Efficacy of glutamine-enriched enteral feeding formulae in critically ill patients: A systematic review and meta-analysis of randomized controlled trials

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Running title: Glutamine-enriched enteral feeding formula and critically ill patients

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ABSTRACT
Critically ill patients usually suffer from catabolic stress that could lead to malnutrition and nutritional support therefore is essential to maintain lean body mass, improve metabolic and immune response and decrease rate of mortality and comorbidity in these patients. This meta-analysis was aimed to evaluate effect of Glutamine-enriched enteral nutrition in critically ill patients. In order to obtain randomized clinical trial studies (RCTs), international databases including MEDLINE and Google scholar and also electronic resources in Iran, including IRAN MEDEX, IRAN DOC, SID, Magiran were systematically searched without language and publication restriction before December 2014. The final included number of studies for meta-analysis was 10. The methodological quality of eligible studies was assessed by four investigators using the Jadad 5-point scale, a scale containing three items describing randomization,blinding and fate of participants. We analyzed data from the included studies using STATA version 12.0, and calculated a pooled odds ratio for dichotomous data and mean differences for continuous data with 95% confidence intervals (CIs). There was no significant difference in mortality in elevated pooled odds ratios ($p$-value=0.0704). A funnel plot was drawn for evaluation of publication bias, but none was found. The fix effect model shows significant reduction in gut permeability in who received enteral feeding enriched with glutamine (-0.84, 95% CI=-1.25 to -0.44), moreover the funnel plot didn’t show publication bias. Based on the available data, our meta-analysis showed that enteral Glutamine (Gln) supplementation increased mortality rate, though non-significantly, but decreased gut permeability significantly.

Key Words: Glutamine, enteral, immune-enhancing formula, critically ill patients, systematic review

INTRODUCTION
Critically ill patients usually suffer from catabolic stress that could lead to malnutrition. In these patients the risk of sepsis, infection, prolonged hospitalization, rate of mortality and intestinal permeability are high due to oxidative stress stimulation and immune system suppression. Nutritional support therefore is essential to maintain lean body mass, improve metabolic and immune response and decrease rate of mortality and comorbidity in these patients. Previous clinic studies have shown that parenteral and enteral nutrition are effective after surgery, trauma, infection and injuries, however, enteral nutrition is more beneficial than parenteral nutrition for improving intestinal endothelium function. Enteral
nutrition plays a role in integrity and function of the gut tract via maintenance of mucosal mass and villi height, proliferation of enterocytes and production of gastro-intestinal (GI) enzymes and hormones.\textsuperscript{1}

Studies have indicated that immune-enhancing formula decrease rate of mortality and infection. So, critically ill patients benefit from immune-enhancing nutrients, it had suggested that glutamine (Gln), an immune nutrient,\textsuperscript{5} is a dispensable amino acid that plays a pivotal role in the synthesis of neuclotides and supplying fuel for enterocytes. It contributes in musin production and integrity of GI membrane via synthesis of N-acethyl glucose amine and N-acethyl galactose amine.\textsuperscript{5,7} In stress and critically illness conditions consumption of Gln is higher than de novo synthesis and Gln plays a role as an indispensable amino acid.\textsuperscript{1} Animal studies have reported that Gln supplementation reduces risk of bacterial translocation, atrophy of intestinal mucosa, intestinal permeability and clinical infection.\textsuperscript{8} However, human clinical trials are inconsistent.\textsuperscript{1,3,5,8} Therefore, conduction a meta-analysis in order to clarification of glutamine effectiveness is required. This meta-analysis was aimed to evaluate effect of Gln-enriched enteral nutrition in critically ill patients.

METHODS

\textit{Literature search strategy}

In order to obtain randomized clinical trial studies (RCTs), international databases including MEDLINE and Google scholar and also electronic resources in Iran, including IRAN MEDEX, IRAN DOC, SID, Magiran were systematically searched without language and publication restriction before December 2014. To achieve the maximum sensitivity of the search strategies and detect all RCTs using enteral feeding supplemented with glutamine in critically ill patients, we appropriately used keywords including: (enteral formula OR enteral nutrition OR enteral feeding) AND glutamine AND (critically ill OR intensive care unit OR severe illness). We also reviewed reference list of selected articles, conference proceedings to identify any articles and data not found using online methods.

\textit{Inclusion and exclusion criteria}

Studies were eligible for inclusion in the present analysis if they met the following criteria: 1) Study design: Only RCTs with matched control group; 2) Patients characteristics: Only adults who were admitted to ICU or who had APACHE scores equal or above 10; 3) Intervention: Enteral formula supplemented with glutamine; and 4) Outcomes: Intestinal permeability, length of hospital stay, sepsis or infection rate, and mortality rate.
Studies were excluded for the following reason: 1) Studies on children and neonate; 2) Animal and laboratory studies; and 3) Studies with designs other than RCT.

Studies selection
Four investigators independently evaluated all abstracts of relevant studies. If abstracts potentially met the inclusion criteria, full texts of these were requested. Any disagreements were resolved through consensus.

Data extraction and quality assessment
Full texts of selected articles were obtained for quality assessment and the following data were extracted by four investigators: First author, year of publication, country, journal name, glutamine dosage, baseline characteristics and previously mentioned outcomes.

The methodological quality of eligible studies was assessed by four investigators using the Jadad 5-point scale, a scale containing three items describing randomization, blinding and fate of participants; we assigned 1 point if randomization was mentioned, 1 additional point if the method of randomization was appropriate and also we deducted 1 point if the method of randomization was inappropriate. Regarding blinding, we assigned 1 point if blinding was mentioned, 1 additional point if the method of blinding was appropriate and again we deducted 1 point if the method of blinding was inappropriate. Finally, we assigned 1 point if the fate of all participants in the trial was known, and if there were no data, the reason should have been stated. The quality scale ranged from 0 to 5. If Jadad score was ≥3 points, the article was considered as a high quality research and if Jadad score was ≤2 points, it was known as a low quality article.9

Statistics
We analyzed data from the included studies using STATA version 12.0 (STATA Corporation, College Station, TX, USA), and calculated a pooled odds ratio for dichotomous data and mean differences for continuous data with 95% confidence intervals (CIs).

To assess heterogeneity across the studies, a statistical test for heterogeneity was performed based on the statistics.10 If the studies were shown to be homogeneous with \( p > 0.05 \) for the Q test, the summary of OR was calculated by a fixed-effects model (the Mantel–Haenszel method) when between-study heterogeneity was absent.11 Otherwise, a random-effects model (the DerSimonian and Laird method) was used,12 publication bias was assessed using funnel plot techniques.
We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to report the research protocol, outcomes and other relevant items in this systematic review.\textsuperscript{13}

**RESULTS**

*Included studies*

As shown in Figure 1, according to our inclusion criteria, in total 1652 potentially relevant articles were found. After deleting duplicate and irrelevant articles, post-reading titles and their abstracts, 48 articles remained for assessing eligibility. Of the 48 articles, 38 were excluded for following reasons: 14 articles did not have full-texts available, and the rest lacked relevant data. Finally, 10 RCTs ultimately included in our current systematic review.\textsuperscript{2-4, 8,14-19} General information about the included articles is listed in Table 1. According to Jaded scores, nine of the trials were high quality and only one of these was low quality.

*Mortality*

A total of 10 eligible studies, 8 RCTs presented data of mortality. For each study, the odds ratio of mortality in patients with glutamine-enriched enteral feeding relative to control group was computed (Figure 2). Before carrying out the analysis and pooling the results, a heterogeneity hypothesis was tested using the chi square test, and found no significant heterogeneity between studies ($p$-value=0.62); hence we pooled estimation of the studies without adjustment for heterogeneity, using the fixed effect model. There was no significant difference in elevated pooled odds ratios ($p$-value= 0.0704). A funnel plot was drawn for evaluation of publication bias, but none was found (Figure 3).

*Length of hospitalization*

Six studies were used for analyzing data about length of hospitalization. The forest plot was used to illustrate mean hospital stay between the two groups in each study (Figure 4). Because of the heterogeneity between studies, the random effect model was used to combine the results of studies ($Q=9.87$, $p<0.001$, $I^2=95\%$). The results of the meta-analysis show no significant difference in mean hospital stay between the two treatment groups (-0.19, 95\% CI=-0.75-0.36). A funnel plot showed evidence of publication bias (Figure 5). This can be due to the low sample size of studies and probably ignore some of the studies and also estimate the mean and variance.
**ICU stay length**

In 7 studies comprising 1267 patients, the author reported the ICU stay length. There was no significant difference was observed in any of the studies (Figure 6). A random effect model of studies found that no significant difference between two groups of patients about length of ICU stays (-0.03, 95% CI=-0.53-0.47). The results indicated heterogeneity between studies ($I^2=93\%$, $p<0.001$). A funnel plot also showed evidence of publication bias (Figure 7).

**Gut permeability**

Researchers in three studies reported gut permeability in an aggregate of 107 patients. Significant lower gut permeability was seen in patients who received enteral feeding enriched with glutamine compared to controls in the Velasco et al. study contrary to two other studies. Overall, the fix effect model shows significant reduction in gut permeability in who received enteral feeding enriched with glutamine (-0.84, 95% CI=-1.25- -0.44) (Fig. 8). We evaluated a funnel plot for evidence of publication bias. There was no significant heterogeneity across studies ($I^2=53\%$, $p$-value=0.12). It was symmetrical, indicating no publication bias (Fig. 9).

**Dependence on ventilator**

In three studies comprising a total of 259 patients, the investigators reported data about ventilator dependency. Mean days of dependence on ventilator between two patients groups shows no significant difference in any of the studies; overall, the random effect model showed no significant difference between the groups of patients (-0.74, 95% CI= -1.84-0.37) (Figure 10). The heterogeneity between studies was significant ($I^2=94\%$, $p<0.001$). Publication bias was seen on the funnel plot (Figure 11).

**DISCUSSION**

Results of the present meta-analysis show that glutamine-enriched enteral feeding significantly decreased gut permeability in critically ill patients and slightly increased mortality rate in these patients, although the latter was not significant. Moreover, it had no significant effect on length of hospitalization, ICU stay length and dependence of ventilator in these patients.

Glutamine is involved in nitrogen transport, nucleotide and arginine synthesis, intestinal mucosal integrity and is also the preferred fuel of enterocytes. Studies have suggested that Gln may be a conditionally essential amino acid in critically ill patients due to decrease in the plasma Gln levels of these patients; decrease of this amino acid in critical illness is
associated with immune dysfunction; in sepsis and shock conditions, Gln acts as a stress signal in muscles.

Results of our study mentioned that a non-significant increase occurred in mortality rate in critically ill patients, similar to which, some RCTs demonstrated significant increase in mortality rate of critically ill patients. The possible mechanism of by which glutamine supplementation can decrease mortality rate was discovered. The bowel metabolizes less glutamine during sepsis, a response that may be related to the decrease in the amount of circulating insulin-like growth factor-1 (IGF-1) which is characteristic of sepsis; however, in the absence of glutamine supplementation, protein anabolic effects of growth hormone, which occur via IGF-1, have been associated with an increased mortality rate. A possible mechanism for this, is profound glutamine depletion as a result of the mobilization of glutamine from protein stores; hence, there is interest in combining glutamine supplementation with growth hormone or IGF-1 therapy. On the other hand, an experimental Study have indicated that Gln by stimulating expression of heat shock proteins (HSPs) lead to reduction in mortality among critically ill patients. Despite the results of these studies, other studies have shown Gln supplementation had no effect on mortality rate, and it even caused increase in mortality rate. However, the possible reason for which was unclear.

In the present meta-analysis, gut permeability significantly decreased in critically ill patients who received Gln-enriched enteral feeding in compared with control. Gln is an important substrate for enterocytes and supplementation of total parental nutrition (TPN) with glutamine-containing dipeptides has been shown to prevent mucosal atrophy and decreased permeability associated with long-term TPN. Gut permeability is a risk factor for infection and inflammation among critically ill patients. Studies have documented that lack of Gln contributes to impaired intestinal barrier and immune functions versus Gln supplementation, which enhances GI integrity and intestinal flora and suppresses bacterial translocation in GI, subsequently promoting functions of intestinal barrier. Consistent with our results about gut permeability, some studies showed that glutamine supplementation can reduce gut permeability in critically ill patients. Enteral feeding in critically ill patients is the preferred route of nutrition, and glutamine and other substrates seem to preserve intestinal mucosal integrity and lymphoid tissue in the gastrointestinal tract, thus avoiding increased intestinal permeability and bacterial translocation, bacterial translocation could amplify the inflammatory response seen in patients with SIRS and facilitate the appearance of bacteremia and secondary infections by enteric microorganisms.
However our findings indicated beneficial effects of Gln-enriched feeding on gut permeability in critically ill patients, the American Society for Parenteral and Enteral Nutrition (ASPEN) and European Society for Parenteral and Enteral Nutrition (ESPEN) do not advise enteral Gln supplementation in critically ill patients due to lack of conclusive results.\textsuperscript{30} Future investigations to obtain conclusive results are recommended.

Chen et al in a meta-analysis on 17 RCTs have reported that Gln supplementation had no effect on mortality and length of hospitalization.\textsuperscript{25} As mentioned earlier in present meta-analysis, Gln supplementation had no any effect on length of hospitalization or length of ICU stay. In a review conducted by Tao et al\textsuperscript{26} on 53 RCTs, Gln supplementation decreased rate of infection (RR: 0.79, 95% CI: 0.71 to 0.78, \( p < 0.001 \)) and length of hospitalization (MD: \(-3.46\) days, 95% CI: \(-4.61\) to \(-2.32\), \( p < 0.001 \)) in critically ill patients, compared with controls. No significant differences were found in mortality rate of critically ill patients and controls; moreover, both the above studies, RCTs that used Gln supplementation either parenteral or enteral were included in analysis; hence effects of enteral Gln on the outcomes of critically ill patients were unclear. Studies have indicated that parenteral administration of Gln can increase plasma Gln level to normal level, contrary to enteral Gln administration, which elevates plasma Gln levels slightly,\textsuperscript{22,36} indicating that the beneficial effects of Gln supplementation observed in this study, may be related mostly to parenteral Glu supplementation.

To the best of our knowledge, this systematic analysis is the first systematic review on the enteral use of Gln supplementation in critically ill patients. One of the strengths of our meta-analysis is that in this study we included RCTs which used just the enteral route of Gln supplementation. Another positive point of present study is that we had defined rigorous inclusion criteria such as excluding burned, malignant and head traumatic patients and incorporated original studies that enrolled large samples of patients in a randomized controlled design.

Some limitations of our analysis that need to be mentioned are; first, our meta-analyses could only take into account sources written in English. Second, some published trials only reported the median and range, using formulas; we estimated the mean and variance of the length of hospitalization and ICU stay length from the median, range and the size of the trial. Third, there was heterogeneity in kinds of infection reported in patients and because of this the sample size was too small to have substantial power to explore the real association in any subgroup of infections.
Conclusion

In summary, based on the available data, our meta-analysis showed that enteral Gln supplementation increased mortality rate, though non-significantly, but decreased gut permeability significantly. According to recent RCTs and systematic meta-analysis studies on glutamine supplementation the Canadian Critical Care Practice Committee revised the Canadian Critical Care Nutrition Guidelines in 2013.37 The recommendation for parenteral Gln was downgraded from “strongly recommended” to “should be considered” with a warning, i.e. “strongly recommend that glutamine not be used in critically ill patients with shock and multi-organ failure”. The Committee also added use of strong caution in using enteral glutamine in all critically ill patients with shock and multi-organ failure because of the results of the recent multicenter study that showed severe complication with the use of combined enteral and parenteral glutamine.38 The current meta-analysis did not provide sufficient evidence for the use of gln-enriched enteral feeding for critically ill patients.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCE


### Table 1. General information of included articles

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Population</th>
<th>Age</th>
<th>Formula</th>
<th>Gln</th>
<th>Control</th>
<th>Randomization Method</th>
<th>Length of supplementation</th>
<th>Jaded score</th>
<th>Glutamine dosage</th>
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<tr>
<td>Boelens et al (18)</td>
<td>2004</td>
<td>Trauma</td>
<td>18-65</td>
<td>Alitra Q</td>
<td>17</td>
<td>17</td>
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<td>4</td>
<td>30.5 g/100 g protein</td>
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<tr>
<td>Hall et al (16)</td>
<td>2003</td>
<td>Mixed ICU</td>
<td>adults</td>
<td>Isocal + Gln</td>
<td>179</td>
<td>183</td>
<td>randomly allocated</td>
<td>10 days</td>
<td>5</td>
<td>20 g/l</td>
</tr>
<tr>
<td>McQuiggan et al (14)</td>
<td>2008</td>
<td>Trauma</td>
<td>adults</td>
<td>Glutasolve</td>
<td>10</td>
<td>10</td>
<td>randomly allocated</td>
<td>10 days</td>
<td>3</td>
<td>0.5 g/kg/d</td>
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<td>adults</td>
<td>Dipeptiven</td>
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<td>300</td>
<td>randomly allocated</td>
<td>28 days</td>
<td>5</td>
<td>30 g/d</td>
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<tr>
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<td>2005</td>
<td>Trauma</td>
<td>adults</td>
<td>Replete + Gln</td>
<td>59</td>
<td>64</td>
<td>sequential rotating</td>
<td>13 days</td>
<td>3</td>
<td>0.6 g/kg/d (20-40 g/day)</td>
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<td>1998</td>
<td>Trauma</td>
<td>18-65</td>
<td>Alitra Q</td>
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<td>31</td>
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<td>15 days</td>
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<td>30.5 g/100 g protein</td>
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<td>Surgical</td>
<td>19-74</td>
<td>ADN Nutricomp</td>
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<td>8</td>
<td>randomly allocated</td>
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<td>Juven</td>
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<td>computer generation</td>
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<td>18-60</td>
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<td>3</td>
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<td>adults</td>
<td>Protina MP + Gln</td>
<td>26</td>
<td>24</td>
<td>block randomization by envelop</td>
<td>5 days</td>
<td>4</td>
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Table 2. Main results of RCTs

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<th>Control</th>
<th>Mortality</th>
<th>Length of hospitalization</th>
<th>Length of ICU stay</th>
<th>Gut permeability</th>
<th>Dependence on ventilator</th>
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<td></td>
<td>Gln N</td>
<td>Control N</td>
<td></td>
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<td>Control Mean±SD</td>
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<td>NR</td>
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<td>14.2±8.3</td>
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<td>Hall et al (16)</td>
<td>179</td>
<td>183</td>
<td>27/179</td>
<td>25±4.33</td>
<td>30±4.33</td>
<td>11±2</td>
<td>13±1.83</td>
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<td>Heyland et al (3)</td>
<td>301</td>
<td>300</td>
<td>97/301</td>
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<td>Schulman et al (19)</td>
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<td>64</td>
<td>10/59</td>
<td>24.1±2.5</td>
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<td>16.7±1.9</td>
<td>15.2±2.1</td>
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<td>Houdijk et al (15)</td>
<td>29</td>
<td>31</td>
<td>2/29</td>
<td>32±3</td>
<td>27.4±4.3</td>
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<td>7</td>
<td>8</td>
<td>NR</td>
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<td>NR</td>
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<td>NR</td>
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<td>57</td>
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<td>NR</td>
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<td>11±12.5</td>
<td>16.5±15.25</td>
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<td>Hernandez et al (8)</td>
<td>8</td>
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<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0.065±0.023</td>
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Figure 1. Flowchart illustrating the details of the search and study selection process.

Records identified through database searching (n=1652)

Records after duplicates removed (n=963)

Records screened (n=689)

Records excluded by title or abstract (n=641)

Full-text not available (n= 14)
Did not had desired data (n= 24)

Full-text articles assessed for eligibility (n=48)

Studies included in meta-analysis (n= 10)
Figure 2. Odds ratios of mortality in patient with glutamine-enriched enteral feeding relative to control group

Figure 3. Funnel plot of odds ratio of mortality in patient with glutamine-enriched enteral feeding relative to control group
Figure 4. Mean difference of length of hospitalization in patient with glutamine-enriched enteral feeding relative to control group

Figure 5. Funnel plot of mean difference of length of hospitalization in patient with glutamine-enriched enteral feeding relative to control group
Figure 6. Mean difference of ICU stay length in patient with glutamine-enriched enteral feeding relative to control group

Figure 7. Funnel plot of mean difference of ICU stay length in patient with glutamine-enriched enteral feeding relative to control group
**Figure 8.** Mean difference of gut permeability in patient with glutamine-enriched enteral feeding relative to control group

<table>
<thead>
<tr>
<th>Study</th>
<th>(95% CI)</th>
<th>% Weight</th>
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<tbody>
<tr>
<td>Velasco et al</td>
<td>-2.11 (-3.41, -0.81)</td>
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<tr>
<td>Hernandez et al</td>
<td>-0.48 (-1.48, 0.51)</td>
<td>16.42</td>
</tr>
<tr>
<td>Conjero et al</td>
<td>-0.75 (-1.22, -0.29)</td>
<td>73.91</td>
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<tr>
<td>Overall</td>
<td>-0.84 (-1.25, -0.44)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Q = 4.28, p = 0.12, I² = 53%

**Figure 9.** Funnel plot of mean difference of gut permeability in patient with glutamine-enriched enteral feeding relative to control group
Figure 10. Mean difference of dependence on ventilator in patient with glutamine-enriched enteral feeding relative to control group

### Dependence on ventilator, mean difference

<table>
<thead>
<tr>
<th>Study</th>
<th>Day (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>Houdijk et al</td>
<td>-0.43 (-0.94, 0.08)</td>
<td>32.90</td>
</tr>
<tr>
<td>Conjero et al</td>
<td>0.00 (-0.45, 0.45)</td>
<td>33.41</td>
</tr>
<tr>
<td>Overall</td>
<td>-0.74 (-1.84, 0.37)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Q=34.56, \( p=0.00 \), I\(^2\)=94%

Figure 11. Funnel plot of mean difference of dependence on ventilator in patient with glutamine-enriched enteral feeding relative to control group