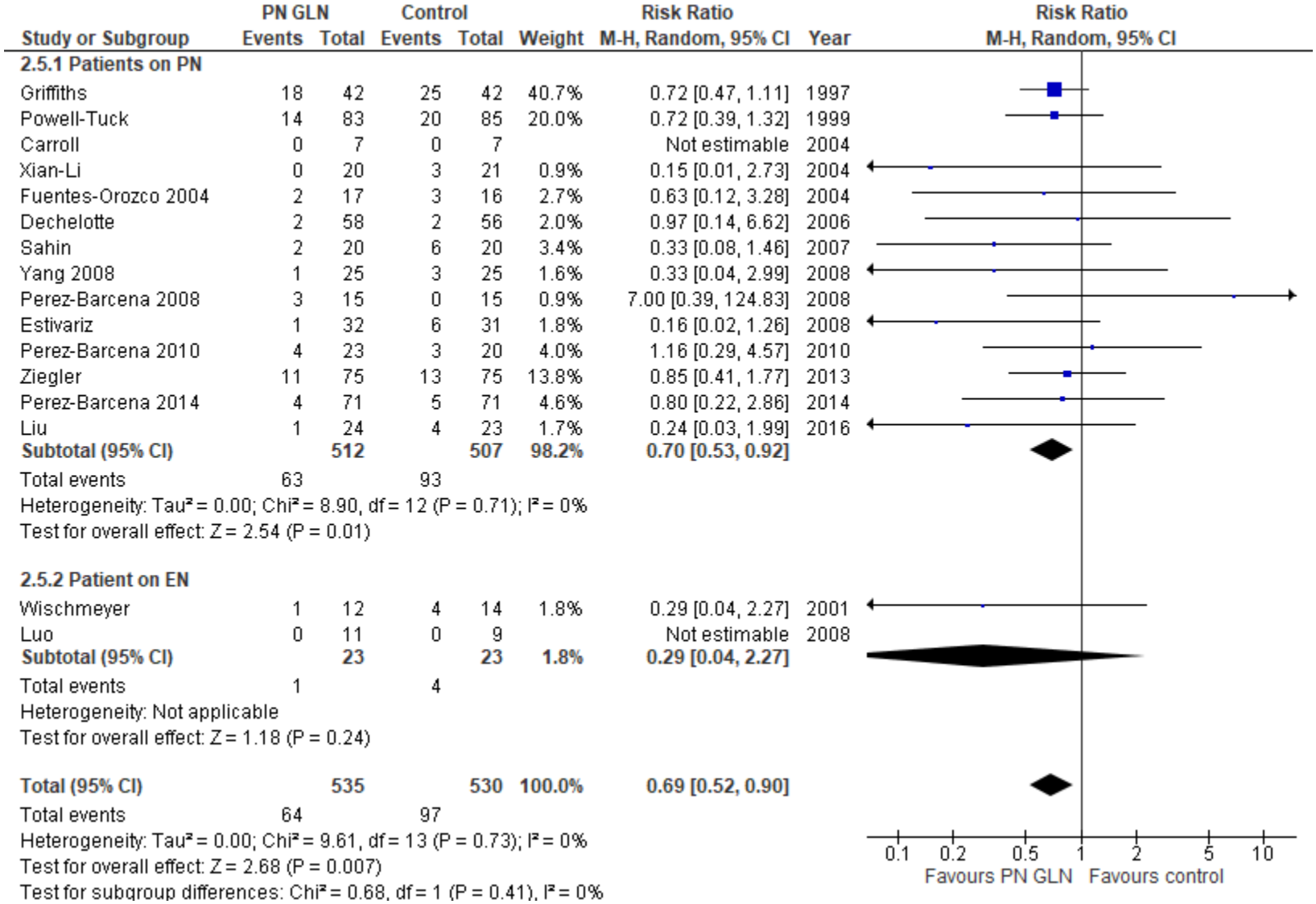


Figure 4. Hospital Mortality (Single vs Multi Centre)

Study or Subgroup	PN Glutamine Events	PN Glutamine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
2.6.1 Single Centre studies							
Griffiths	18	42	25	42	40.7%	0.72 [0.47, 1.11]	1997
Powell-Tuck	14	83	20	85	20.0%	0.72 [0.39, 1.32]	1999
Wischmeyer	1	12	4	14	1.8%	0.29 [0.04, 2.27]	2001
Fuentes-Orozco 2004	2	17	3	16	2.7%	0.63 [0.12, 3.28]	2004
Xian-Li	0	20	3	21	0.9%	0.15 [0.01, 2.73]	2004
Carroll	0	7	0	7		Not estimable	2004
Sahin	2	20	6	20	3.4%	0.33 [0.08, 1.46]	2007
Luo	0	11	0	9		Not estimable	2008
Yang 2008	1	25	3	25	1.6%	0.33 [0.04, 2.99]	2008
Perez-Barcena 2008	3	15	0	15	0.9%	7.00 [0.39, 124.83]	2008
Estivariz	1	32	6	31	1.8%	0.16 [0.02, 1.26]	2008
Perez-Barcena 2010	4	23	3	20	4.0%	1.16 [0.29, 4.57]	2010
Liu	1	24	4	23	1.7%	0.24 [0.03, 1.99]	2016
Subtotal (95% CI)		**331**		**328**	**79.5%**	**0.65 [0.48, 0.89]**	
Total events	47		77				
Heterogeneity: Tau² = 0.00; Chi² = 9.08, df = 10 (P = 0.52); I² = 0%							
Test for overall effect: Z = 2.73 (P = 0.006)							
2.6.2 Multi-center studies							
Dechelotte	2	58	2	56	2.0%	0.97 [0.14, 6.62]	2006
Ziegler	11	75	13	75	13.8%	0.85 [0.41, 1.77]	2013
Perez-Barcena 2014	4	71	5	71	4.6%	0.80 [0.22, 2.86]	2014
Subtotal (95% CI)		**204**		**202**	**20.5%**	**0.85 [0.46, 1.55]**	
Total events	17		20				
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 2 (P = 0.99); I² = 0%							
Test for overall effect: Z = 0.54 (P = 0.59)							
Total (95% CI)		**535**		**530**	**100.0%**	**0.69 [0.52, 0.90]**	
Total events	64		97				
Heterogeneity: Tau² = 0.00; Chi² = 9.61, df = 13 (P = 0.73); I² = 0%							
Test for overall effect: Z = 2.68 (P = 0.007)							
Test for subgroup differences: Chi² = 0.57, df = 1 (P = 0.45), I² = 0%							

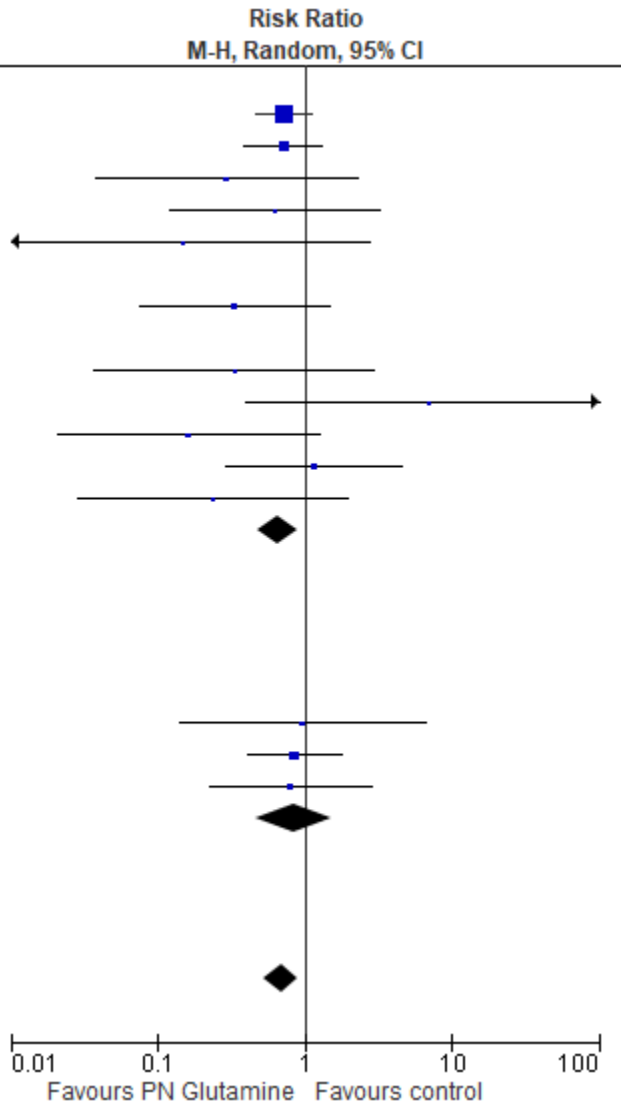


Figure 5. Infectious Complications (EN vs. PN)

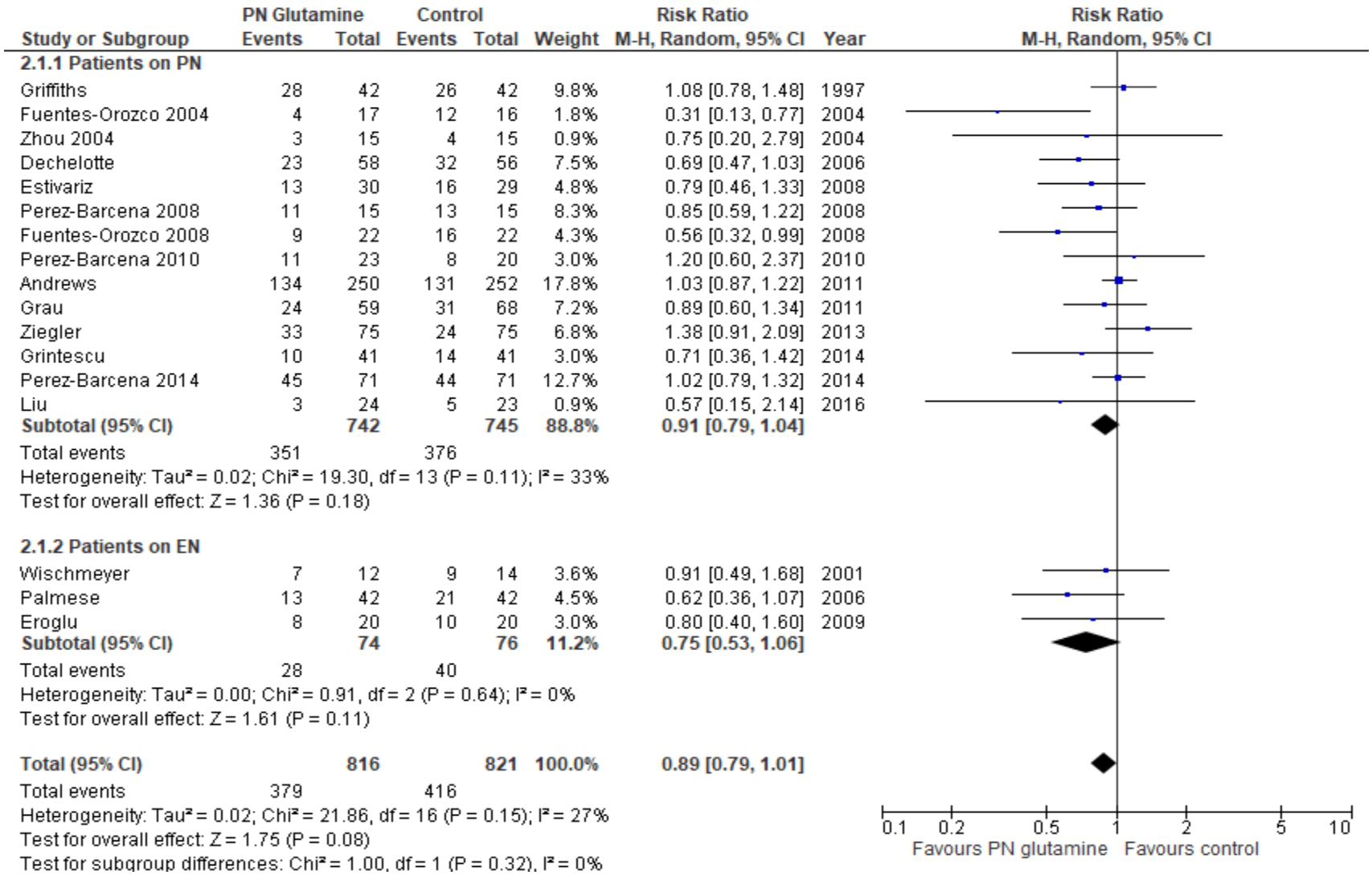


Figure 6. Infectious Complications (Single vs. Multicentre)

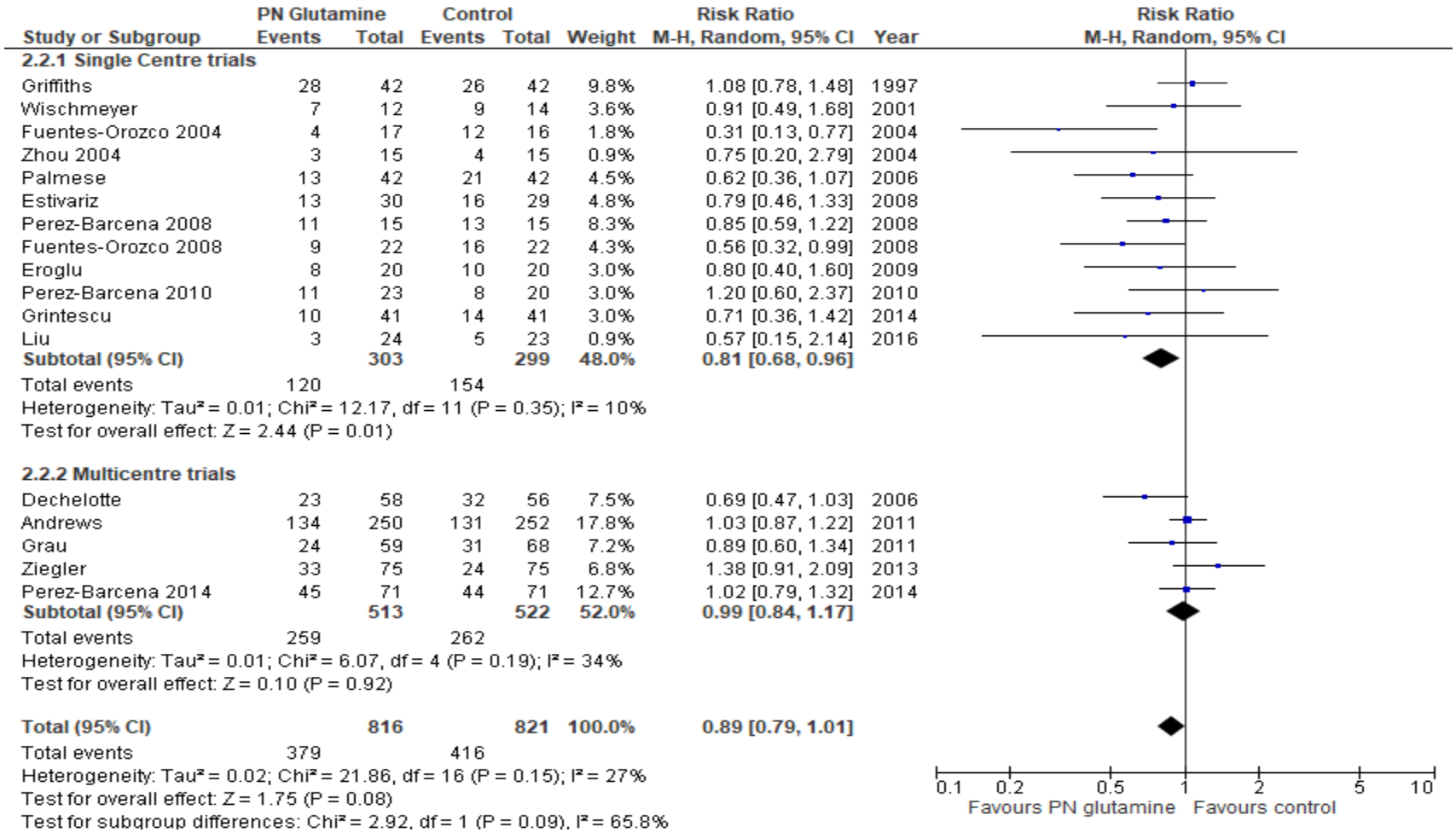


Figure 7. Ventilator Associated Pneumonia (EN vs. PN)

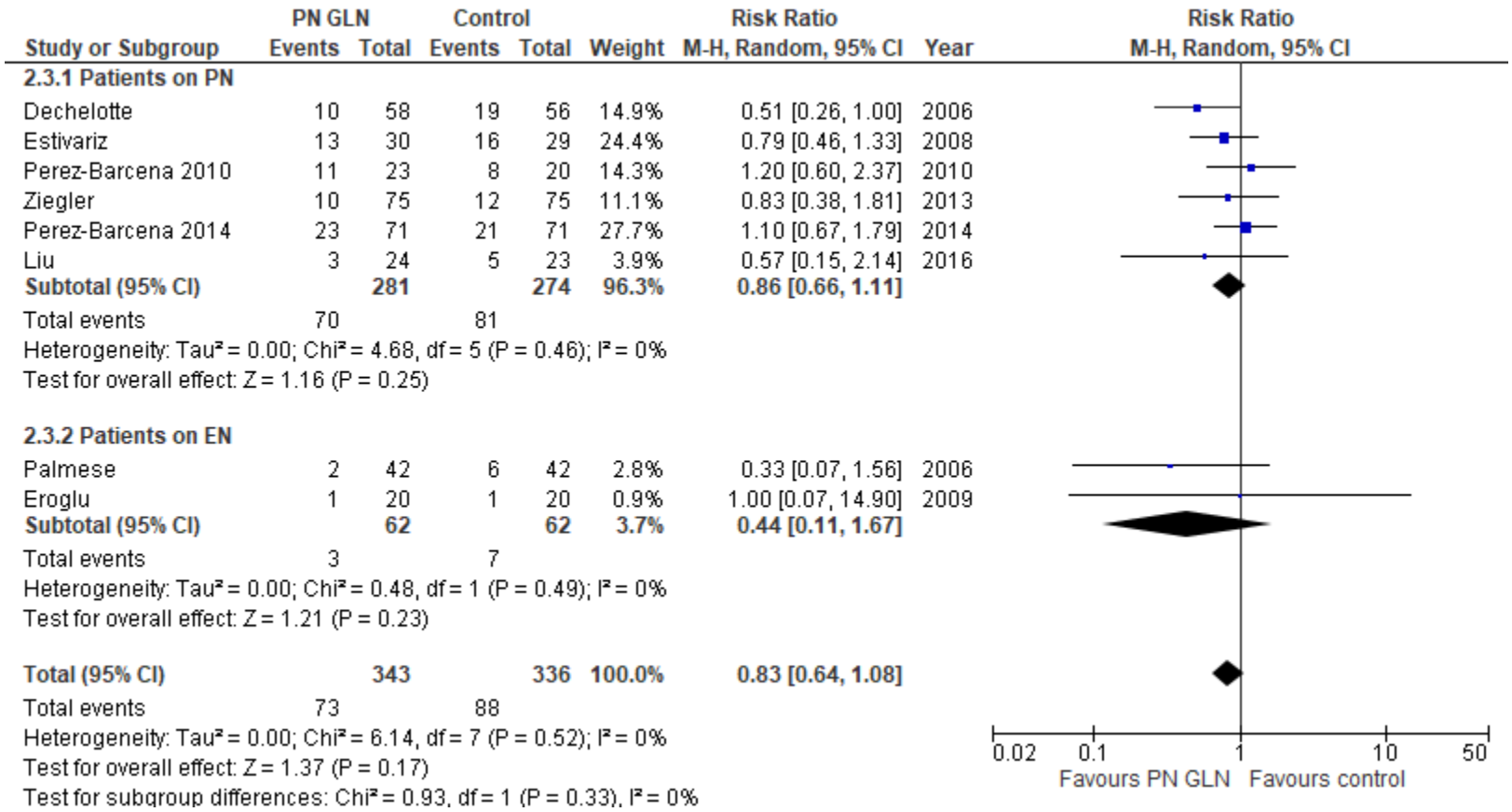


Figure 8. Ventilator Associated Pneumonia (Single vs. Multicentre)

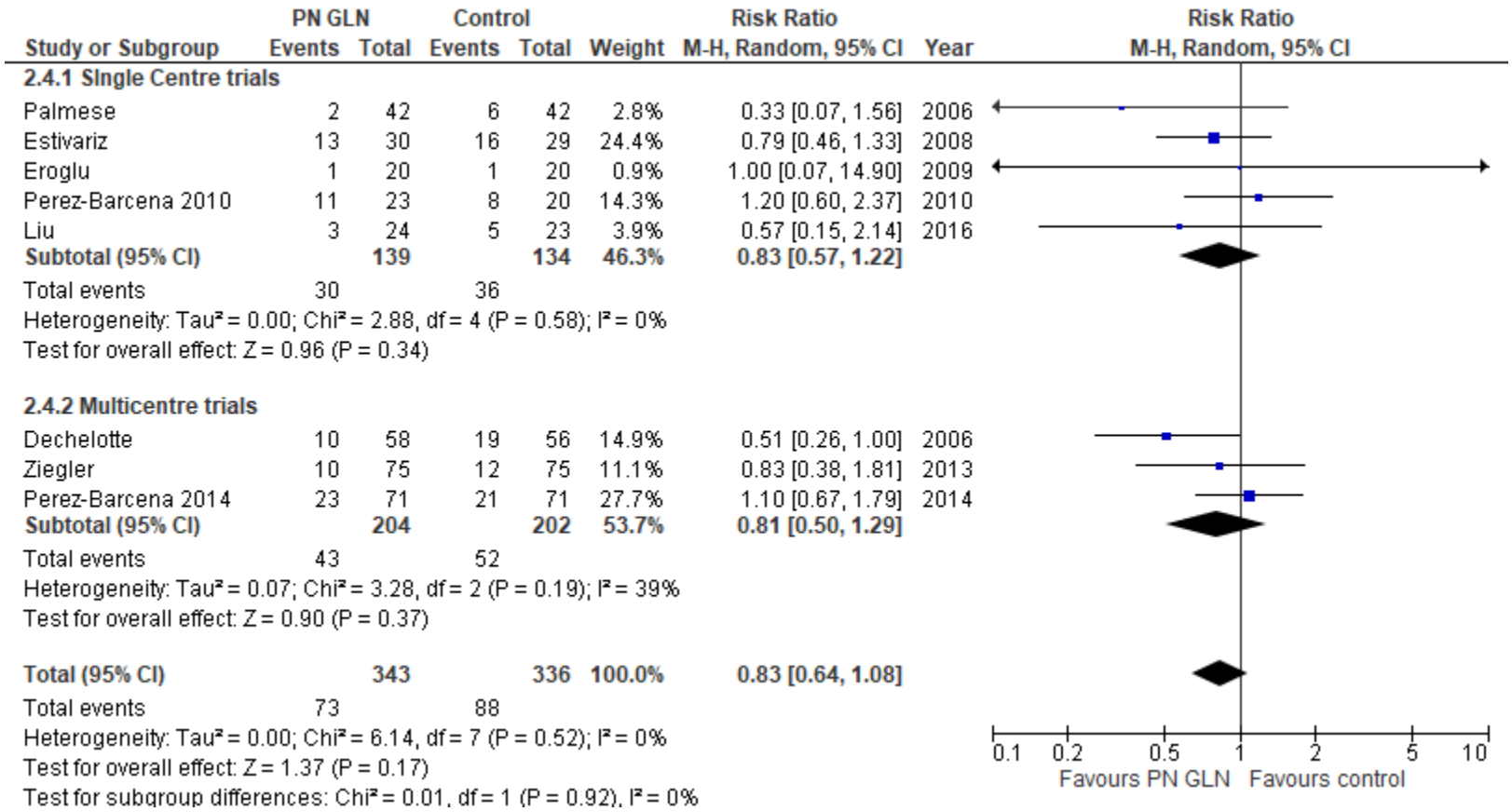


Figure 9. ICU LOS (EN vs. PN)

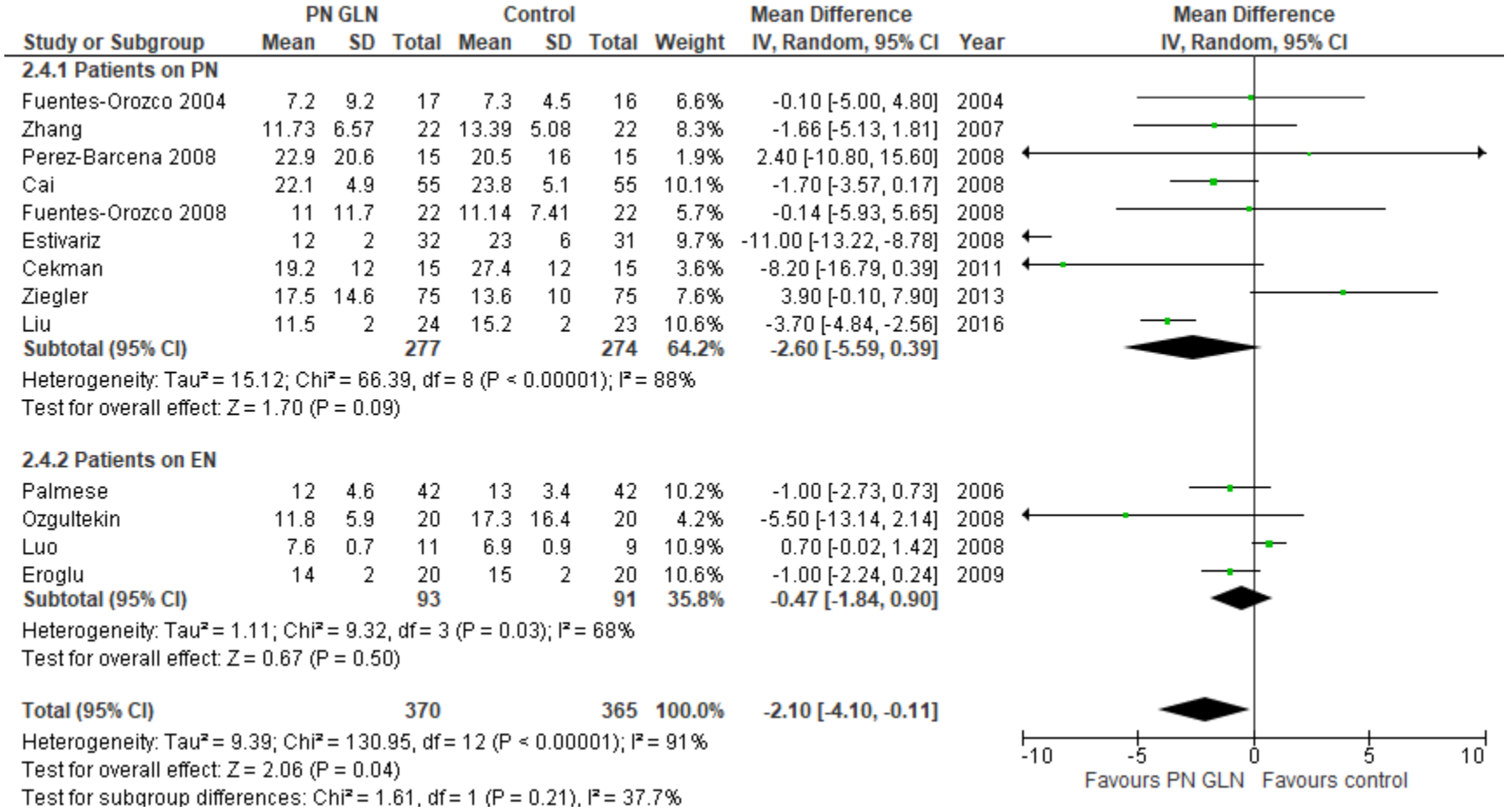


Figure 10. ICU LOS (Single vs. Multicentre trials)

Study or Subgroup	PN GLN Mean	PN GLN SD	PN GLN Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Year
2.7.1 Single trials									
Fuentes-Orozco 2004	7.2	9.2	17	7.3	4.5	16	6.6%	-0.10 [-5.00, 4.80]	2004
Palmese	12	4.6	42	13	3.4	42	10.2%	-1.00 [-2.73, 0.73]	2006
Zhang	11.73	6.57	22	13.39	5.08	22	8.3%	-1.66 [-5.13, 1.81]	2007
Ozgultekin	11.8	5.9	20	17.3	16.4	20	4.2%	-5.50 [-13.14, 2.14]	2008
Luo	7.6	0.7	11	6.9	0.9	9	10.9%	0.70 [-0.02, 1.42]	2008
Perez-Barcena 2008	22.9	20.6	15	20.5	16	15	1.9%	2.40 [-10.80, 15.60]	2008
Cai	22.1	4.9	55	23.8	5.1	55	10.1%	-1.70 [-3.57, 0.17]	2008
Fuentes-Orozco 2008	11	11.7	22	11.14	7.41	22	5.7%	-0.14 [-5.93, 5.65]	2008
Estivariz	12	2	32	23	6	31	9.7%	-11.00 [-13.22, -8.78]	2008
Eroglu	14	2	20	15	2	20	10.6%	-1.00 [-2.24, 0.24]	2009
Cekman	19.2	12	15	27.4	12	15	3.6%	-8.20 [-16.79, 0.39]	2011
Liu	11.5	2	24	15.2	2	23	10.6%	-3.70 [-4.84, -2.56]	2016
Subtotal (95% CI)			**295**			**290**	**92.4%**	**-2.60 [-4.65, -0.54]**	
Heterogeneity: Tau² = 9.19; Chi² = 124.65, df = 11 (P < 0.00001); I² = 91%									
Test for overall effect: Z = 2.47 (P = 0.01)									
2.7.2 Multicentre trials									
Ziegler	17.5	14.6	75	13.6	10	75	7.6%	3.90 [-0.10, 7.90]	2013
Subtotal (95% CI)			**75**			**75**	**7.6%**	**3.90 [-0.10, 7.90]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.91 (P = 0.06)									
Total (95% CI)			**370**			**365**	**100.0%**	**-2.10 [-4.10, -0.11]**	
Heterogeneity: Tau² = 9.39; Chi² = 130.95, df = 12 (P < 0.00001); I² = 91%									
Test for overall effect: Z = 2.06 (P = 0.04)									
Test for subgroup differences: Chi² = 7.99, df = 1 (P = 0.005), I² = 87.5%									

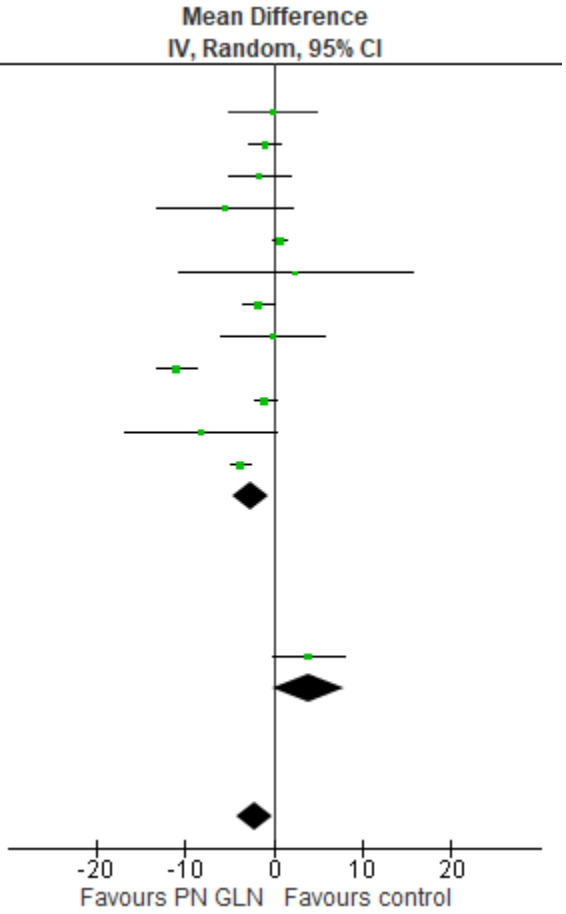


Figure 11. Hospital LOS (EN vs. PN)

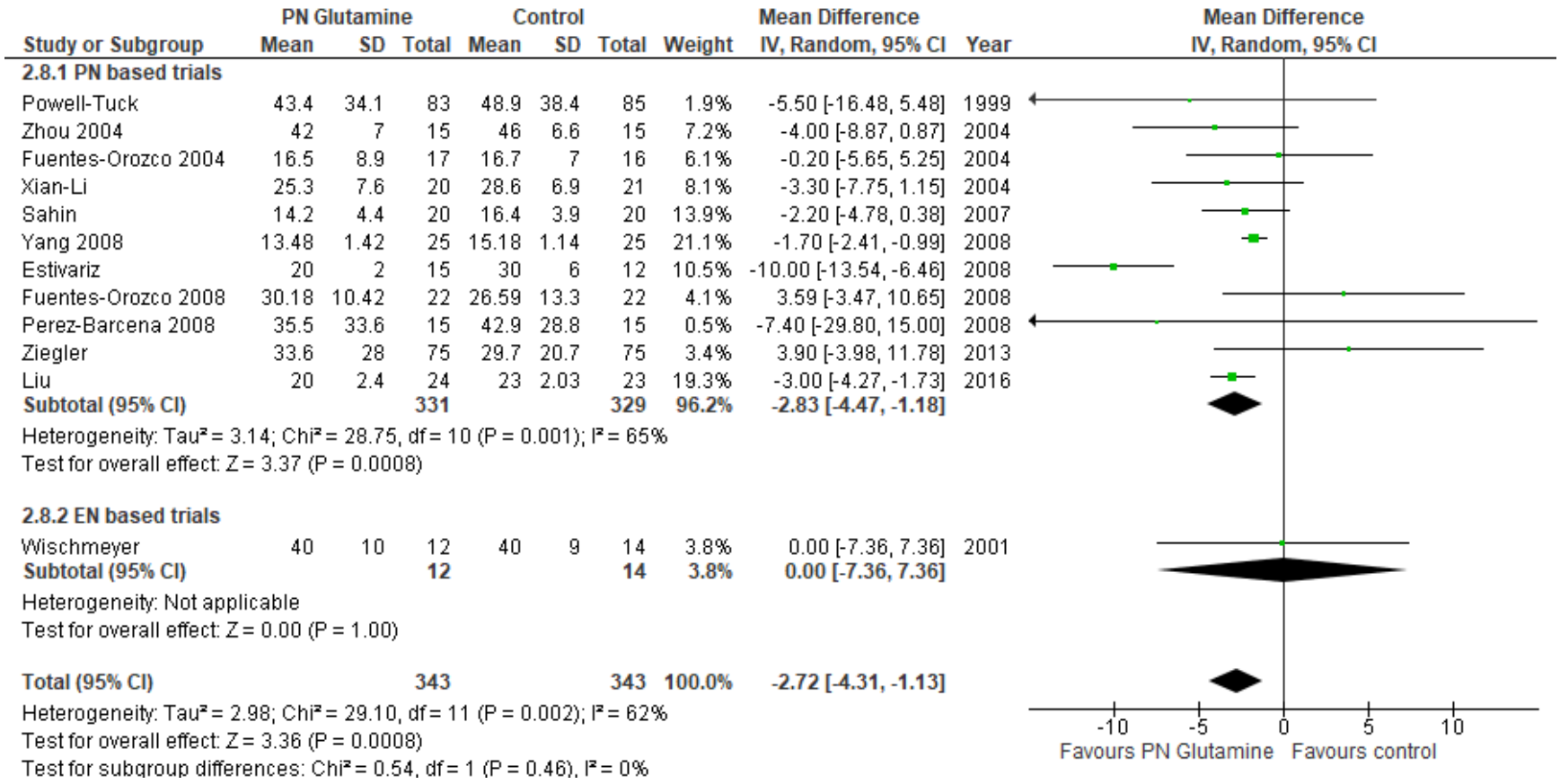


Figure 12. Hospital LOS (Single vs. Multicentre trials)

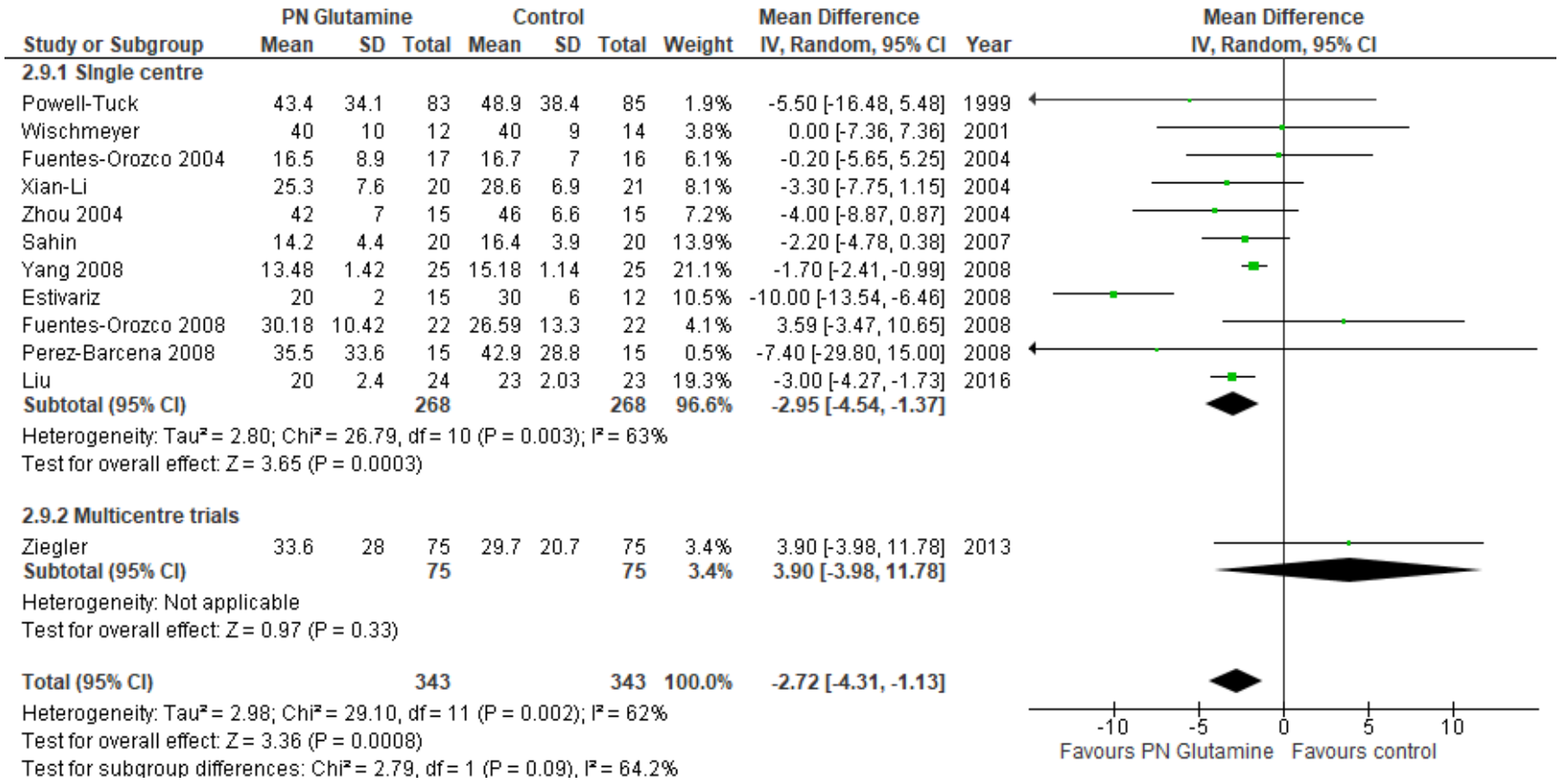
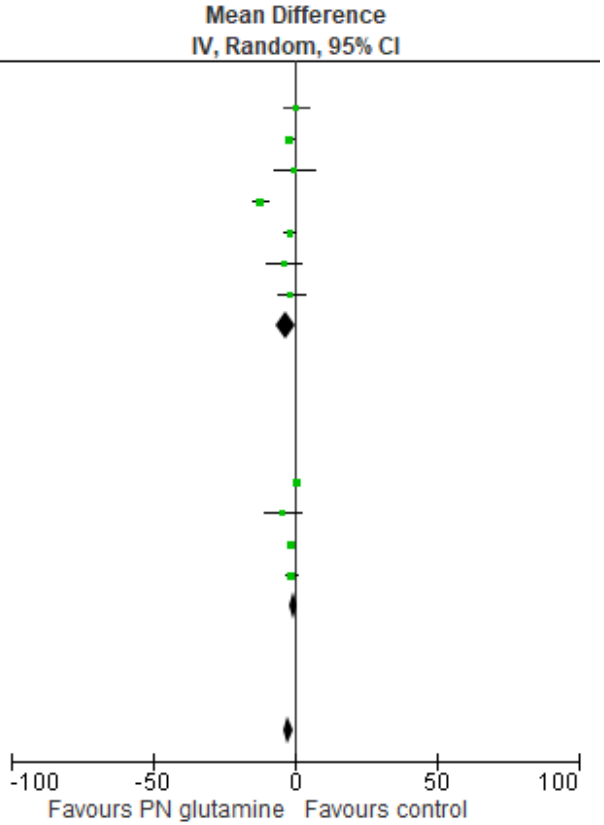


Figure 13. Mechanical Ventilation

Study or Subgroup	PN Glutamine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
2.10.1 Patients on PN									
Fuentes-Orozco 2004	4.88	8.2	17	4.47	4.4	16	7.2%	0.41 [-4.04, 4.86]	2004
Zhang	5.27	1.78	22	7.18	2.76	22	12.6%	-1.91 [-3.28, -0.54]	2007
Perez-Barcena 2008	14	10	15	14	10	15	4.1%	0.00 [-7.16, 7.16]	2008
Estivariz	9	2	15	21	5	12	9.7%	-12.00 [-15.00, -9.00]	2008
Cai	15.6	5.7	55	17.2	5.9	55	11.3%	-1.60 [-3.77, 0.57]	2008
Perez-Barcena 2010	15.2	8.2	23	18.9	11.1	20	5.3%	-3.70 [-9.61, 2.21]	2010
Koksal	13	12.2	30	14.3	5.4	30	6.7%	-1.30 [-6.07, 3.47]	2014
Subtotal (95% CI)			**177**			**170**	**56.9%**	**-3.10 [-6.32, 0.11]**	
Heterogeneity: Tau² = 14.34; Chi² = 41.86, df = 6 (P < 0.00001); I² = 86%									
Test for overall effect: Z = 1.89 (P = 0.06)									
2.10.2 Patients on EN									
Palmese	6	1.7	42	5	2.5	42	13.2%	1.00 [0.09, 1.91]	2006
Ozgultekin	10.1	4.4	20	14.4	14	20	4.7%	-4.30 [-10.73, 2.13]	2008
Luo	5	1	14	6	1	9	13.3%	-1.00 [-1.84, -0.16]	2008
Eroglu	8	3	20	9	3	20	11.9%	-1.00 [-2.86, 0.86]	2009
Subtotal (95% CI)			**96**			**91**	**43.1%**	**-0.46 [-1.94, 1.03]**	
Heterogeneity: Tau² = 1.42; Chi² = 12.39, df = 3 (P = 0.006); I² = 76%									
Test for overall effect: Z = 0.60 (P = 0.55)									
Total (95% CI)			**273**			**261**	**100.0%**	**-2.16 [-3.89, -0.43]**	
Heterogeneity: Tau² = 5.65; Chi² = 73.91, df = 10 (P < 0.00001); I² = 86%									
Test for overall effect: Z = 2.45 (P = 0.01)									
Test for subgroup differences: Chi² = 2.15, df = 1 (P = 0.14), I² = 53.4%									



Included Studies

1. I) Griffiths RD, Jones C, Palmer TE. Six-month outcome of critically ill patients given glutamine- supplemented parenteral nutrition. Nutrition Apr;13(4):295-302, 1997.
ii) Griffiths RD, Allen KD, Andrews FJ, Jones C. Infection, multiple organ failure, and survival in the intensive care unit: influence of glutamine-supplemented parenteral nutrition on acquired infection. Nutrition 2002;18(7-8):546-52.
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Excluded Articles

#	Reason excluded	Citation
1	Elective surgery pts	O'Riordain MG, Fearon KC, Ross JA, Rogers P, Falconer JS, Bartolo DC, Garden OJ, Carter DC. Glutamine-supplemented total parenteral nutrition enhances T-lymphocyte response in surgical patients undergoing colorectal resection. Ann Surg. 1994 Aug;220(2):212-21.
2	Not ICU pts (excluded respiratory failure patients)	DeBeaux A, O'Riordain M, Ross J, et al. Glutamine supplemented total parenteral nutrition reduces blood mononuclear cell interleukin-8 release in severe acute pancreatitis. Nutrition 1998:14 (3):261-265.
3	Elective surgery pts	Morlion BJ, Stehle P, Wachtler P, Siedhoff HP, Köller M, König W, Fürst P, Puchstein C. Total parenteral nutrition with glutamine dipeptide after major abdominal surgery: a randomized, double-blind, controlled study. Ann Surg. 1998 Feb;227(2):302-8.
4	Elective surgery pts	Jacobi CA, Ordemann J, Zuckermann H, Döcke W, Volk HD, Müller JM. [The influence of alanyl-glutamine on immunologic functions and morbidity in postoperative total parenteral nutrition. Preliminary results of a prospective randomized trial]. Zentralbl Chir. 1999;124(3):199-205.
5	Elective surgery pts	Mertes N, Schulzki C, Goeters C, Winde G, Benzing S, Kuhn KS, Van Aken H, Stehle P, Fürst P. Cost containment through L-alanyl-L-glutamine supplemented total parenteral nutrition after major abdominal surgery: a prospective randomized double-blind controlled study. Clin Nutr. 2000 Dec;19(6):395-401.
6	Elective surgery pts	Spittler A, Sautner T, Gornikiewicz A, Manhart N, Oehler R, Bergmann M, Függer R, Roth E. Postoperative glycyl-glutamine infusion reduces mmunosuppression: partial prevention of the surgery induced decrease in HLA-DR expression on monocytes. Clin Nutr. 2001 Feb;20(1):37-42.
7	Couldn't get mortality information from authors	Hájek R, Hude P, Horky P, Baltusová E, Bosáková H, Řehořková D. Dipeptivan a ovlivněni inumitnich funkci u polytraumat. Anest noedkl Péče; 12(5):252-255, 2001.
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