



Year: 2013

A systematic literature review and meta-analysis of randomized clinical trials of parenteral glutamine supplementation

Bollhalder, Lea ; Pfeil, Alena M ; Tomonaga, Yuki ; Schwenkglenks, Matthias

Abstract: **BACKGROUND** AIMS: Glutamine supplementation has been associated with reduced mortality, infections and hospital length of stay in critically ill patients and patients undergoing major surgery. We carried out a meta-analysis to examine randomized clinical trial (RCT)-based evidence of these effects. **METHODS:** Based on a systematic database search, RCTs published since 1990 were included if they evaluated the effect of parenteral glutamine supplementation against a background of parenteral nutrition. Enteral (tube) feeding in a proportion of patients was allowable. Information on RCT methodology, quality and outcomes was extracted. Random effects meta-analysis followed the DerSimonian-Laird approach. **RESULTS:** Forty RCTs were eligible for meta-analysis. Parenteral glutamine supplementation was associated with a non-significant 11% reduction in short-term mortality (RR = 0.89; 95% CI, 0.77-1.04). Infections were significantly reduced (RR = 0.83; 95% CI, 0.72-0.95) and length of stay was 2.35 days shorter (95% CI, -3.68 to -1.02) in the glutamine arms. Meta-analysis results were strongly influenced by one recent trial. An element of publication bias could not be excluded. **CONCLUSION:** Parenteral glutamine supplementation in severely ill patients may reduce infections, length of stay and mortality, but substantial uncertainty remains. Unlike previous meta-analyses, we could not demonstrate a significant reduction in mortality.

DOI: <https://doi.org/10.1016/j.clnu.2012.11.003>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-68926>

Journal Article

Originally published at:

Bollhalder, Lea; Pfeil, Alena M; Tomonaga, Yuki; Schwenkglenks, Matthias (2013). A systematic literature review and meta-analysis of randomized clinical trials of parenteral glutamine supplementation. *Clinical Nutrition*, 32(2):213-223.

DOI: <https://doi.org/10.1016/j.clnu.2012.11.003>

**A systematic literature review and meta-analysis of randomized clinical trials of
parenteral glutamine supplementation**

Lea Bollhalder, Alena M Pfeil, Yuki Tomonaga, Matthias Schwenkglenks

Online Supplement – Additional Results

ICU admission status

Patient group	Study	Ref.	Endpoints available			ICU admission			Inclusion in sensitivity analysis		Reason in absence of explicit information		
			Mor.	Inf.	LOS	Yes	Partially	Unclear	Yes	No			
Surgery	O'Riordain 1994	34		x					x		Gastrointestinal surgery		
	Morlion 1998	35			x				x		Gastrointestinal surgery		
	Jacobi 1999	36		x					x		Gastrointestinal surgery		
	Jiang 1999	37	0	x	x				x		Gastrointestinal surgery		
	Mertes 2000	56	x		x	x				x			
	Karwowska 2001	52	0	0	x				x	x	Elective aortic aneurysm repair		
	Neri 2001	38	0	x	x				x		x	Gastrointestinal surgery	
	Spittler 2001	57		x	x	x				x			
	Goeters 2002	29	x		x	x					x		
	Lin 2002	39	0	0					x		x	Gastrointestinal surgery	
	Exner 2003	58		0	x	x					x		
	Fuentes-Orozco 2004	59	x	x	x	x					x		
	Klek 2005	40		x	x				x			x	Gastrointestinal surgery
	Yao 2005	41		x	x				x			x	Gastrointestinal surgery
	Jo 2006	42	x	x	x				x			x	Gastrointestinal surgery
	Estivariz 2008	64	x	x		x					x		
	Yeh 2008	43	0	x	x				x			x	
	Asprey 2009	27		x					x			x	
	Engel 2009	67	0	x	x	x					x		Cardiac surgery with cardiopulmonary
	Fan 2009	44		x	x				x			x	Gastrointestinal surgery
Lu 2011	45		x					x			x	Gastrointestinal surgery	
Critical illness	Griffiths 1997/2002	54,55	x	x	x	x					x		
	De Beaux 1998	53	0	x					x	x		Pancreatitis patients, severe	
	Wischmeyer 2001	31	x	x	x	x					x		
	Ockenga 2002	32	x	x	x				x			x	Pancreatitis, partially non-severe
	Tjäder 2004	60	x			x					x		
	Xian-Li 2004	61	x	x	x				x	x		Pancreatitis patients, severe	
	Zhou 2004	62		x	x				x	x		Burns patients; burn size ranging from 30% to 50% of total body surface	
	Sahin 2007	33	x		x				x			x	Pancreatitis, partially non-severe
	Cai 2008	28	x		x	x					x		
	Duska 2008	51	x			x					x		
Fuentes-Orozco 2008	65	x	x	x	x					x			
Mixed	Powell-Tuck 1999	46	x	x	x				x			x	
	Déchelotte 2006	63	x	x	x	x					x		
	Pérez-Barcena 2008	66	x	x	x	x					x		
	Pérez-Barcena 2010	68	x		x	x					x		
	Andrews 2011	10	x	x	x	x					x		
	Cekmen 2011	69	x		x	x					x		
	Grau 2011	70	x	x	x	x					x		
	Wernerman 2011	30	x			x					x		

Table S1: ICU admission status and inclusion in sensitivity analyses where only studies of patients admitted to the ICU were retained. Studies where only a proportion of patients were admitted to the ICU were excluded in these sensitivity analyses. In the absence of explicit information, the criteria described in the main article applied; a brief description is provided in the rightmost column. Ref., Reference number in main article; Mor., Mortality; Inf., Infection; LOS, Length of Stay; ICU, Intensive Care Unit.

Impact on Infectious Morbidity

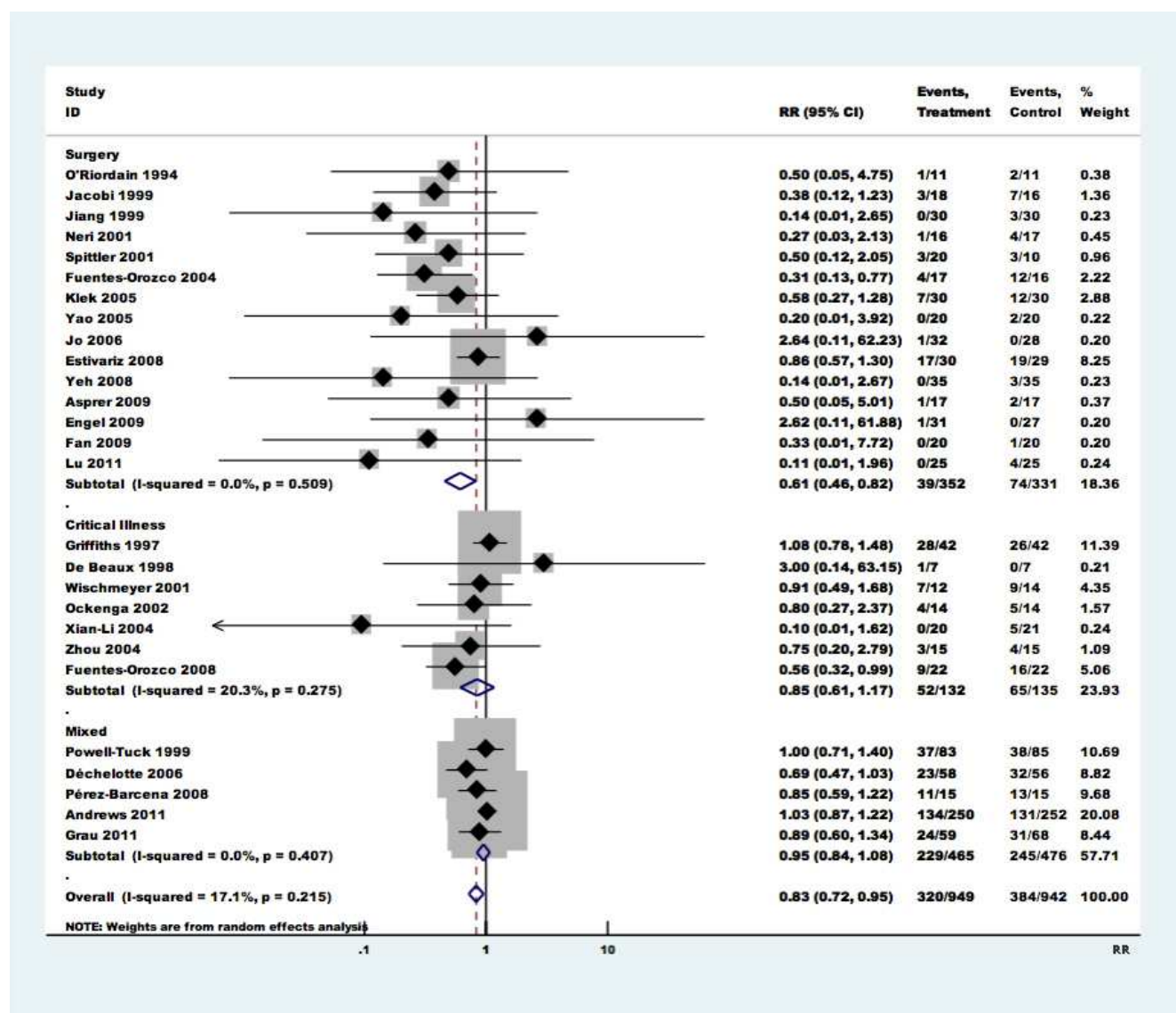


Figure S1: Forest plot of effect of glutamine supplementation on infections.

Subgroup Analyses 1

Subgroup Analysis	MORTALITY			INFECTIONS			LOS		
	Number of Trials [n]	Number of Patients [N]	Effect on Mortality [RR (95% CI), p]	Number of Trials [n]	Number of Patients [N]	Effect on Infections [RR (95% CI), p]	Number of Trials [n]	Number of Patients [N]	Effect on LOS [WMD (95% CI), p]
Glutamine Dosage									
Low Dose (≤ 0.20 g/kg BW/day)	6	788	1.05 (0.87 - 1.27), p=0.615	8	789	1.00 (0.85 - 1.18), p=0.971	10	969	-2.20 (-4.89 - 0.50), p=0.111
Surgical	2	128	0.74 (0.33 - 1.63), p=0.448	6	259	0.42 (0.15 - 1.18), p=0.099	7	329	-3.42 (-4.97 - -1.88), p=0.000
Critically ill	3	158	0.88 (0.52 - 1.46), p=0.610	1	28	0.80 (0.27 - 2.37), p=0.687	2	138	-2.94 (-6.26 - 0.38), p=0.082
Mixed	1	502	1.11 (0.90 - 1.38), p=0.326	1	502	1.03 (0.87 - 1.22), p=0.717	1	502	4.30 (3.16 - 5.44), p=0.000
High Dose (> 0.20 g/kg BW/day)	16	1338	0.69 (0.54 - 0.88), p=0.003	19	1102	0.79 (0.67 - 0.93), p=0.006	20	1140	-2.29 (-3.65 - -0.94), p=0.001
Surgical	3	133	0.44 (0.14 - 1.41), p=0.166	9	424	0.54 (0.35 - 0.83), p=0.006	8	363	-2.43 (-4.10 - -0.75), p=0.004
Critically ill	6	280	0.64 (0.45 - 0.92), p=0.017	6	239	0.83 (0.56 - 1.22), p=0.345	6	265	-1.23 (-2.90 - 0.44), p=0.150
Mixed	7	925	0.76 (0.54 - 1.08), p=0.126	4	439	0.86 (0.71 - 1.04), p=0.111	6	512	-4.77 (-10.69 - 1.16), p=0.115
Duration of Administration									
Short Duration (≤ 9 days)	12	1649	0.96 (0.81 - 1.13), p=0.600	20	1626	0.93 (0.83 - 1.04), p=0.203	19	1625	-2.10 (-3.87 - -0.33), p=0.020
Surgical	2	97	1.46 (0.19 - 11.34), p=0.719	12	561	0.45 (0.27 - 0.76), p=0.003	11	531	-2.79 (-4.21 - -1.36), p=0.000
Critically ill	3	155	0.71 (0.48 - 1.05), p=0.086	3	124	1.05 (0.79 - 1.39), p=0.744	2	110	0.00 (-1.68 - 1.67), p=0.997
Mixed	7	1397	1.02 (0.85 - 1.23), p=0.836	5	941	0.95 (0.84 - 1.08), p=0.429	6	984	-1.83 (-7.14 - 3.48), p=0.499
Long Duration (> 9 days)	10	477	0.65 (0.45 - 0.93), p=0.019	6	235	0.62 (0.42 - 0.93), p=0.020	10	454	-2.37 (-3.36 - -1.39), p=0.000
Surgical	3	164	0.57 (0.28 - 1.13), p=0.108	2	92	0.56 (0.20 - 1.57), p=0.271	3	131	-2.34 (-3.91 - -0.78), p=0.003
Critically ill	6	283	0.67 (0.43 - 1.14), p=0.148	4	143	0.59 (0.37 - 0.94), p=0.026	6	293	-2.33 (-3.77 - -0.90), p=0.001
Mixed	1	30	0.50 (0.15 - 1.64), p=0.252				1	30	-8.20 (-17.05 - 0.65), p=0.069
Time Delay before Start of Treatment									
Short delay (≤ 48 hours)	4	173	0.66 (0.45 - 0.97), p=0.035	4	168	1.00 (0.76 - 1.30), p=0.972	6	243	-3.95 (-7.66 - -0.24), p=0.037
Surgical				1	30	0.50 (0.12 - 2.05), p=0.335	2	75	-6.10 (-9.14 - -3.06), p=0.000
Critically ill	3	143	0.68 (0.45 - 1.03), p=0.067	3	138	1.02 (0.76 - 1.30), p=0.879	3	138	-2.07 (-6.44 - 2.29), p=0.352
Mixed	1	30	0.50 (0.15 - 1.64), p=0.252				1	30	-8.20 (-17.05 - 0.65), p=0.069
Long delay (> 48 hours)	8	1238	0.97 (0.72 - 1.32), p=0.854	5	732	0.97 (0.85 - 1.11), p=0.678	4	702	-1.78 (-8.62 - 5.07), p=0.611
Surgical	1	63	0.16 (0.02 - 1.27), p=0.083	1	59	0.87 (0.57 - 1.30), p=0.487			
Critically ill	2	60	1.26 (0.31 - 5.23), p=0.744	1	14	3.00 (0.14 - 63.15), p=0.480			
Mixed	5	1115	1.06 (0.87 - 1.29), p=0.574	3	659	0.98 (0.85 - 1.13), p=0.815	4	702	-1.78 (-8.62 - 5.07), p=0.611

Subgroup Analysis	MORTALITY			INFECTIONS			LOS		
	Number of Trials [n]	Number of Patients [N]	Effect on Mortality [RR (95% CI), p]	Number of Trials [n]	Number of Patients [N]	Effect on Infections [RR (95% CI), p]	Number of Trials [n]	Number of Patients [N]	Effect on LOS [WMD (95% CI), p]
Study Quality									
Low Quality (≤ 3.5 points^a)	9	457	0.79 (0.53 - 1.16), p=0.221	14	570	0.68 (0.50 - 0.93), p=0.015	18	851	-3.42 (-4.68 - -2.17), p=0.000
Surgical	3	165	0.75 (0.35 - 1.61), p=0.460	10	457	0.48 (0.29 - 0.81), p=0.005	12	559	-3.18 (-4.63 - -1.73), p=0.000
Critically ill	4	219	0.72 (0.44 - 1.16), p=0.176	3	83	0.65 (0.14 - 3.03), p=0.585	4	219	-2.35 (-3.71 - -0.99), p=0.001
Mixed	2	73	1.85 (0.37 - 9.12), p=0.452	1	30	0.85 (0.59 - 1.22), p=0.368	2	73	-14.63 (-20.93 - -8.32), p=0.000
High Quality (> 3.5 points^a)	13	1669	0.85 (0.69 - 1.04), p=0.117	13	1321	0.87 (0.74 - 1.02), p=0.080	12	1258	-0.44 (-2.69 - 1.80), p=0.700
Surgical	2	96	0.37 (0.10 - 1.39), p=0.139	5	226	0.49 (0.23 - 1.06), p=0.071	3	133	-1.68 (-3.50 - 0.13), p=0.069
Critically ill	5	219	0.71 (0.49 - 1.03), p=0.072	4	184	0.87 (0.63 - 1.20), p=0.394	4	184	-0.40 (-2.66 - 1.87), p=0.731
Mixed	6	1354	0.99 (0.82 - 1.19), p=0.932	4	911	0.95 (0.81 - 1.11), p=0.519	5	941	0.25 (-4.69 - 5.18), p=0.923
Disease Severity									
Lower Severity (bg mortality ≤ 0.20)	11	882	0.77 (0.48 - 1.24), p=0.282	11	542	0.69 (0.52 - 0.94), p=0.017	12	579	-3.77 (-5.24 - -2.30), p=0.000
Surgical		193	0.54 (0.18 - 1.62), p=0.274	6	315	0.48 (0.22 - 1.06), p=0.069	7	323	-3.08 (-4.10 - -2.05), p=0.000
Critically ill	11	89	0.64 (0.08 - 5.31), p=0.678	3	83	0.65 (0.14 - 3.03), p=0.585	2	69	-4.32 (-7.39 - -1.25), p=0.006
Mixed	1	600	0.86 (0.49 - 1.50), p=0.592	2	144	0.77 (0.59 - 1.01), p=0.056	3	187	-14.26 (-20.51 - -8.02), p=0.000
Higher Severity (bg mortality > 0.20)	6	1244	0.87 (0.72 - 1.04), p=0.126	6	951	0.99 (0.87 - 1.11), p=0.820	10	1199	0.07 (-2.54 - 2.68), p=0.956
Surgical	4	68	0.67 (0.30 - 1.53), p=0.347				1	68	6.60 (-13.10 - 26.30), p=0.511
Critically ill		349	0.71 (0.53 - 0.96), p=0.028	3	154	0.86 (0.58 - 1.27), p=0.448	5	304	-0.93 (-2.14 - 0.272), p=0.129
Mixed		827	0.94 (0.71 - 1.26), p=0.692	3	797	1.01 (0.88 - 1.16), p=0.915	4	827	0.19 (-4.81 - 5.20), p=0.940

Table S2: Subgroup analyses by patient type. Bg mortality, background mortality risk defined as the risk of death in the control group; BW, body weight; LOS, length of stay; WMD, weighted mean difference; ^a Score points ascribed to the studies in the quality assessment according to a modified Jadad score.

Subgroup Analyses 2

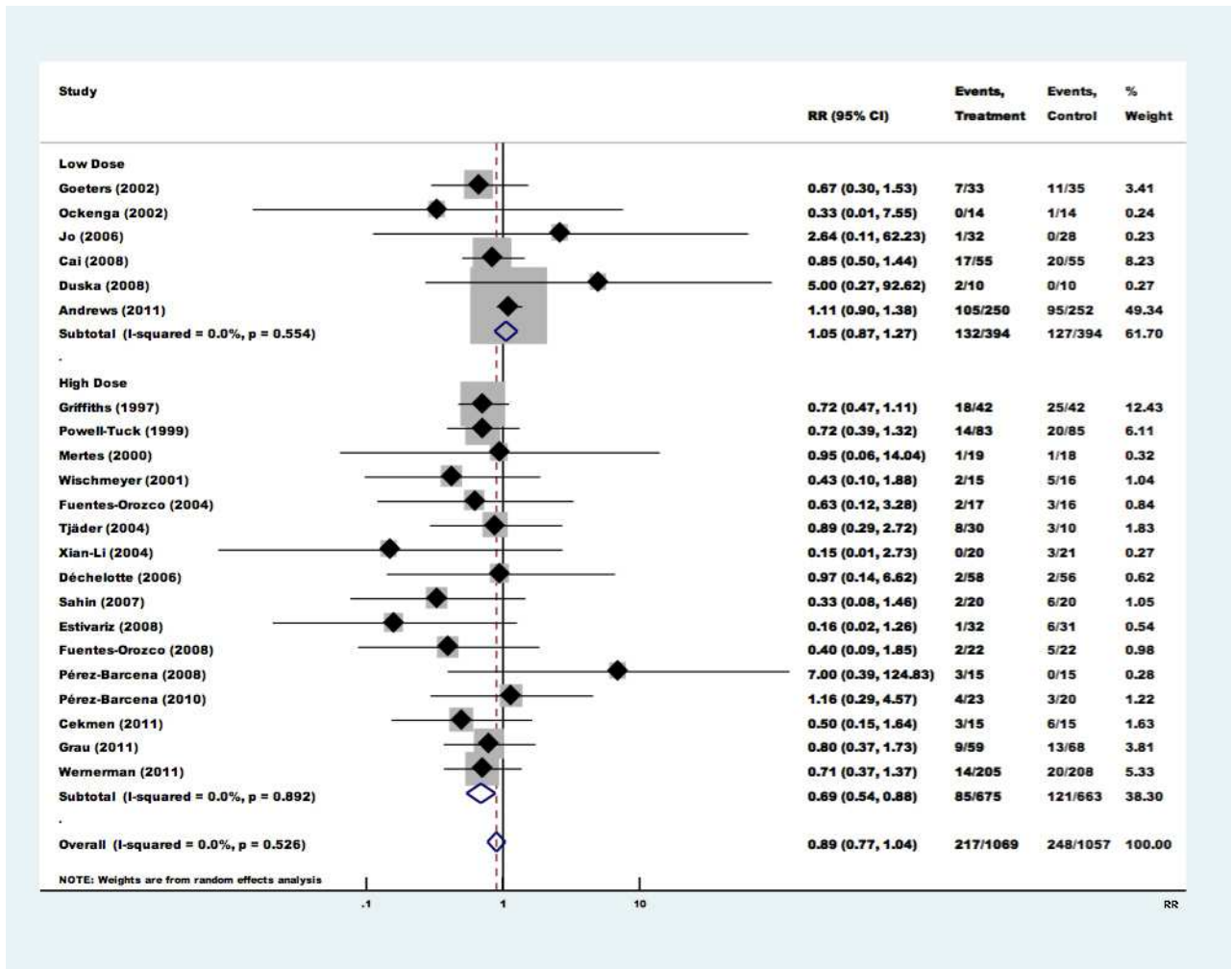


Figure S2: Forest plot of effect of different doses of parenteral glutamine on short-term mortality.

Multivariate meta-regression analysis – short-term mortality

Meta-regression	Number of obs	=	22
REML estimate of between-study variance	tau2	=	0
% residual variation due to heterogeneity	I-squared_res	=	0.00%
Proportion of between-study variance explained	Adj R-squared	=	100.00%
Joint test for all covariates	Model F(2,19)	=	5.79
With Knapp-Hartung modification	Prob > F	=	0.0109

logrr	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]
High Gln Dose	-.4480297	.1592667	-2.81	0.011	-.7813788 -.1146807
Long Duration	-.4324095	.2040148	-2.12	0.047	-.8594173 -.0054017
Constant	.1344956	.106165	1.27	0.221	-.0877102 .3567014

Table S3: Multivariate meta-regression model for RR of short-term mortality.

Adj., adjusted; Coef., coefficient; Conf., confidence; High gln dose, glutamine dose >0.20 g/kg body weight/day; I-squared_res, residual I²; Log RR, logarithm of relative risk; Long admin., duration of administration >9 days; obs, observations; REML, restricted maximum likelihood; Std. Err., standard error; t, t statistic. NOTE: N influenced by availability of covariate information.

Multivariate meta-regression analysis – hospital length of stay

Meta-regression	Number of obs	=	22
REML estimate of between-study variance	tau2	=	4.053
% residual variation due to heterogeneity	I-squared_res	=	60.22%
Proportion of between-study variance explained	Adj R-squared	=	62.70%
Joint test for all covariates	Model F(3,18)	=	5.86
With Knapp-Hartung modification	Prob > F	=	0.0056

MDLOS	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]
High Gln Dose	-3.216805	1.412193	-2.28	0.035	-6.183713 -.2498967
High Quality	3.691031	1.607237	2.30	0.034	.3143526 7.06771
High Disease Sev.	2.763086	1.467469	1.88	0.076	-.3199523 5.846125
Constant	-3.114436	1.075951	-2.89	0.010	-5.374924 -.8539469

Table S4: Multivariate meta-regression model for weighted mean difference of hospital length of stay. Adj., adjusted; Coef., coefficient; Conf., confidence; High gln dose, glutamine dose >0.20 g/kg body weight/day; High qual. study, high quality study (see legend to Table S1); I-squared_res, residual I²; obs, observations; REML, restricted maximum likelihood; Sev. disease, higher disease severity (background mortality >0.20); Std. Err., standard error; t, t statistic; WMD, weighted mean difference. NOTE: N influenced by availability of covariate information.

Risk of Bias Across Studies

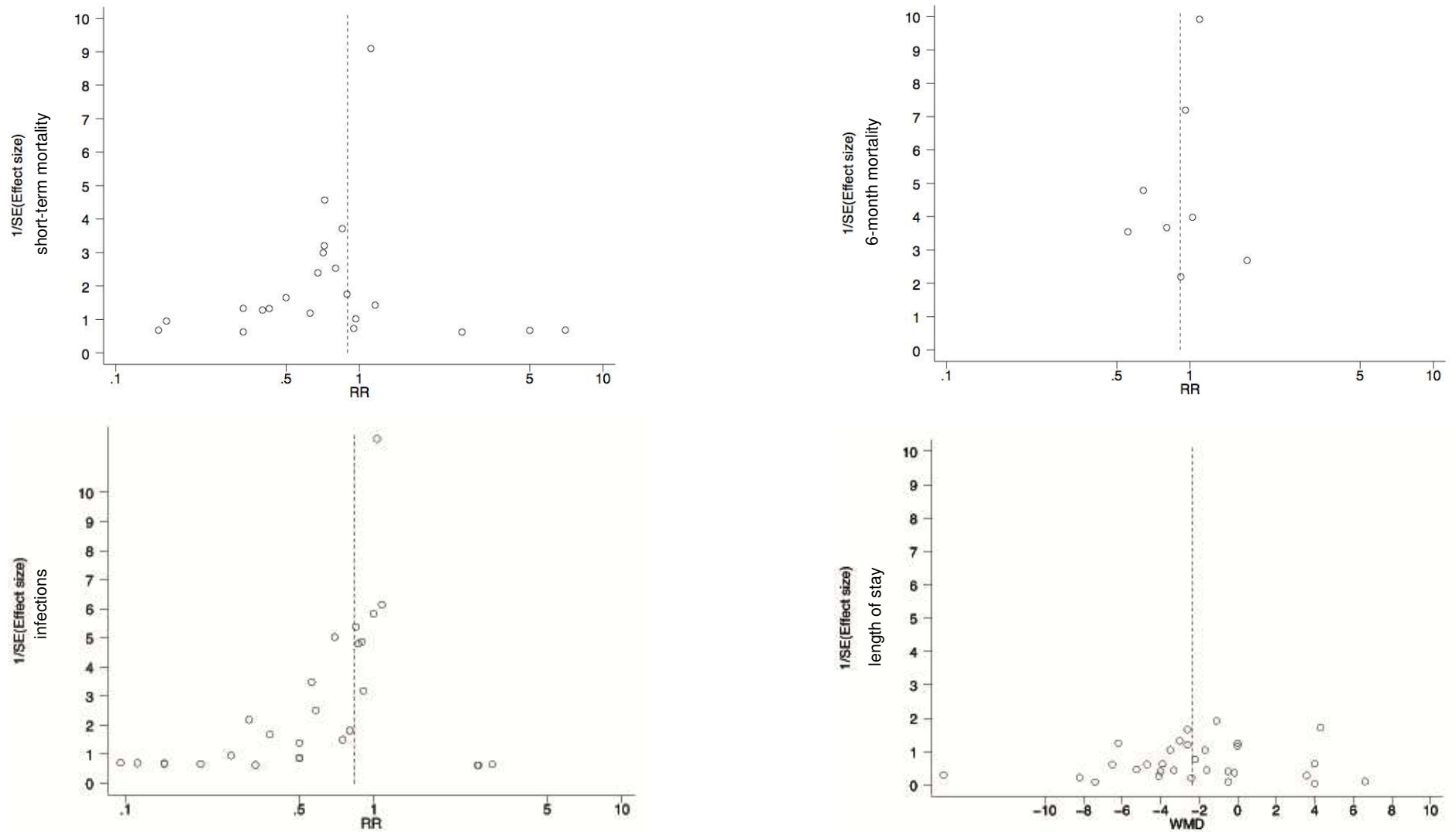


Figure S3: Funnel plots of short-term mortality, 6-month mortality, infectious complications and LOS. SE, standard error; WMD, weighted mean difference.