Citrulline as a marker of intestinal function and absorption in clinical settings: a systematic review and meta-analysis

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Statement 2: The present study does not report results of a clinical trial and it did not involve primary research on humans.

Abstract
Background: Citrulline has been described as a marker of intestinal function or absorption but evidence varies according to clinical settings.
Objective: To examine the evidence of plasma citrulline as a marker of intestinal function and absorption in various clinical settings.
Methods: Studies were examined for p-values, means and standard deviations, correlation coefficients or other metrics depicting the association of citrulline with intestinal function. A random effects model was used to produce a pooled estimate. A hierarchical summary receiver operating curve model was fitted for diagnostic accuracy measures.
Results: Citrulline levels are correlated strongly with small bowel length in short bowel syndrome patients (r=0.67). Citrulline is strongly negatively correlated (r=-0.56) with intestinal disease severity with regards to enteropathies (coeliac disease, tropical enteropathy, Crohn's disease, mucositis, acute rejection in intestinal transplantation). Citrulline cut-off levels have an overall sensitivity and specificity of 80% and 84% respectively. Citrulline levels in untreated coeliac patients compared to controls were reduced by 10μmol/L. Citrulline levels increase with gluten free diet and with improvement of enteropathy. Citrulline is decreased in critical illness and sepsis.
Conclusion: These findings allow us to advocate quite reasonably that citrulline is a marker of acute and chronic intestinal insufficiency.
Keywords: citrulline, meta-analysis, short bowel syndrome, enteropathy, systematic review

Key summary

1. Summarise the established knowledge on this subject

- Citrulline is a non-protein amino acid, and in humans its plasma content is derived largely from the amount produced in enterocytes of the small bowel.
- Certain clinical conditions have been identified in which citrulline has been used as a marker of intestinal function.
- It is not clear whether citrulline levels reflect intestinal function (notably absorption), enterocyte mass, both or other.

2. What are the significant and/or new findings of this study?

- Citrulline is positively correlated with small bowel length in short bowel syndrome with lower citrulline levels are indicative of intestinal insufficiency.
- Citrulline is moderately correlated with enteral absorption in various conditions.
- Citrulline is negatively correlated with disease severity in intestinal enteropathies.
- Citrulline cut-off levels have a sensitivity and specificity of 80%; 20μmol/L seems to be the most prevalent cut-off level.

Introduction

Citrulline is a non-protein amino acid, and in humans its plasma content is derived largely from the amount produced in enterocytes of the small bowel.[1] Citrulline's first isolation from the juice of the watermelon has been attributed to Koga and Ohtake[2, 3] and Wada.[4] Certain clinical conditions have been identified in which citrulline has been used as a marker of intestinal function.[5-7] However, it is not clear whether citrulline levels reflect intestinal function (notably absorption), enterocyte mass, or both, with its current use being interchangeable. Hence, due to citrulline's unique metabolism, this systematic review aims to answer whether citrulline is a successful indicator of intestinal enterocyte mass and absorption and what clinical conditions it has been utilized in as a marker.

Methods

The inclusion criterion for this systematic review was any empirical study describing investigation of citrulline in relation to intestinal function. PRISMA guidelines and MOOSE checklist for systematic reviews and meta-analyses were used.[8, 9] Electronic database searches were conducted with no year limits. The quality of studies was assessed with elements from Cochrane Collaboration's tool[10] and the RTI Item Bank for Observational Studies.[11, 12] For the meta-analysis, studies were examined for *p*-values, means and standard deviations, correlation coefficients or other metrics depicting the association of citrulline with intestinal function. Metrics were converted to the standardized mean difference (SMD),[13, 14] mean difference (MD),[15] and/or correlation coefficient (CC). A random effects model was used to produce a pooled estimate of the SMDs/MDs/CCs. Heterogeneity was quantified using the I^2 statistic and further investigated with subgroup analysis and meta-regression. Publication bias was assessed using funnel plots, Egger's test, Begg's test and Rosenthal's number.[16-19] The CC is converted to the Fisher's *z* for all analyses.[15] Regarding diagnostic accuracy data, a hierarchical summary receiver operating curve (HSROC) model was fitted to provide a summary receiver operating curve and to allow derivation of pooled sensitivity and specificity estimates.[20] The methods in more detail are described in the Supplementary Materials.

Results

From 463 initial studies, 131 were included in the systematic review and 63 in the meta-analyses performed (Figure 1). Overall number of patients was 4,292 (mean 68, range 6-847) with mean age 31.6 years, male percentage 50.9% and BMI 21.9kg/m^2. Twenty three studies involved children and forty involved adults and the majority of studies were conducted in Europe (45 studies). Mean citrulline value from all studies was 23.2μmol/L and citrulline was mostly measured with High Performance Liquid Chromatography (HPLC). Main findings from all studies are shown in Supplementary Tables 1-6, grouped by condition. There was a strong presence of detection bias and almost 50% confounding bias (Figure 2, Supplementary Figure 1). Reporting bias was also an issue that arose from the papers.

--Figure 1, Figure 2 here--

Necrotizing Enterocolitis (NEC)

Four studies have assessed citrulline levels in patients with NEC (Supplementary Table 1). Risk of bias was low in most studies. The MD indicated a significant decrease in citrulline levels by -7.8μmol/L (95% CI [-14.7, -0.9]; I^2=98%) compared to control, which indicated a strong decrease when the SMD was analysed -1.44 (95% CI [-2.80, -0.07]; I^2=96%). Celik, Demirel [21] described that the area under the receiver operating characteristic (ROC) curve for citrulline to differentiate NEC from controls was 0.88 (95% CI [0.77, 0.99]) and cut-off level of citrulline was 13.15μmol/L with a sensitivity of 80% and a specificity of 82% but no association with duration of parenteral nutrition was noted. Similarly, Ioannou, Diamanti [22] noted that the area under the ROC curve for plasma citrulline to discriminate neonates with NEC from control neonates was 0.86 (95% CI [0.77, 0.96]). The citrulline level that maximized the test's sensitivity and specificity was 17.75μmol/L, with a sensitivity of 76% and a specificity of 87%.

Intestinal Transplantation

Measurement of citrulline levels has been investigated as a possible indicator of intestinal transplant rejection. Thirteen studies were identified in the literature search and two groups have published quite extensively in the

field: the University of Miami, School of Medicine[23] and the Mount Sinai School of Medicine[24] (Supplementary Table 2).
These studies' focus is the ability of citrulline levels to predict the grade of acute cellular rejection and the cut-off value of citrulline levels that yield a high possibility of acute cellular rejection. There was presence of detection bias and confounding because not all studies assessed possible confounders of associations. Also, there is a strong possibility of reporting bias and attrition bias, because many papers are published in *Transplantation Proceedings*, which publishes short reports from transplant centres (Supplementary Figure 1). The initial studies by the Miami group described a moderate negative CC of citrulline levels with rejection (Pappas, Saudubray [25] reported CC=-0.590) but in the recent studies by Ruiz, Tryphonopoulos [26] and Hibi, Nishida [27], which include up to around 10,000 plasma citrulline samples, correlation reaches up to a strong -0.977 with acute cellular rejection. The CCs are shown in Supplementary Figure 2 without meta-analysis due to severe heterogeneity.
Two other trends were noted in the transplantation articles: first, citrulline appears to normalize after a certain amount time post transplantation and this is a significant factor against rejection;[28-31] secondly, the cut-off value of citrulline predicting rejection varies. The Miami group have described that citrulline levels have a very high negative predictive value for moderate or severe acute rejection (negative prognostic value=99% with cut-off level 13μmol/L; sensitivity=96.4% with particularly high specificity in adult patients);[27, 32, 33] but the Mount Sinai Group did not find that citrulline had satisfactory diagnostic accuracy to discern rejection.[34] Multiple parameters need to be taken into account when measuring citrulline in this group, including time after surgery, renal function, graft pathology, infection, sepsis, donor and patient anthropometrics.[24, 29, 34]

Short Bowel Syndrome (SBS)

Thirty five papers and abstracts were identified which included eventually 26 studies (Supplementary Table 3). Quality assessment showed possibilities of reporting, attrition and detection bias (Figure 2).

Citrulline and Residual Small Bowel Length

Twenty one studies were analysed and the random effects analysis of CCs produced a pooled effect of 0.67 (95% CI [0.39, 0.84], range [0.26, 0.99]), which indicates a strong correlation (Figure 3). In addition there was evidence of publication bias (funnel plot asymmetry, Egger's test p=0.001 but Begg's test p=0.156, Fail-safe N=5,286) and high heterogeneity (I^2=97%, p<0.001) (Figure 4).

--Figure 3, Figure 4 here--

When analysed by subgroups, heterogeneity remained high with respect to patient type, measurement method, but was reduced in studies from the USA, Spain and Italy. (Supplementary Figure 3). Meta-regression also did not identify any heterogeneity with respect to male percentage, mean age, mean BMI, mean citrulline concentration and mean small bowel length (Supplementary Table 7).

Citrulline between SBS Patients and Healthy Controls

Twelve studies were analysed and the random effects model showed that citrulline levels were decreased by -12μmol/L (95% CI [-16.3, -7.7]) (SMD -1.34, 95% CI [-1.77, -0.91]); there was heterogeneity (MD: I^2=92%, p<0.001; SMD: I^2=80%, p<0.001) (Figure 6A) but no publication bias (symmetric funnel plot, Egger's test p=0.606, Begg's test p=0.537, Fail-safe N=853) (Supplementary Figure 5B).

Citrulline Levels in Parenteral Nutrition (PN) Dependent vs PN Independent Patients

Twelve studies were analysed comparing levels of citrulline in patients who needed PN against patients who were weaned off PN. The random effects model showed that citrulline levels were decreased by -13.3μmol/L (95% CI [-17.6, -9.0]) (SMD -1.58, 95% CI [-2.09, -1.08]); there was heterogeneity (MD: I^2=89%, p<0.001; SMD: I^2=79%, p<0.001) but no publication bias (symmetric funnel plot, Egger's test p=0.174, Begg's test p=0.451, Fail-safe N=753) (Supplementary Figures 4A and 5D).
Sixteen studies described diagnostic accuracy results (Supplementary Table 8). Overall, citrulline levels have a sensitivity of 82.5% and specificity 82% (Supplementary Table 9, Supplementary Figure 6). Since thirteen studies compared citrulline levels at a cut-off level of 20μmol/L to discern among SBS patients who needed

PN or not, the meta-analysed sensitivity and specificity reflect mostly that. Any heterogeneity present is due to different cut-off levels and comparison groups.

Teduglutide and Citrulline Levels

There have been four studies studying the effect of teduglutide – a GLP-2 analogue which acts as a growth factor in patients with SBS – on citrulline levels (Supplementary Table 3). Three studies compared citrulline levels in patients who received teduglutide against patients who received placebo in Crohn's disease and SBS. The random effects model showed that citrulline levels in teduglutide vs placebo were increased by 12.4μmol/L (95% CI [5.5, 19.3]) (SMD 1.02, 95% CI [0.47, 1.58]) and there was heterogeneity (MD: I^2=85%, p=0.001; SMD: I^2=73%, p=0.02). Four studies provided citrulline levels of patients who received teduglutide at the end of treatment compared to their baseline. The random effects model showed that citrulline levels in teduglutide at end of treatment vs baseline were increased by 15.3μmol/L (95% CI [12.5, 18.2]) (SMD 1.21, 95% CI [1.00, 1.43]); there was no heterogeneity (MD: I^2=16, p=0.31; SMD: I^2=0%, p=0.56) (Supplementary Figures 4B,C).

Enteropathies

Villous Atrophy Syndrome

Eleven studies were used in meta-analyses in this category which included cases that had coeliac disease or other enteropathy (Supplementary Table 4). Meta-analyses firstly compare citrulline levels in diseased patients against controls, then those who had received gluten free diet (GFD) compared to those who had not, and finally association of citrulline levels with disease severity. Severity of disease was categorised broadly and included either histological diagnoses, worsening symptoms or any other metric reported by authors which indicated severity of the enteropathy. Severity is to be considered as a scale by which higher values indicate more severe disease and lower values indicate less severe disease. The random effects model showed that citrulline levels in coeliac disease patients compared to control were decreased by -9.7μmol/L (95% CI [-13.8, -5.6]) (SMD -0.99, 95% CI [-1.30, -0.67]); there was heterogeneity (MD: I^2=89%, p<0.001; SMD: I^2=78%, p<0.001) but no publication bias (symmetric funnel plot, Egger's test p=0.247, Begg's test p=0.283) (Figure 6A, Supplementary Figure 5C). The random effects model showed that citrulline levels were decreased by -8.2μmol/L (95% CI [-10.4, -5.9]) (SMD -1.08, 95% CI [-1.42, -0.75]) in those patients who had not received GFD compared to those who had (Supplementary Figure 4D).[35-39]

Crohn's Disease

Citrulline levels were compared between Crohn's disease patients and controls in two studies.[40, 41] The random effects model showed that citrulline levels in patients vs controls was decreased by -9.7μmol/L (95% CI [-12.6, -6.7]) (SMD -1.19, 95% CI [-1.63, -0.75]); there was no heterogeneity (MD: I^2=0%, p=0.90; SMD: I^2=0%, p=0.99) (Figure 6A).

Acute Mucosal Enteropathy and Cancer Treatments

Acute mucosal enteropathy can cause a significant loss of enterocytes. Fourteen studies were used in meta-analysis in this category which included cases of patients had received chemoradiation for bone marrow transplant, cancer or other malignant disorder (Supplementary Table 5). Generally:

1. Citrulline decreases in the initial phase of treatment and then increases while the initial gastrointestinal toxicity related to treatment seem to reside.
2. Citrulline decrease is related to higher doses of treatment and is usually inversely correlated with severity of gastrointestinal toxicity. Meta-analysis was performed on this outcome since 14 studies were identified.

The random effects model showed that citrulline levels were negatively correlated with severity of gastrointestinal toxicity with a moderate correlation of -0.41 (95% CI [-0.51, -0.30]); there was no heterogeneity (I^2=43%, p=0.04) and no publication bias (symmetric funnel plot, Egger's test p=0.009, Begg's test p=0.102) (Figure 6B, Supplementary Figure 5F).

Critical Illness Patients

Twenty five studies were diagnosed investigating citrulline levels in patients with critical illness (Supplementary Table 6). The majority of studies involves patients in intensive care settings which attempt to

correlate decrease in citrulline levels with severity of condition or other sepsis markers. No meta-analyses were performed on these studies due to different measurement methods and inability to extract common outcomes. The following comments can be made:

1. Citrulline appears decreased in most studies and is related to critical illness and markers of sepsis or inflammation.
2. This decrease in citrulline does not necessarily mean that there is intestinal dysfunction since in inflammatory responses and as severe as critical illness, nitric oxide and arginine are depleted through inflammatory pathways hence leading to the reduction of citrulline.[42] This is also corroborated by the fact that citrulline levels increase once critical condition is overcome.
3. Citrulline seems to act as a negative inflammatory marker.

Citrulline Levels: An Overall Assessment

Diagnostic Accuracy

Overall sensitivity of citrulline levels appear to be satisfactory 80% (95% CI [69%-87%]), specificity was 84% (95% CI [77%-89%]) and the diagnostic odds ratio was 20.03 (Supplementary Table 9, Supplementary Figure 7). The sROC curve indicates overall satisfactory diagnostic accuracy of citrulline levels (Figure 5).

--Figure 5 here--

Citrulline Levels in Diseased Patients vs Controls

The random effects model showed that citrulline levels in patients vs controls (30 studies) was decreased by -11.2μmol/L (95% CI [-13.8, -8.6]) (SMD -0.53, 95% CI [-0.69, -0.36]); there was heterogeneity (MD: I^2=95%, p=0.002; SMD: I^2=68.7%, p<0.001) (Figure 6A). No publication bias was observed (symmetric funnel plot, Egger's test p=0.969, Begg's test p=0.986) (Supplementary Figure 5A).

Citrulline Levels as a Marker of Intestinal Disease Severity

Citrulline levels were described in association with disease severity in 28 studies. The random effects model showed that citrulline levels were negatively correlated with severity of disease with a moderate correlation of -0.56 (95% CI [-0.70, -0.37]) (Figure 6B); there was heterogeneity (I^2=95%, p<0.001); but no publication bias (symmetric funnel plot, Egger's test p=0.356, Begg's test p=0.722) (Supplementary Figure 5E). Interestingly, we can see that only in Crohn's disease citrulline is not associated with disease severity (Figure 6B).

--Figure 6 here—

Citrulline and Absorptive Function

Fourteen studies reported an association of citrulline levels with the level of intestinal absorption. Absorption was assessed with the D-xylose absorption test,[40, 43-48] oral or enteral nutrition tolerance,[49-51] and nutrient absorption tests with bomb calorimetry and measuring oral/enteral intake in comparison to faecal and other loses.[52-54] The random effects model showed that citrulline levels were positively correlated with enteral absorption with a moderate correlation of 0.50 (95% CI [0.26, 0.68]) (Figure 7) but there was heterogeneity (I^2=90%, p<0.001).

--Figure 7 here--

Conclusion

The present study is the first meta-analysis on the association of citrulline with gut function. Although citrulline appears to be a strong marker of enterocyte mass, its correlation with intestinal absorption is weaker. This correlation appears clinically significant in SBS. In other conditions where short bowel is not an issue, there is a decrease in mean citrulline compared to healthy controls and citrulline decrease can be correlated to the degree of disease severity. Its interpretation however needs to take into account other factors because its diagnostic accuracy is satisfactory but not completely exclusive of negative cases and it might as well produce

false positive cases. There were various thresholds for discerning a high from low citrulline level but the level of 20μmol/L seems to be most prevalent.

In critical illness the interpretation of a low citrulline as a marker of intestinal dysfunction should be treated with caution – in a similar manner that a low albumin in a critical ill patients needs to be cautiously interpreted as malnutrition. The availability of nitric oxide and arginine during septic and inflammatory states is decreased hence decreasing citrulline and in this context citrulline could be a negative inflammatory marker – without excluding enteropathy of acute illness.

Limitations of the present meta-analysis stem from various sources of heterogeneity and possibility of publication bias, detection bias and confounding bias. It was a pattern in the present review that many studies did not analyse confounding factors such as other amino acids, renal function (citrulline's pathways involve a renal component) and inflammatory state. Also different methods exist for plasma citrulline measurement, sample preparation, population parameters, disease severity, absorption, and small bowel length. Although heterogeneity is partially explained by geographical factors, ultimately this reflects different clinical and analytical practices throughout the world. The random effects models performed take heterogeneity into account and thus were the preferred method of analysis. Standardization of measurement methods and practices will possibly allow for comparable and more homogeneous results, resulting in meaningful clinical interpretation.

Although interest in citrulline originated from intestinal failure and intestinal transplant medicine, we believe that its application extends to the general gastroenterologist since it has to do with intestinal function per se. Is the bowel working? This exact question has led investigation into citrulline's response in enteropathies such as Crohn's disease, coeliac disease, critical care enteropathy, and mucositis related to bone marrow transplant and chemo-radiotherapy so far. Serial citrulline measurements seem to reflect patterns of mucosal barrier injury and hence are associated with septic episodes in transplant and critical illness patients, setting the ground for use as a marker of early intestinal dysfunction. Its use in SBS is multifactorial, assisting towards the decision of the absorptive capacity of the bowel and hence the need for PN. Nevertheless, citrulline needs be considered within the individual patient context due to measurement variations between centres, countries and populations, with unequal normal ranges and average values. The presence of heterogeneous results in the present systematic review reflects this, possibly also explaining its current niche status (as yet).

In conclusion, citrulline concentration is decreased compared to controls in intestinal compromise states; it has a sensitivity and specificity of ~80%; it is negatively correlated with disease severity in intestinal enteropathies; it is positively correlated with small bowel length in short bowel syndrome; and it is moderately correlated with enteral absorption in various conditions. Overall, lower citrulline levels are indicative of acute or chronic intestinal insufficiency.

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Declaration of Conflicting Interest

The Authors declare that there is no conflict of interest.

Figure

Figure 1 Flow chart for systematic review of studies.

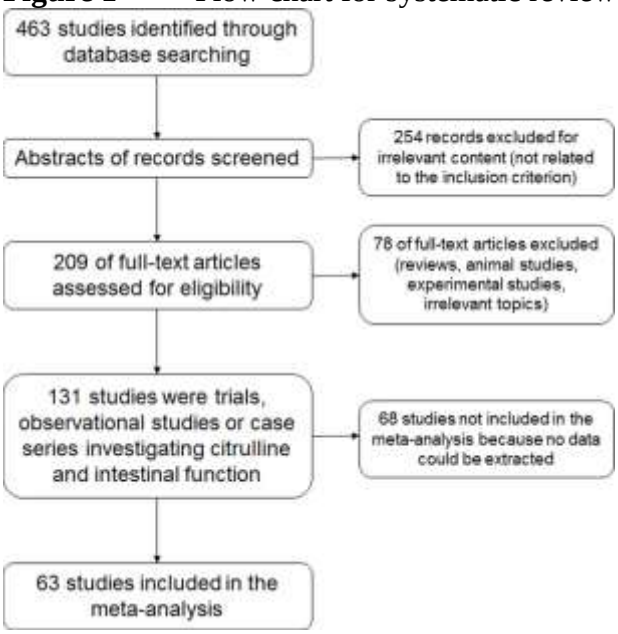


Figure 2 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies (all studies).

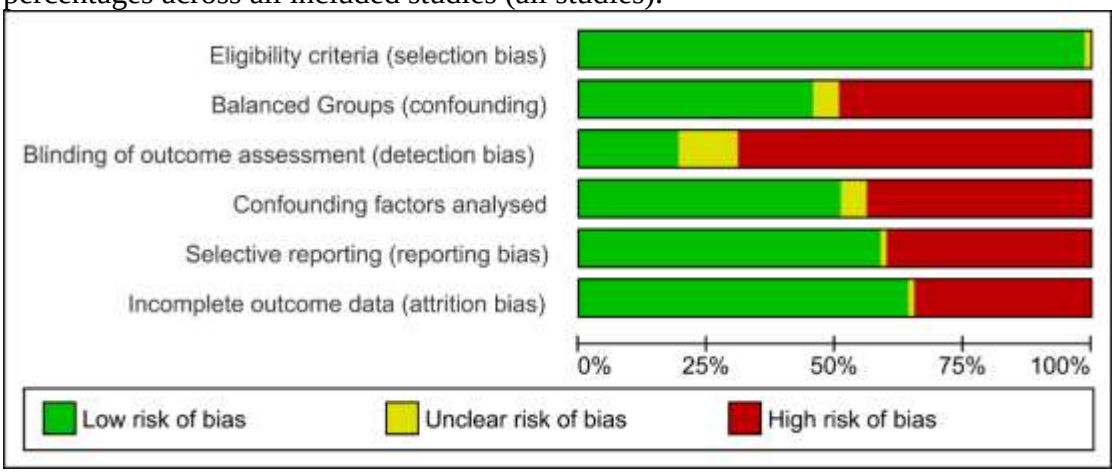


Figure 3 Forest plot. Correlation coefficient with small bowel length in short bowel syndrome.

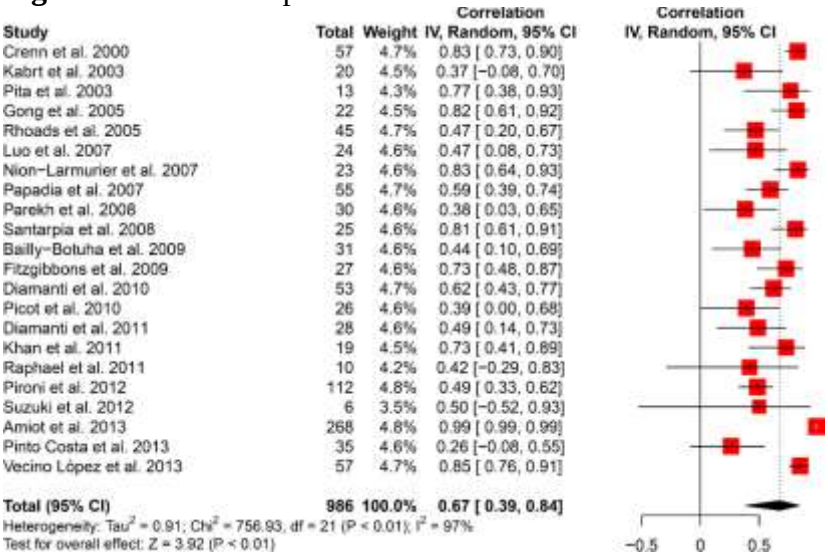


Figure 4 Funnel plot. Correlation coefficient with small bowel length in short bowel syndrome – there is asymmetry in the plot indicating publication bias.

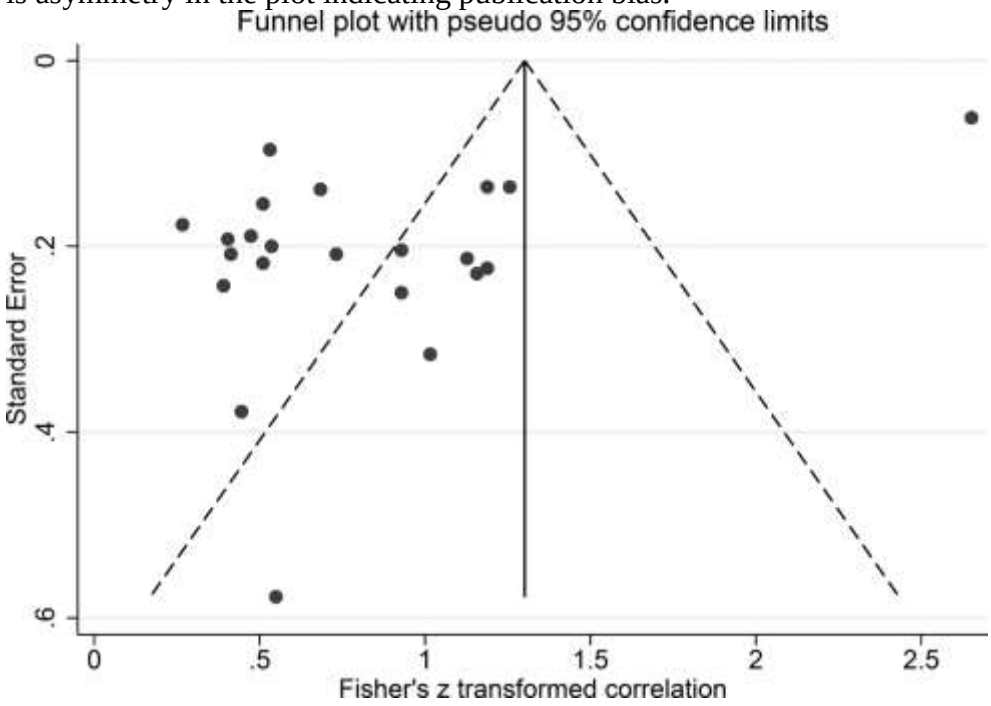


Figure 5 Summary ROC curve for all studies of diagnostic accuracy (26 studies).

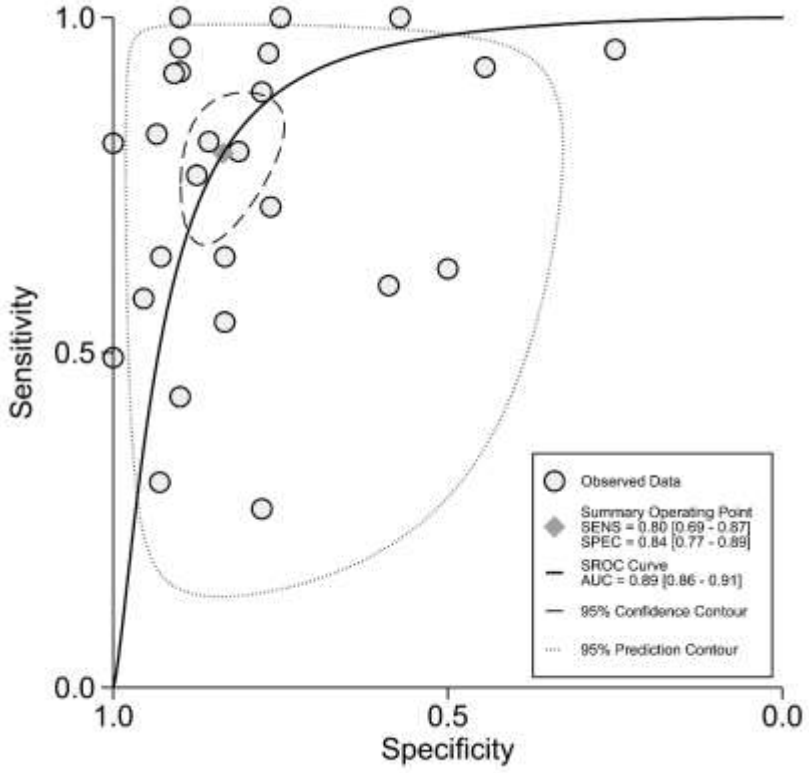


Figure 6 A. Forest plot with overall weighted mean difference of patients with a condition against controls (30 studies). B. Forest plot with correlation coefficients with severity in all available studies (28 studies).

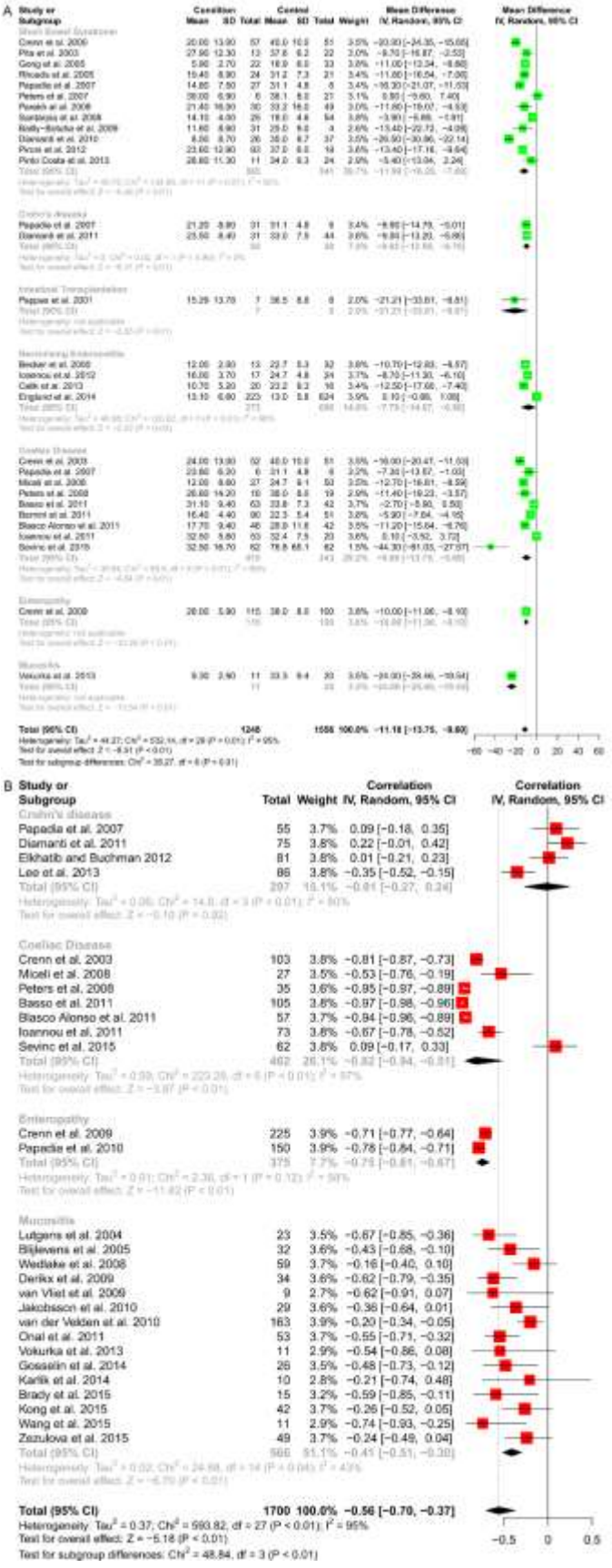
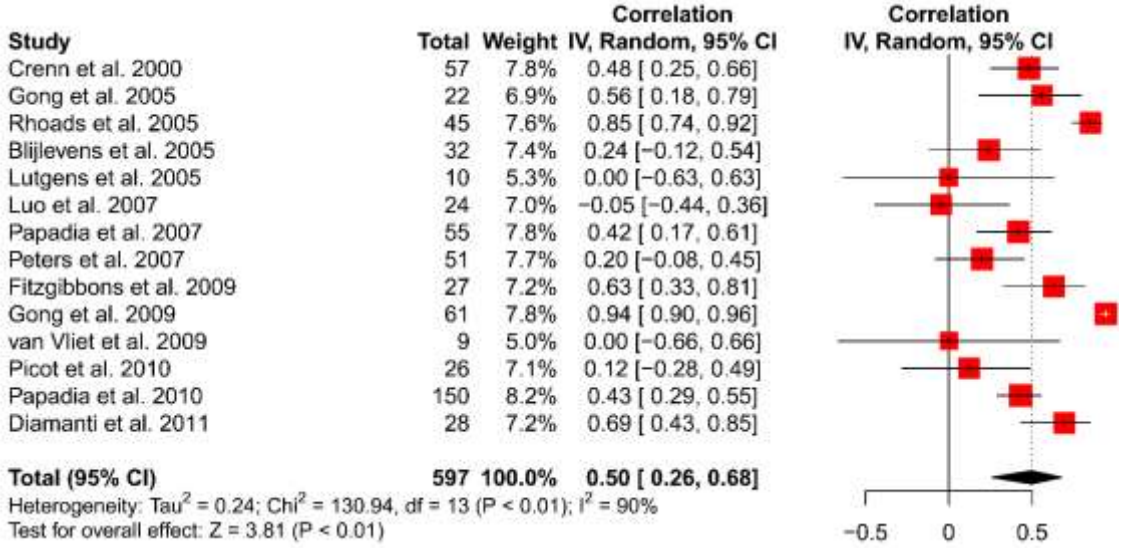


Figure 7 Forest plot with correlation coefficients of citrulline levels with enteral absorption (14 studies).



Supplementary Materials

Abbreviations

AUC: Area under the curve
BMI: Body mass index
CC: Correlation coefficient
CD: Crohn's disease
CeD: Coeliac disease
CI: Confidence interval
df: Degrees of freedom
FN: False negatives
FP: False positives
GFD: Gluten free diet
GLP-2: Glucagon-like peptide-2
HIV: Human immunodeficiency virus
HPLC: High performance liquid chromatography
HPN: home parenteral nutrition
HSROC: Hierarchical summary receiver operating curve
IEC: Ion exchange chromatography
IF: Intestinal failure
MD: Mean difference
MOOSE: Meta-analysis of Observational Studies in Epidemiology
NEC: Necrotising enterocolitis
P/p: p-value
PN: Parenteral nutrition
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROC: Receiver operating curve
RTI: Research Triangle Institute
SBS: short bowel syndrome
SE: Standard error
SMD: Standardised mean difference
sROC: summary Receiver operating curve
TMS: tandem mass spectrometry
TN: true negative
TP: true positives
WMD: Weighted mean difference
μ: micro
μM: μmol/L

Supplementary Methods

Study Eligibility Criteria

The inclusion criteria for this systematic review were: any empirical study (abstract and full paper) describing investigation of citrulline in relation to the term intestinal function. Intestinal function was considered in a very broad term and could mean enterocyte mass, diarrhoea, absorption, or even deranged citrulline levels in correlation with a compromised gut. The only papers that were excluded were those whose object of investigation was not related to intestinal function. There was no restriction to language of papers and the types of interventions could include observational studies, randomized controlled trials, case series and case reports. For the meta-analysis papers had to provide sufficient data to produce an effect measure.

Search Strategy and Terms

PRISMA guidelines and MOOSE checklist for systematic reviews and meta-analyses were used [8, 9]. Electronic database searches were conducted in Google Scholar, Pubmed/Medline, Scopus, EMBASE and Cochrane Library with no year limits. Publisher databases were also searched (Sciencedirect.com, link.springer.com, Wiley library Online, Highwire Press, Nature.com, Ovid, Cambridge University Press). The search keywords were: citrulline, intestine, gut, bowel, intestinal, mucositis, Crohn's disease, short bowel, radiotherapy, cancer, sepsis, absorption, enterocyte, critically ill, and colitis. The date of search was up until 1 July 2015. The bibliographies from all included manuscripts and hand searching of relevant gastroenterology and nutrition journals were used to identify further references. The present study does not report results of a clinical trial and it did not involve primary research on humans.

Study Selection, Data Extraction and Quality Assessment

The resulting studies (in abstract form) were assessed against the inclusion criteria. When there was insufficient information available in the abstract, the full text was reviewed. Then, data were extracted from the selected studies including: author, year of publication, aim of the study, country, continent, sample size, mean age, male percentage, study design, results. The quality of studies (risk of bias) was assessed with elements from Cochrane Collaboration's tool[10] and the RTI Item Bank for Observational Studies,[11, 12] which assess selection, attrition, detection and confounding biases. For the meta-analysis, studies were examined for *p*-values, means and standard deviations, correlation coefficients or other metrics depicting the association of citrulline with intestinal function. Metrics were converted to the standardized mean difference (SMD) [13, 14] or weighted mean difference (WMD), where means and standard deviations for groups under comparison were identified,[15] and/or correlation coefficients (CCs). Examples of outcomes included correlations of citrulline levels with small bowel length, with absorption tests/enteral caloric intake, differences in citrulline between tests groups and controls etc. Particularly, we included studies that satisfied the following criteria: a) for correlations of citrulline with small bowel length, only short bowel syndrome; b) for absorptive marker correlations, all patient groups c) for gastrointestinal disease severity, all patient groups. Where available, diagnostic accuracy data were also collected.

Statistical Analysis

Quantitative analysis was performed with Stata 12.0 (StataCorp LP, Texas), Review Manager 5.3 (Cochrane Collaboration, Copenhagen), SPSS 22.0 (IBM Corp., Armonk, NY), and R (R Foundation for Statistical Computing, Vienna, Austria). SMDs/WMDs/CCs were extracted from studies when available. The strength of association was categorized as following: small, SMD = 0.2; moderate, SMD = 0.5; and large, SMD = 0.8; WMD has units and reflects the units of the outcome under description; small, CC = 0.1; moderate, CC = 0.3; and large, CC = 0.5.[55, 56] A random effects model was used to produce a pooled estimate of the SMDs/WMDs/CCs. With the random effect model, studies are weighted by the inverse of their variance with tau-squared (τ^2), taking into account the within study variance for estimating the correlation coefficient in each study and the between studies variance (e.g. because of different designs or methods used but also possible biological reasons) [57]. Statistical heterogeneity was assessed using Cochran's *Q* test, which examines the null hypothesis that all studies are evaluating the same effect [58]. Statistical significance for heterogeneity was set as $p \leq 0.10$. Heterogeneity was quantified using the I^2 statistic, indicating the percentage of total variation across studies that is due to heterogeneity rather than chance [58]. I^2 value of 0 % was considered to indicate no observed heterogeneity whilst a value > 50 % substantial heterogeneity [19, 59-61]. Heterogeneity was further investigated with subgroup analysis and meta-regression. Publication bias was assessed using funnel plots, Egger's test, Begg's test and Rosenthal's number [16-18]. A funnel plot was created for the clinical measures with more than 10 studies [62]. This is a scatter plot of the effect estimates from individual studies against a

measurement of the study's sample size or precision. Resemblance of a symmetrical inverted funnel supports that findings are due to sampling variation alone; thus, absence of bias [62].

Regarding correlation coefficients, it is common practice not to perform syntheses on the correlation coefficient itself because the variance depends strongly on the correlation. Rather, the correlation is converted to the Fisher's *z* scale (not to be confused with the *z*-statistics used with significance tests), and all analyses are performed using the transformed values. The results, such as the summary effect and its confidence interval, would then be converted back to correlations for presentation. The transformation from sample correlation *r* to Fisher's *z* is given by $z = 0.5 \times \ln\left(\frac{1+r}{1-r}\right)$. The variance of *z* is $V_z = \frac{1}{n-3}$ and the standard error is $SE_z = \sqrt{V_z}$, where *n* is the sample size of the study. We then convert each of these values back to correlation units using $r = \frac{e^{2z}-1}{e^{2z}+1}$.

Regarding diagnostic accuracy data, following the robust construction of the diagnostic 2 × 2 tables, specificity, sensitivity, and 95% CI for each of the included studies was calculated. A hierarchical summary receiver operating curve (HSROC) model was fitted to provide a summary receiver operating curve and to allow derivation of pooled sensitivity and specificity estimates [20]. As suggested by the Cochrane Diagnostic Test Accuracy group (http://srdta.cochrane.org/), no analyses of study heterogeneity were performed, as these tests do not account for heterogeneity explained by phenomena, such as positivity threshold effects [10].

Supplementary Tables

Supplementary Table 1. Necrotizing enterocolitis studies.

No	Authors	Settings (sample and design)	Main Results
1	Becker, Wu [63]	• Aim: to determine whether premature infants who have necrotizing enterocolitis have deficiencies in glutamine and arginine • 4-month prospective cohort study of serum amino acid and urea levels in premature infants • Serum amino acid and urea levels were measured by high-pressure liquid chromatography and enzymatic methods • Control (n = 32), necrotizing enterocolitis (n = 13) (comparable for birth weight, gestational age, and Apgar scores)	• Days 7, 14, 21: Median values of glutamine: 37 % to 57 % lower in the necrotizing enterocolitis group compared to control group ($p < 0.05$) • Days 7 and 14: Median values of arginine, glutamine, alanine, lysine, ornithine, and threonine were decreased by 36 % to 67 % ($p < 0.05$) in the necrotizing enterocolitis group • Citrulline levels were decreased in the necrotizing enterocolitis group compared to control ($p < 0.05$)
2	Ioannou, Diamanti [22]	• Plasma citrulline levels were measured prospectively in 17 preterm neonates with necrotizing enterocolitis stage II during the entire course of the disease • Serial citrulline determinations in 24 healthy preterm neonates on 2, 7, 14, 21 and 28 days of life, served as reference values	• In healthy preterm neonates plasma citrulline levels showed a progressive increase in relation to age • In neonates presenting with necrotizing enterocolitis, mean citrulline levels were significantly lower as compared to controls' citrulline levels (day of life 7: 16.85 ± 4.2 vs 20.5 ± 4.5 μmol/L, $p < 0.05$; day of life 14: 18 ± 4.2 vs 23.5 ± 4.3 μmol/L, $p < 0.01$; day of life 21: 17 ± 2.5 vs 30 ± 5.7 μmol/L, $p < 0.01$) • Optimal citrulline cut-off distinguishing necrotizing enterocolitis patient from controls: 17.75 μmol/L (sensitivity 76%, specificity 87%) • Plasma citrulline at presentation correlated inversely with the duration of parenteral nutrition ($r=-0.49$, $p<0.05$)
3	Celik, Demirel [21]	• Plasma citrulline levels of neonates with a gestational age less than 32 weeks and ≤ 1500 g who developed necrotizing enterocolitis stage II/III were measured by high-performance liquid chromatography • 36 preterm infants including 20 with necrotizing enterocolitis and 16 controls	• Median citrulline levels of necrotizing enterocolitis and control groups were 8.6 and 20.18 μmol/L ($p < 0.05$), and cut-off level of citrulline was 13.15 μmol/L with a sensitivity of 80% and a specificity of 82% • Median arginine levels of necrotizing enterocolitis and control groups were 22.02 and 39.89 μmol/L ($p < 0.05$), and cut-off level of arginine was 28.52 μmol/L with a sensitivity of 70% and a specificity of 75% • Blood sampling day, gender, and parenteral or enteral nutrition did not affect amino acid levels
4	Englund, Rogvi [64]	• Aim: To determine whether citrulline concentrations measured in neonatal dried blood spots could predict necrotizing enterocolitis • National Danish registries were retrospectively searched to identify 361 babies born between 2003 and 2009, diagnosed with necrotizing enterocolitis and a valid citrulline concentration • Control group: 1083 healthy new-borns (three controls for every new-born with necrotizing enterocolitis, matched for birthweight and gestational age)	• Neonatal dried blood spots were collected between 2 and 21 days of life, with a median of 8 days • Necrotizing enterocolitis was not associated with low citrulline concentration ($p = 0.73$)

Supplementary Table 2. Intestinal transplantation studies.

No	Authors	Settings (sample and design)	Main Results
1	Pappas, Saudubray [25]	• Aim: To investigate impact of acute cellular rejection of intestinal allografts on serum citrulline levels • Sample: healthy volunteers (n = 6), patients who underwent small bowel transplant (n = 7) • Concurrent measurement of serum citrulline levels with characterization of acute cellular rejection • Rejection confirmed by biopsy and graded by standardized criteria	• Controls vs post-transplantation samples: significantly higher mean citrulline concentrations at any rejection grade • Mean concentrations declined significantly as rejection severity increased • Statistically significant overall downward trend ($p < 0.05$) • In sequential measurements, citrulline levels increased significantly over time with declining severity of rejection • Significant increase in mean citrulline concentrations between post-transplant days 3-16 and 52-60 ($p < 0.01$)
2	Gondolesi, Fishbein [24]	• Aim: To investigate impact of acute cellular rejection of intestinal allografts on serum citrulline levels • Concurrent measurement of plasma citrulline levels with histopathological diagnosis from biopsy [acute cellular rejection (normal, indeterminate, mild, or moderate), viral enteritis (cytomegalovirus or adenovirus), and for other miscellaneous histological diagnoses • Sample: 9 consecutive intestinal transplant recipients • Thirty-two citrulline measurements	• Mean citrulline levels o overall: 17.5 ± 13.3 μmol/L (range, 0.8 to 68 μmol/L) o normal biopsies:26 ± 15.7 μmol/L o indeterminate biopsies: 11.9 ± 7.7 μmol/L o mild rejection: 15.4 ± 7.5 μmol/L o moderate rejection: 5.5 ± 0.7 μmol/L o viral enteritis: 9.3 ± 5.85 μmol/L o functional bowel biopsies (n = 22) vs dysfunctional bowel biopsies (n = 10): 19.3 ± 13.6 μmol/L vs 7.8 ± 4.7 μmol/L; p = 0.0001 • Pearson correlation coefficient between citrulline levels and rejection: -0.425 ($p = 0.05$) • Spearman's rho correlation coefficient between citrulline levels and rejection: -0.52 ($p < 0.01$)
3	Pappas, Saudubray [28]	• Aim: To investigate impact of rejection of intestinal allografts on serum citrulline levels • 10 pre-transplant samples, 11 control specimens, 49 post-transplant samples from 7 patients along with 1 pre-transplant serum sample from each patient and 6 samples from healthy controls, 83 sequential serum samples from 11 patients (5 children, 6 adults), median follow-up 26 days • All samples obtained within 3 days of biopsy	• Pre-transplant specimens vs healthy controls: significant difference in mean citrulline ($p < 0.01$) • Mean citrulline levels declined significantly with increasing acute cellular rejection in post-transplant period • Mean citrulline levels: pre-transplant: 20.1 ± 10.3 μmol/L vs control: 40.0 ± 7.3 μmol/L ($p < 0.01$)
4	Gondolesi, Kaufman [29]	• Aim: To analyse plasma citrulline in intestinal transplant recipients without rejection or other histological abnormalities • Sample: 40 patients • Plasma citrulline measured with high performance liquid chromatography Beckman amino acid analyser (within 24 h of protocol or clinically indicated endoscopic biopsy procured > 6 and < 360 days post-transplant) • Measurements included for analysis corresponded to normal (or minimally abnormal) biopsies that remained so for 7 days • Criteria met in: 145 samples, 10 adults and 14 children	• Mean citrulline levels: o overall: 34.0 ± 19.9 μmol/L o between 6 and 30 days post-transplant: 22.2 ± 13.2 μmol/L o between 30 and 60 days post-transplant: 34.9 ± 17.2 μmol/L ($p = 0.001$) o between 60 and 90 days post-transplant: 43.6 ± 15.8 μmol/L ($p = 0.001$) o stable until end of first year • Plasma citrulline lower in 13 patients with body surface area ≤ 1 m^2 vs 11 patients with body surface area ≥ 1.1 m^2 ($p = 0.0001$) • Plasma citrulline increased linearly during first 120 days in both body surface area groups ($r = 0.573$, $r = 0.512$; $p = 0.0001$)
5	Pappas, G Tzakis [30]	• Aim: To compare serum citrulline concentrations with biopsy-based grades of rejection • Sample: 26 isolated intestinal and multivisceral transplant recipients • Other factors recorded: patient and donor age and sex, ischemia time, serum creatinine, type of transplant. • Straight-line fitting of citrulline levels over time (stepwise linear regression)	• Median time-to-achieve normal citrulline (≥ 30 μmol/L): 79 days post-transplant (n=21) • Significantly higher maximum grade of rejection after 14 days post-transplant linked to longer time-to-achieve normal citrulline ($p < 0.00001$) and not receiving a multivisceral transplant ($p = 0.0005$) • Normalization of citrulline levels did not occur in some cases with moderate-to-severe rejection

No	Authors	Settings (sample and design)	Main Results
6	Pappas, Tzakis [31]	• Aim: To compare serum citrulline concentrations with biopsy-based grades of rejection • Sample: 26 isolated intestinal and multivisceral transplant recipients • Serum citrulline concentrations determined by ion exchange chromatography and compared to biopsy-based grade of ACR. • Other factors recorded: patient and donor age and sex, ischemia time, serum creatinine • Straight-line fitting of citrulline levels over time (stepwise linear regression)	• Time to achieve normal citrulline (>30 μmol/L): 1-730 days post-transplant (n = 21) with increasing citrulline levels over time • Longer time-to-achieve normal citrulline: independent predictor of maximum acute cellular rejection ($p < 0.0001$) and average acute cellular rejection ($p = 0.0059$) 14 days post-transplant.
7	Yu, Tuteja [65]	• Aim: To investigate correlation between plasma and dried blood spot specimen citrulline concentrations after intestinal transplantation • Plasma and dried blood spot samples were analysed by hydrophilic interaction chromatography tandem mass spectrometry • Correlation analysed by type of surgery, sonication time, dried blood spot citrulline levels, the time interval between the blood sample collection and assay date	• Very strong linear correlation between the plasma and dried blood spot citrulline concentrations ($r = 0.87$, $p < 0.001$) • Correlation was maintained when evaluating only intestinal transplant recipients • Sonication time, citrulline concentrations, length of time to assay date: no effect on strength of correlation ($p > 0.05$)

8	David, Gaynor [23]	• Aim: To determine whether serum citrulline level within 30 days of acute rejection could predict rejection episode
		• Comparison of mean citrulline level determined within 30 days of the start of an acute rejection episode against mean citrulline level during a rejection-free period
		• Sample: 22 patients who experienced 37 episodes
			• Mean serum citrulline levels:
			  ○ Mild rejection (12 episodes): 15.0 ± 2.3 μmol/L (prior) vs 18.8 ± 2.4 μmol/L (rejection-free periods) ($p = 0.17$)
			  ○ Moderate to severe rejection (25 episodes): 12.4 ± 1.1 μmol/L (prior) vs 18.8 ± 2.0 μmol/L (rejection-free periods) ($p = 0.002$)

9	Gondolesi, Ghirardo [34]	• Aim: To determine sensitivity and specificity of plasma citrulline as diagnostic tool for allograft injury • 403 citrulline samples within 24 h of intestinal biopsy in 49 patients • Correlation of citrulline with mucosal damage and histopathological diagnoses	• Significant mucosal damage vs intestines with no or mild injury: plasma citrulline 22.9 ± 15.4 vs 38 ± 23.2 μmol/L ($p < 0.0001$) • Sensitivity and specificity of the test were 80% and 58.1% for rejection, and 56.5% and 66% for viral enteritis
10	David, Selvaggi [32]	• Aim: to determine citrulline cut-off levels for diagnosis of acute rejection and predictors of citrulline levels post-transplant • Dried blood spot citrulline samples from 57 intestinal transplant recipients at or beyond 3 months post-transplant • Stepwise linear regression was performed to determine significant predictors patients' citrulline levels	• Seven significant predictors of lower citrulline levels were identified: presence of mild, moderate, or severe acute cellular rejection, presence of bacteraemia or respiratory infection; paediatric age; and time from transplant to sample ($p < 0.00001$) • A cut-off level citrulline 13 μmol/L had high sensitivity for detecting moderate or severe acute cellular rejection negative predictive value were high (96.4%, 99%, respectively). Specificity was 54% to 74% in children and 83% to 88% in adults.
11	David, Szutan [33]	• Aim: To determine the significant value of citrulline level in the post-transplant setting, which would correlate with complications of rejection and infection • 2,135 dried blood spot citrulline samples were obtained from 57 small intestine transplant recipients three months or more after post-transplant	• A cut-off level citrulline 13 μmol/L had high sensitivity for detecting moderate or severe acute cellular rejection (96.4%) • Specificity was high (54%-74% in children and 83%-88% in adults), and the negative predictive value was >99%

12	Ruiz, Tryphonopoulos [26]	• Aim: To evaluate the correlation of plasma citrulline and rejection episodes in intestinal transplantation
		• From January 2007 until present, citrulline was measured from small bowel patients and examined for correlation with rejection status of the graft as defined by graft biopsies
		• 5195 citrulline samples were analysed
			• Average serum citrulline levels decreased significantly when patients presented a rejection episode
			  ○ No rejection: 17.38 μmol/L
			  ○ mild rejection, 13.05 μmol/L
			  ○ moderate rejection, 7.98 μmol/L
			  ○ severe rejection, 6.05 μmol/L

13	Hibi, Nishida [27]	• Aim: To investigate the association between citrulline levels acute cellular rejection to identify a cut-off point of citrulline that predicts acute cellular rejection beyond 3 months postransplant in the paediatric patient population. • 13,499 citrulline samples were prospectively collected from 111 consecutive paediatric intestinal/multivisceral transplant recipients. 2,155 were obtained concurrently with intestinal biopsies (1995-2011) • 185 acute cellular rejection episodes observed among 74/111 patients (median follow-up: 4.4 years).	• Citrulline levels were inversely proportional to the severity of acute cellular rejection. • Negative predictive values for any type of acute cellular rejection (cut-off, 20 μmol/L) and moderate/severe acute cellular rejection (cut-off, 10 mumol/L) were 95% and 99%, respectively. • When patients were divided according to graft size, diagnostic accuracy using the same cut-off was identical. • Subgroup analysis by the timing of citrulline measurement prior to biopsy varying from 1 to 7 days demonstrated comparable results.

Supplementary Table 3. Studies regarding short bowel syndrome.

No	Authors	Settings (sample and design)	Main Results
1	Crenn, Coudray-Lucas [66, 67]	• 57 patients post-absorptive citrulline concentration was measured and parenteral nutrition dependence was used to define permanent (n = 37) and transient (n = 20) intestinal failure • Absorptive function, studied over a 3-day period, was evaluated by net digestive absorption for protein and fat • Relations between quantitative values were assessed by linear regression analysis and cut-off citrulline threshold, for a diagnosis of intestinal failure by linear discriminant analysis	• Short bowel syndrome vs controls (n = 51): 20 ± 13 vs. 40 ± 10 μmol/L ($p < 0.001$) • Citrulline levels were correlated to small bowel length ($p < 0.0001$, $r = 0.86$) and to net digestive absorption of fat, but not to body mass index and creatinine clearance • A cut-off level of 20 μmol/L classified short bowel patients with permanent intestinal failure with high sensitivity (92%), specificity (90%), positive predictive value (95%), and negative value (86%) and was a more reliable indicator (odds ratio 20.0, 95% CI 1.9-206.1) than anatomic variables (odds ratio 2.9, 95% CI 0.5-15.8) to separate transient from permanent intestinal failure
2	Pita, Wakabayashi [68, 69]	• Sample: 13 short bowel syndrome patients (7 men; 60.2 ± 15.2 years) • Groups according to remnant bowel length (Group A: 61-150 cm, n =6; Group B: > 60 cm, n =7) • Plasma urea-cycle amino acids, ammonium and urinary orotic acid were determined	• Regarding citrulline, Group B levels were significantly lower vs controls ($p < 0.001$) • Comparisons between patient groups showed higher arginine in Group A ($p < 0.05$) and non-statistically lower citrulline in Group B

3	Kábrt, Hyánek [70]	• Sample: adult patients with short bowel syndrome (n = 20)
		  ○ 10 on long-term parenteral nutrition
		  ○ 10 not on parenteral nutrition
		  ○ Controls: 9 normal subjects
		• Nutritional assessment with anthropometry and laboratory parameters
		• Post-absorptive plasma concentrations of amino acids determined by ion exchange chromatography
			• Total amino acids and non-essential amino acids were same in all groups.
			• Essential amino acid/non-essential amino acid and branched-chain amino acid/total amino acid ratios were significantly lower in the short bowel syndrome patient group than in the normal controls.
			• Concentration of citrulline was significantly lower only in the group of short bowel syndrome patients who had to remain on total parenteral nutrition.

4	Gong, Zhu [47, 71]	• Aim: To investigate the significance of serum citrulline in evaluating the remnant small bowel enterocytes mass and absorptive function in short bowel patients • Serum citrulline concentrations were determined using high-performance liquid chromatography in 22 short bowel syndrome patients and 33 healthy controls • Five-hour urine D-xylose excretion and digestive protein absorption were measured using high-performance liquid chromatography and micro-Kjeldahl method	• Serum citrulline levels were significantly lower in short bowel syndrome patients compared with healthy controls • In short bowel syndrome patients, citrulline correlated with remnant small bowel length ($r = 0.82$, $p < 0.001$), surface area ($r = 0.86$, $p < 0.001$), 5-h urine D-xylose excretion ($r = 0.56$, $p = 0.007$), and digestive protein absorption ($r = 0.48$, $p = 0.046$). • Citrulline level in six patients receiving rehabilitation therapy correlated with intestinal protein absorption ($r = 0.79$, $p = 0.063$) and urine D-xylose excretion ($r = 0.81$, $p = 0.053$).
5	Rhoads, Plunkett [49]	• Aim: To determine whether serum citrulline levels correlate with total parenteral nutrition independence in children with short bowel syndrome • Study design: serum amino acid profiles over a 24-month interval from all infants with short bowel syndrome 3 weeks to 4 years of age. • Remaining small intestine length was recorded at surgery, and % of enteral calories tolerated was determined in 24 infants with short bowel syndrome and 21 age-matched controls	• In patients with short bowel syndrome, serum citrulline correlated linearly with tolerated enteral calories ($r = 0.85$, $p < 0.001$) and bowel length ($r = 0.47$, $p < 0.03$) • A citrulline cut-off level of19 μmol/L had 94% sensitivity and 67% parenteral nutrition independence. • Mean citrulline levels: • short bowel syndrome weaned off parenteral nutrition:30 ± 2 μmol/L • short bowel syndrome subsequently weaned off parenteral nutrition: 20 ± 2 μmol/L • short bowel syndrome parenteral nutrition: 11 ± 2 μmol/L • Controls: 31 ± 2 μmol/L
6	Luo, Fernández-Estívariz [52]	• Aim: To examine whether plasma citrulline and glutamine concentrations are biomarkers of residual small intestinal length and nutrient absorptive functions in adult short bowel syndrome patients • Sample: 24 patients on parenteral nutrition in a double-blind, randomized trial of individualized dietary modification ± recombinant human growth hormone • intestinal absorption studies and plasma measurements of citrulline and glutamine were performed	• Residual small bowel length was positively correlated with baseline plasma citrulline ($r = 0.467$, $p = 0.028$) • No significant correlations between absolute citrulline and glutamine concentrations and the percent absorption of nutrient substrates at any time point were observed. • No correlation between the change in citrulline and glutamine concentration and the change in % nutrient absorption was observed
7	Nion-Larmurier, Seksik [72]	• Twenty-three patients who had a bowel resection and a provisional ileostomy were studied in the month before and months after recovery • Basal citrulline levels were measured before and after restoration of continuity on 16 operated patients and prospectively in 7.	• Citrulline levels (mean ± SD) before recovery were 20.9 ± 8.6 μmol/L (n = 23) • Citrulline levels correlated to the length of bowel length ($r = 0.83$; $p = 0.002$)

No	Authors	Settings (sample and design)	Main Results
8	[40,] Papadia, Sherwood [73, 74]	• Sample: (a) Crohn's disease with massive small bowel resection leaving < 50 cm (n = 6), (b) Crohn's disease with 50-150 cm remaining (n = 9), (c) Crohn's disease with no resection but active inflammation (n = 7), (d) Crohn's disease without resection or active inflammation (n = 9), (e) mesenteric infarction with resection leaving < 50 cm (n = 6), (f) mesenteric infarction leaving 50-150 cm (n= 6), (g) active coeliac disease (n = 6), (h) healthy volunteers (n = 6). • Post-absorptive fasting plasma citrulline was measured using reverse-phase, high performance liquid chromatography. Absorptive capacity and permeability were also measured after oral sugar-mix ingestion	• Plasma citrulline strongly correlated with small bowel length ($p < 0.0001$) and xylose absorption ($p < 0.001$) • No correlation was found with C-reactive protein, permeability, albumin, sedimentation rate, white cell count, or platelet count. • Citrulline levels in Crohn's disease and mesenteric infarction with small bowel length 50-150 cm vs less than 50 cm: 21.0 vs 9.2 μmol/L ($p < 0.0004$), respectively
9	[53,] Peters, Wierdsma [75, 76, 77]	• Aim: to explore diagnostic value of fasting citrulline concentrations to detect decreased intestinal energy absorption in patients with recently diagnosed coeliac disease (n=15), refractory coeliac disease (n = 9)and short bowel syndrome (n = 16) • Fasting plasma citrulline concentrations were determined by high performance liquid chromatography in 40 adult patients and 21 healthy subjects. • Intestinal energy absorption capacity using bomb calorimetry was determined	• Mean citrulline levels: o Refractory celiac disease vs healthy subjects: 28.5 ± 9.9 vs 38.1 ± 8.0 μmol/L, $p < 0.05$ o Coeliac disease vs healthy subjects 28.5 ± 9.9 vs 38.1 ± 6.4 μmol/L, $p < 0.05$ • Mean intestinal energy absorption capacity: o Short bowel syndrome patients vs healthy subjects: 64.3 ± 18.2 vs 90.3 ± 3.5%, $p < 0.001$ o Refractory celiac disease vs healthy subjects: 64.3 ± 18.2 vs 82.3 ± 11.7%, $p < 0.01$ o Coeliac disease vs healthy subjects 64.3 ± 18.2 vs 89.2 ± 3.4%, $p < 0.001$ • No relation was observed between fasting plasma citrulline concentration and intestinal energy absorption capacity (r=0.09, P=0.56, area under the ROC curve 0.50)
10	Parekh, Natowicz [78]	• Sample: 49 healthy controls with an intact gastrointestinal tract and no known metabolic or digestive diseases and 30 short bowel syndrome (< 200cm small bowel) patients dependent on parenteral • Venous post-absorptive plasma amino acid concentrations were measured in all subjects after an 8 hour fast	• Mean citrulline levels: Short bowel syndrome patients vs healthy controls: 21.4 vs 33.2 μmol/L $p = 0.0002$ • Area under the ROC curve was 0.82 (95% CI: 0.71, 0.93) and a citrulline cut-off of 20 μmol/L had 100% specificity and 56.6% sensitivity. • Citrulline increased by 1.65 μmol/L with every 5 year increase in age ($p = 0.044$) • Citrulline increased by 4.9 μmol/L for every 50cm increase in small bowel length ($p = 0.018$) • Citrulline decreased by 9 μmol/L for every 1000 kcal/day increase in parenteral nutrition ($p < 0.0001$)
13	Santarpia, Catanzano [79]	• Sample: 25 patients with short bowel syndrome after at least 18 months since last digestive circuit modification; 24 of them were again evaluated 1 year later. • Ten patients were weaned off parenteral nutrition and 15 were dependent on parenteral nutrition. • Fifty-four healthy volunteers (28 women and 26 men) served as controls.	• Five amino acids (citrulline, leucine, isoleucine, valine and tyrosine) were significantly lower in all short bowel syndrome patients versus controls, whereas glutamine was significantly higher. • Only serum citrulline measured was significantly related to small bowel length.
14	Bailly-Botuha, Colomb [80]	• Prospective plasma citrulline assays were performed in 31 children with short bowel syndrome • Median age was 16 months and median follow-up was 14 months	• Plasma citrulline at inclusion showed a positive correlation with residual short bowel length. • Follow-up values correlated negatively with intestinal failure severity. • Plasma citrulline increased over time during or after weaning from parenteral nutrition (from 15.8 ± 11.5 μmol/L to 19.3 ± 3.8 μmol/L) but remained stable and low in patients who continued on parenteral nutrition (6.5 ± 3.0 μmol/L at inclusion and 7.7 ± 6.0 μmol/L at last follow-up).
15	Fitzgibbons, Ching [50]	• Aim: To evaluate the relationship between citrulline and parenteral nutrition independence in children with short bowel syndrome • Sample: Retrospective review of all patients in a multidisciplinary paediatric intestinal rehabilitation clinic with a recorded citrulline between January 2005 and December 2007 (n = 27)	• Citrulline levels correlated positively with bowel length ($r = 0.73$; $p < 0.0001$) and were a strong predictor of parenteral nutrition independence ($p = 0.002$; area under the ROC curve = 0.88; 95% CI 0.75-1.00). • Optimal citrulline cut-off point distinguishing patients who reached parenteral nutrition independence was 15 μmol/L (sensitivity = 89%; specificity = 78%).
16	Gong, Zhu [48]	• Aim: To evaluate long-term clinical significance of enteral nutrition in weaning adult short bowel patients off parenteral nutrition undergoing intestinal rehabilitation therapy • Sample: 61 adult patients with small bowel length 47.95 ± 19.37 cm were retrospectively analysed	• Nutritional and anthropometric parameters, urine 5-hr D-xylose excretion and serum citrulline levels all increased significantly after intestinal rehabilitation therapy and on follow-up compared with baseline

No	Authors	Settings (sample and design)	Main Results
17	Picot, Garin [54]	• Twenty-six patients with small bowel disruption and double enterostomy were treated with chyme reperfusion • Faecal wet weight, nitrogen and fat absorption, parenteral nutrition delivery and citrulline were measured before and after the initiation of chyme reperfusion with a median follow-up of 30 days.	• Chyme reperfusion decreased the intestinal wet weight output and parenteral nutrition dependence • Chyme reperfusion was associated with a rise in net nitrogen and fat digestive absorption and citrulline (17.0 ± 10.0 vs 31.0 ± 12.0 μmol/L, p = 0.0001). • Before the initiation of chyme reperfusion, citrulline levels correlated positively with the absorptive post-duodenal small bowel length (r = 0.39, p = 0.04), but not with the total post-duodenal small bowel length (r = 0.11, P = 0.60).
18	[51,] Noto, Diamanti [81, 82,] Diamanti, Noto [83]	• Sample: Between March 2005 and March 2010, 28 short bowel syndrome patients on parenteral nutrition • Citrulline levels and enteral intake determinations were measured on inclusion and at 6-month intervals	• Citrulline significantly correlated with the residual duodenum-jejunum length (r^2 = 0.22, p = 0.0113) and with enteral intake (r^2 = 0.20, p = 0.016, r^2 = 0.48, p = 0.0001) • Baseline citrulline over 10 μmol/L and a longitudinal increase >25% provided a weak association with bowel adaptation (likelihood ratios 2.6 and 2.4, respectively), unlike residual small bowel length ≥ 20 cm and the presence of > 50% of the colon.
19	Khan, Miserachs [84]	• Sample: Serum citrulline was measured in 19 subjects with short bowel syndrome; 10 females and 17 were on parenteral nutrition • Age: 7 months to 21 years; Bowel length: 5 to 150 cm, and percentage of parenteral nutrition providing 0-100% of caloric intake.	• Citrulline levels decreased with increased parenteral nutrition intake (r = 0.69) • Citrulline levels correlated with bowel length (r = 0.73)
20	Pironi, Lauro [85, 86, 87]	• Sample: Nineteen healthy subjects and 93 short bowel syndrome patients were studied, 67 on home parenteral nutrition and 26 stable on oral diet	• Mean citrulline levels: • Healthy subjects: 37 μmol/L • Short bowel syndrome patients on oral diet: 33 μmol/L • Short bowel syndrome patients on home parenteral nutrition 20 μmol/L (p < 0.001). • Citrulline cut-off of 14 μmol/L had sensitivity 49%, specificity 100%, p < 0.001; for distinguishing between short bowel syndrome on parenteral nutrition vs oral diet
21	Raphael, Nurko [88]	• Design: Open-labelled pilot study in a limited access program for cisapride. • Indications were short bowel syndrome with underlying dysmotility and difficulty advancing enteral feeds despite standard therapies and without evidence of anatomic obstruction. • Patients received cisapride 0.1 to 0.2 mg/kg per dose for 3 to 4 doses per day.	• Ten patients were enrolled in a multidisciplinary paediatric intestinal rehabilitation program. • Median (IQR) residual bowel length was 102 (85-130) cm. Median (IQR) citrulline level was 14.5 (10.5-31.3) μmol/L. • Seven patients improved in enteral tolerance during treatment and 2 were weaned completely from parenteral nutrition.
22	Suzuki, Kanamori [89]	• Design: To measure plasma citrulline in six patients with intestinal dysfunction who were in the acute and chronic phase for more than 6 months.	• Four patients out of six could be withdrawn from total parenteral nutrition, and their plasma citrulline level increased up to 15 μmol/L • Two patients, who could not be withdrawn from parenteral nutrition, showed very low levels of plasma citrulline throughout the treatment course (under 15 μmol/L)
23	Amiot, Messing [90]	• Sample: 268 non-malignant short bowel syndrome patients • Home parenteral nutrition dependence and survival rate were studied with univariate and multivariate analysis.	• Home parenteral nutrition dependence was significantly decreased with an early (<6 months) plasma citrulline concentration >20 μmol/l, a remaining colon >57% and a remnant small bowel length >75 cm
24	Pinto Costa, Serodio [91]	• Sample: Case-control study, 11 patients with short bowel syndrome, 13 patients submitted to malabsorptive bariatric surgery and 11 healthy controls. • Plasma levels of amino acids were determined, before and after a stimulation test with oral L-glutamine, by ion exchange chromatography.	• Citrulline levels were lower in short bowel patients (28.6 ± 11.3 vs 35.5 ± 11 in operated obese vs 32.2 ± 6.6 μmol/L in controls; p > 0.05) and lower than 25.5 μmol/L in 54.5% of them • Relative variation of citrulline levels at the 80th minute of test was lower in short bowel patients with high predictive capacity of a short bowel ≤ 50 cm (area under ROC curve = 0.823; p = 0.038).

25	Vecino Lopez, Andres Moreno [92]	• Plasma citrulline concentration was determined by chromatography in 57 patients (age 0.5-18 years) admitted to the Intestinal Rehabilitation Unit with intestinal failure.
		• Group I: short bowel syndrome totally dependent on parenteral nutrition
		• Group II: short bowel syndrome under mixed enteral-parenteral nutrition
		• Group III: Intestinal failure weaned off parenteral nutrition after a rehabilitation period
		• Group IV: small bowel transplanted patients weaned off parenteral nutrition and on a normal diet
			• Mean plasma citrulline levels:
			  ○ Group I (n = 15): 7.1 ± 4.1 μmol/L
			  ○ Group II (n = 11): 15.8 ± 8.9 μmol/L
			  ○ Group III (n = 13): 20.6 ± 7.5 μmol/L
			  ○ Group IV (n = 25): 28.8 ± 10.1 μmol/L
			• Values were significantly lower in group I compared to groups II-IV (p < 0.001), and in group II compared to groups III-IV (p < 0.001). Citrulline was correlated with remnant small bowel length (r = 0.85, p< 0.05).
			• In group IV citrulline levels decreased >50% in 3 patients who developed moderate-severe rejection, and in one patient who developed viral enteritis

Teduglutide studies			

No	Authors	Settings (sample and design)	Main Results
1	Buchman, Katz [93]	• Design: Subjects with moderate-to-severe Cronh's disease randomized to placebo or 1 of 3 doses of teduglutide (0.05, 0.10, or 0.20 mg/kg daily) (n = 100) • Primary outcome: the percentage of subjects in each group that responded to treatment, defined as a decrease in Crohn's Disease Activity Index score	• Mean baseline Crohn's Disease Activity Index score was 290.8 ± 57.6, similar across groups • Plasma citrulline was similar across groups at baseline, but increased substantially over time in all teduglutide groups when compared with placebo at week 8
2	Jeppesen, Gilroy [94], Seidner, Joly [95]	• Sample: 83 patients randomised to receive subcutaneous teduglutide 0.10 mg/kg/day (n = 32), 0.05 mg/kg/day (n = 35) or placebo (n = 16) once daily • Responders were subjects who demonstrated reductions of ≥ 20% in parenteral volumes from baseline at weeks 20 and 24	• Three teduglutide-treated patients were completely weaned off parenteral support. • Villus height, plasma citrulline concentration and lean body mass were significantly increased with teduglutide compared with placebo
3	Seidner, Joly [95], Gilroy, O'Keefe [96], Jeppesen, Tappenden [97, 98]	• 24-week study of short bowel syndrome patients who were given subcutaneous teduglutide (0.05 mg/kg/d; n = 43) or placebo (n = 43) once daily. • Parenteral support was reduced if 48-hour urine volumes exceeded baseline values by ≥ 10% • The primary efficacy end point was number of responders	• There were significantly more responders in the teduglutide group (27/43) than the placebo group (13/43, p = 0.002). • At week 24, the mean reduction in parenteral support volume in the teduglutide group was 4.4 ± 3.8 L/week compared with 2.3 ± 2.7 L/week in the placebo group (p < 0.001). • Teduglutide increased plasma concentrations of citrulline, a biomarker of mucosal mass.
4	Naimi, Madsen [99]	• Sample: Eight short bowel syndrome patients (5 Females, 60 ± 7 years; remnant small bowel 111 ± 62 cm) • Design: open-label, sequential study comparing continuous GLP-2 vs three times per day GLP-2 • Post-absorptive plasma citrulline, reflecting enterocyte mass, was measured by high performance liquid chromatography.	• Both GLP-2 dosing regimens reduced diarrhoea and increased wet weight absorption • Significant increases in plasma citrulline (continuous GLP-2: 7.5 ± 7 μmol/L and three times per day GLP-2: 12.7 ± 8 μmol/L; p = 0.001) suggesting intestinotrophic effects in relation to GLP-2 treatment, are followed by increases in relative absorption of energy, carbohydrate and fat.

Supplementary Table 4. Coeliac disease, Crohn's disease and enteropathy studies.

No	Authors	Settings (sample and design)	Main Results
1	Crenn, Vahedi [35]	• Aim: To evaluate citrulline as a marker of severity and extent of villous atrophy in patients without intestinal resection. • Sample: ○ 42 patients with coeliac disease and 10 patients with non-celiac villous atrophy disease were studied by plasma postabsorptive citrulline and biological dosages, biopsies of proximal (duodenojejunal) small bowel and distal ileum (n = 25), or measurement of vitamin B12 absorption (n = 4). ○ 9 patients were re-evaluated after following a gluten-free diet for 1 year ○ Controls: 51 healthy subjects and 10 severely malnourished patients with anorexia nervosa with no intestinal mucosal abnormalities	• Plasma citrulline concentrations: Villous atrophy vs healthy subjects: 24 vs 40μmol/L, $p < 0.001$ • Three cut-offs identifies:<10 μmol/L for patients with diffuse total villous atrophy, 10-20 μmol/L for patients with proximal-only total villous atrophy, and 20-30 μmol/L for patients with partial villous atrophy • Plasma citrulline concentration was correlated to the severity and extent of villous atrophy ($r = 0.81$; $p < 0.001$) and to albumin levels ($r = 0.47$; $p < 0.01$). • Receiver operating characteristic curves indicated that plasma citrulline concentration was the best biological variable to predict villous atrophy • Following a 1-year gluten-free diet, plasma citrulline concentration increased in histologically responsive but not in unresponsive patients
2	Hozyasz, Szaflarska-Popławska [36]	• Aim: To determine amino acid concentrations in coeliac disease patients on gluten-free diet and gluten-containing diet • Sample: 61 patients with coeliac disease • Whole blood citrulline were determined in dried blood spots by tandem mass spectrometry	• Mean citrulline levels were higher in patients on strict gluten-free diet comparing to those newly diagnosed (32.2 ± 8.7 vs 24.9 ± 5.7 μmol/L; p=0.025)
3	[40,] Papadia, Sherwood [73, 74]	• See Supplementary Table 3 for details	
4	[53,] Peters, Wierdsma [75, 76, 77]	• See Supplementary Table 3 for details	
5	Miceli, Poggi [37]	• Sample: 50 healthy volunteers, 21 patients with untreated coeliac disease and 6 patients with refractory coeliac disease • Serum citrulline levels and duodenal lesions were evaluated at the time of diagnosis, and after at least 24 months of gluten-free diet • Serum citrulline concentrations were determined by ion exchange chromatography.	• In comparison to healthy volunteers, serum citrulline concentrations were significantly lower in untreated and refractory coeliac disease patients • No significant difference was found between untreated and refractory coeliac disease patients and between patients with different patterns of clinical presentation or various degrees of duodenal lesions • After a gluten-free diet, mean serum citrulline concentration increased
6	Crenn, De Truchis [100, 101]	• Sample: 6 groups of HIV patients (n = 115): 1) undetectable viral load without chronic diarrhoea (a; n = 40) and with protease inhibitor-associated toxic chronic diarrhoea (b; n = 26), 2) detectable viral load and CD4 > 200/mm^3 without (a; n = 6) and with (b; n = 11) chronic diarrhoea, and 3) detectable viral load and CD4 <200/mm^3 without chronic diarrhoea (a; n = 7) and with opportunistic intestinal infections or HIV enteropathy (b; n = 25) • The influence of diarrhoea on citrulline was assessed by comparing subgroups a and b with healthy control subjects (n = 100).	• Citrulline was slightly decreased (22-30 μmol/L) in groups 1b and 2b • Citrulline levels in control subjects vs patients without chronic diarrhoea (groups 1a, 2a, and 3a): 38 ± 8 vs 36 ± 6 μmol/L • In group 3b, a citrulline concentration <10 μmol/L was associated with a clinical indication for parenteral nutrition ($p < 0.05$). • Citrulline correlated positively with albumin ($p < 0.01$) and BMI ($p < 0.05$) and negatively with C-reactive protein ($p < 0.01$). • When anti-infectious and nutritional therapies were successful, citrulline normalized in 2-12 weeks
7	[46,] Papadia, Dhaliwal [102, 103]	• Post-absorptive fasting serum citrulline was measured in 150 tropical enteropathy patients (n = 44, HIV) with reverse phase, high performance liquid chromatography. • Absorptive capacity and permeability were measured after intrajejunal instillation of 4 sugars with assay by thin-layer chromatography. • Morphometric analysis was carried out on jejunal biopsies	• HIV positive vs HIV negative patients: median serum citrulline 19 (17-24) vs 27 (23-33) μmol/L; $p < 0.001$ • There were statistically significant correlations ($p < 0.005$) between citrulline and: crypt depth; villous height/crypt depth ratio; Shenk-Klipstein score; and xylose absorption, only in the HIV positive
8	Diamanti, Knafelz [41,] Panetta, Diamanti [104]	• Sample: 31 Crohn's disease patients and 44 controls (2008-2010) • Analysis: Differences between groups, at baseline, in plasma citrulline and glutamine and between their baseline and final values during the prospective survey, and correlation between baseline values of citrulline and duration of disease, C-reactive protein, and faecal calprotectin	• Mean citrulline value • Controls vs Crohn's disease: 33.0 ± 7.5 vs 23.5 ± 8.4 μmol/L ($p < 0.0001$) • Crohn's disease patients with small bowel disease vs ileo-colonic disease: 14.2 ± 5.5 vs 24.7 ± 8.0 μmol/L, $p = 0.0037$ • Citrulline ≤ 22 μmol/L had sensitivity of 100% and specificity of 98% for differentiating control subjects from Crohn's disease patients with small bowel disease

No	Authors	Settings (sample and design)	Main Results
9	Bernini, Bertini [105]	• Sample: 61 overt coeliac disease patients, 29 patients with potential coeliac disease, and 51 control subjects were examined by proton nuclear magnetic resonance of their serum and urine	• Potential coeliac disease largely shares the metabonomic signature of overt coeliac disease. Most metabolites found to be significantly different between control and coeliac disease subjects were also altered in potential coeliac disease
10	Blasco Alonso, Serrano Nieto [38]	• Sample and design: Observational case-control study longitudinal in children 16 months to 14 years: 48 with untreated coeliac disease, 9 coeliac children under gluten free diet and 35 non-coeliac healthy children. • Plasma amino acids concentration was measured along with other clinical and analytical data	• Cases vs Controls: citrulline, arginine and glutamine 17.7 μmol/L, 38.7 μmol/L, 479.6 μmol/L respectively vs 28.9 μmol/L, 56.2 μmol/L, 563.7 μmol/L • Citrulline levels are significantly lower in the severe degrees of atrophy vs mild ones (13.8 μmol/L vs 19.7 μmol/L, $p < 0.05$)

11	Ioannou, Fotoulaki [39]	• Sample: Fasting-plasma citrulline levels were determined by high-performance liquid chromatography in 23 patients with coeliac disease before gluten-free diet (ii) 20 patients with coeliac disease under treatment for more than 2 years responsive to gluten-free diet, (iii) 10 children with gastrointestinal symptoms and normal small bowel biopsy, and (iv) 20 healthy controls.
		• In group (i), citrulline levels were also measured after 1, 3, 6, and 12 months on a gluten-free diet
			• Mean plasma citrulline levels:
			  ○ Lower in untreated patients with coeliac disease 24.5 ± 4.9 μmol/L vs
			  ▪ patients on a gluten-free diet: 31.2 ± 6.7 μmol/L, $p < 0.001$
			  ▪ patients with gastrointestinal symptoms and normal intestinal mucosa 30.3 ± 4.7 μmol/L, $p < 0.01$
			  ▪ and healthy controls: 32.4 ± 7.5 μmol/L, $p < 0.00$
			• In untreated patients with coeliac disease, there was an inverse correlation between citrulline concentrations and severity of villous atrophy ($r = -0.67$, $p < 0.01$)
			• After 1 month on a gluten-free diet, patients had significantly higher levels than before diet ($p < 0.05$) and after 3 months on diet, levels were similar to those observed in the healthy controls

12	Elkhatib and Buchman [106]	• Sample: 81 outpatients aged 18 to 65 years (mean, 40.6 ± 15.4 years) with a known history of Crohn's disease • Crohn's disease activity was measured by Harvey-Bradshaw Index and was correlated to the plasma citrulline concentration measured simultaneously (ion chromatography) • Spearman correlation coefficients were used to assess for an association between the 2 variables	• The mean plasma citrulline concentration was normal • It failed to distinguish between active and inactive patients based on the Harvey-Bradshaw Index (27.8 μmol/L, $p = 0.991$). • There was no significant linear association between the ranks of citrulline and ranks of Harvey-Bradshaw Index ($r = 0.012$, $p = 0.915$) • No association between plasma citrulline concentration and Harvey-Bradshaw Index ($p = 0.583$) • No difference in plasma citrulline concentrations among those with confirmed inflammation by imaging or endoscopy ($p = 0.583$)
13	Lee, Ko [107]	• Sample: 63 Crohn's Disease, 23 ulcerative colitis • Disease severity was assessed by paediatric Crohn's disease activity index, paediatric ulcerative colitis activity index, simplified endoscopic activity score for Crohn's disease, C-reactive protein, and erythrocyte sedimentation rate • Subgroup analysis whether correlations between plasma citrulline levels and disease activity depend on small bowel involvement in patients with Crohn's Disease.	• Plasma citrulline levels correlated negatively with C-reactive protein ($r = -0.332$, $p = 0.008$), erythrocyte sedimentation rate ($r = -0.290$, $p = 0.022$), and paediatric Crohn's disease activity index ($r = -0.424$, $p = 0.001$) in patients with Crohn's disease. • Plasma citrulline levels were lower in patients with jejunal involvement vs those without ($p = 0.027$) • In subgroup analysis, patients with Crohn's disease with jejunal involvement showed significantly negative correlations of plasma citrulline levels with CRP ($r = -0.628$, $p = 0.016$) and paediatric Crohn's disease activity index ($r = -0.632$, $p = 0.015$); no correlation was noted in patients without jejunal involvement and the simplified endoscopic activity score for Crohn's disease • No significant correlations of plasma citrulline levels with inflammatory parameters in ulcerative colitis
14	Basso, Capriati [108]	• Design and Sample: Cross-sectional study of children and adolescent patients with coeliac disease ($n = 48$) and controls ($n = 42$) • Citrulline was measured with high performance liquid chromatography and correlated with disease severity	• Citrulline was significantly lower in coeliac disease patients compared to control subjects • Citrulline levels were negatively correlated with disease severity • A citrulline cut-off level of 27 μmol/L produced a sensitivity of 43% and specificity 90%
15	Sevinc, Akar [109]	• Sample: 62 children with classic coeliac disease, 62 age and sex matched healthy control • Plasma amino acid levels measured with tandem mass spectrometry.	• Coeliac children had significant lower plasma levels of citrulline, glutamine and cystine than controls ($p < 0.05$) • Alanine, asparagine, glutamic acid, hydroxyproline, isoleucine, leucine, phenylalanine, proline, serine, threonine and valine were significantly higher in coeliac children than in controls ($p < 0.05$) • No significant difference in levels of arginine, argininosuccinate, aspartic acid, glycine, homocysteine, hydroxylysine, lysine, methionine, ornithine, tryptophan, tyrosine, histidine levels between celiac children and healthy controls ($p > 0.05$)

Supplementary Table 5. Gastrointestinal toxicity from chemo-radiation therapies studies.

No	Authors	Settings (sample and design)	Main Results
1	Lutgens, Granzier [110], Blijlevens, Lutgens [111]	• Sample: 32 haematopoietic stem cell transplant recipients following intensive myeloablative therapy during the first 3 weeks after transplantation when patients have oral mucositis	• Significant decline in serum concentrations of citrulline following intensive myeloablative therapy during the first 3 weeks after transplantation when patients have oral mucositis and a markedly disturbed gut integrity • Closer inspection of citrulline concentrations of 12 patients confirmed that decline corresponded to the onset of oral mucositis and altered gut integrity
2	Lutgens, Deutz [112]	• Sample: 23 patients were studied weekly during treatment and at intervals of 2 weeks and 3 and 6 months after treatment by post-absorptive plasma citrulline concentration and clinical toxicity grading. • The interrelationship between these variables and the correlation with small-bowel dose and volume parameters were investigated.	• During fractionated radiotherapy, citrulline concentration significantly decreased as a function of the radiation dose ($p < 0.001$) and the volume of small bowel treated ($p = 0.001$) • Plasma citrulline concentration correlated with clinical toxicity during the last 3 weeks of treatment. As a whole, citrulline concentration correlated better with radiation dose and volume parameters than clinical toxicity grading.
3	Blijlevens, Donnelly [44]	• Sample: 32 haematopoietic stem cell transplant recipients following intensive myeloablative therapy.	• Significant increase of interleukin-8, lipopolysaccharide-binding protein and C-reactive protein indicating mucosal barrier injury as measured by gut integrity, daily mucositis score and serum citrulline concentrations
4	Blijlevens, Donnelly [113]	• Design: Prospective, randomised, double-blinded, placebo-controlled pilot study of parenteral nutrition supplemented with 0.57 g/kg glutamine-dipeptide in a homogeneous group of 32 allogeneic stem cell transplant recipients to determine its effect on mucosal barrier injury • Mucosal barrier injury measured by sugar permeability tests, daily mucositis score, daily gut score, and citrulline concentrations	• The daily gut score was significantly lower for the glutamine group on day 7 post-transplant ($p = 0.001$) whilst citrulline was lower ($p = 0.03$) for the placebo group on day 21 post-transplant • Albumin was significantly lower in the placebo group on day 21 post-transplant (32 ± 4 vs 37 ± 3, $p = 0.001$) whilst C-reactive protein was higher (74 ± 48 vs 34 ± 38, $p = 0.003$)
5	Lutgens, Blijlevens [45]	• Design: Prospective study, 10 patients with haematological malignancies who were receiving myeloablative therapy had gut toxicity assessed with sugar permeability tests. • Serum citrulline concentrations also were determined using archival serum samples	• Sensitivity and specificity were better for the citrulline assay compared with sugar permeability tests • Maximum gut damage assessed with the citrulline assay was observed 1-2 weeks earlier compared with the sugar permeability test • Citrulline indicated recovery of gut damage at 3 weeks after transplantation, whereas most sugar permeability tests remained abnormal
6	Herbers, Blijlevens [114]	• 29 patients with high-dose melphalan 200 mg/m^2 to prepare for an autologous Peripheral blood stem cell transplantation • Plasma samples from each patient starting before the myeloablative regimen and three times per week thereafter until discharge	• Baseline citrulline concentration was 27.6 ± 4.0 μmol/L, and citrulline concentrations declined rapidly thereafter reaching a nadir averaging 6.7 ± 2.7 μmol/L, 12 days after starting melphalan. • Citrulline concentrations, only increased gradually and were still low (12 ± 4 μmol/L) at discharge. • Their mean citrulline concentrations were lower at 5.5 ± 1.5 μmol/L than were those of patients without bacteraemia (10.2 ± 3.9 μmol/L)
7	Wedlake, McGough [115]	• Sample: 59 patients (30 males) with mixed pelvic malignancies, receiving 45-70 Gy were recruited • At baseline and weeks 4 or 5 of radiotherapy, blood samples for citrulline, C-reactive protein, eosinophil cationic protein and stool samples for faecal calprotectin were obtained	• Citrulline ($p = 0.02$) and faecal calprotectin ($p = 0.01$) values changed significantly between baseline and 4 or 5 weeks. • Inflammatory Bowel Disease Questionnaire - Bowel Subset fell significantly (mean fall = 10 points). Changes in markers did not correlate with symptoms.
8	Derikx, Blijlevens [116]	• Sample: 34 adult patients with haematological malignancy received allogeneic haematopoietic stem cell transplant 12 days after myeloablative conditioning with a regimen known to induce oral and intestinal mucosal barrier injury • Serum levels of citrulline, intestinal fatty acid binding protein and ileal bile acid-binding protein were measured on transplant days -12, -6, 0, +7, +14 and +21.	• Myeloablative conditioning resulted in a significant decrease in serum citrulline with the nadir on day 7 post-transplant; thereafter, levels rose gradually. • A significant decrease in intestinal fatty acid binding protein and ileal bile acid-binding protein levels occurred from the day of transplant until day +14.
9	van Vliet, Tissing [43]	• Sample: Children with acute myeloid leukaemia • Investigations: various mucosal barrier injury-related clinical and laboratory tests, reflecting clinical severity (NCI symptomatic adverse events criteria), daily gut score, inflammation (plasma and faecal interleukin-8, faecal calprotectin), enterocytic loss (plasma citrulline, ratio faecal human DNA/total DNA) and intestinal permeability (sugar absorption tests)	• Intestinal mucosal barrier injury as detected by the NCI adverse events criteria was found in 55% of chemotherapy cycles, correlating well with the continuous daily gut score ($n = 55$, $r = 0.581$; $p < 0.001$) • Intestinal cell loss as measured by the ratio faecal human DNA/total DNA and plasma citrulline correlated well with both NCI criteria ($r = 0.357$, $p = 0.005$; $r = -0.482$, $p < 0.001$) and daily gut score ($r = 0.352$, $p = 0.009$; $r = -0.625$, $p < 0.001$) • Plasma interleukin-8 correlated strongly to plasma citrulline ($r = -0.627$; $p < 0.001$).

No	Authors	Settings (sample and design)	Main Results
10	Herbers, Feuth [117]	• Sample and design: Citrulline concentrations were determined at baseline and at least once weekly after the start of myeloablative chemotherapy until 30 days thereafter among 94 allogeneic or autologous haematopoietic stem-cell transplant recipients. • Intestinal mucosal damage was described either by level of citrulline on each day, on the basis of different thresholds of citrulline indicating the severity of villous atrophy, or by area under the curve using reciprocal value of 10/citrulline.	• Regimens that incorporated idarubicin induced the most severe intestinal toxicity. • Scores based on the level of citrulline, using severity thresholds, and on the area under the reciprocal curve are able to discriminate between the damage induced by different high-dose chemotherapy regimens.
11	Jakobsson, Ahlberg [118]	• Sample: 29 women undergoing pelvic radiotherapy for anal or uterine cancer were prospectively followed • Fatigue and diarrhoea were assessed using patient self-reported questionnaires • Plasma citrulline concentration, as a sign of intestinal injury, and C-reactive protein, orosomucoid, albumin, alpha-1-antitrypsin, and haptoglobin, as signs of systemic inflammation, were analysed.	• Fatigue increased significantly ($p < 0.001$) and citrulline decreased significantly ($p < .001$) during treatment. • A significant negative correlation ($r = -0.40$; $p < 0.05$) was found between fatigue and epithelial atrophy in the intestine (as assessed by plasma citrulline) after 3 weeks of treatment and a significant positive correlation ($r = 0.75$; $p < 0.001$) was found between fatigue and diarrhoea.
12	van der Velden, Herbers [119, 120]	• Sample: Retrospective analysis in 163 stem-cell transplant recipients of which data had been collected prospectively on intestinal damage (citrulline), inflammation (C-reactive protein), and neutrophil count. • Six different conditioning regimens were studied; 5 myeloablative and 1 non-myeloablative • Linear mixed model multivariate and AUC analyses were used to define the role of intestinal damage in post-SCT inflammation.	• In the 5 myeloablative regimen there was a striking pattern of inflammatory response that coincided with the occurrence of severe intestinal damage • This contrasted with a modest inflammatory response seen in the non-myeloablative regimen in which intestinal damage was limited. • With linear mixed model analysis the degree of intestinal damage was shown the most important determinant of the inflammatory response, and both neutropenia and bacteraemia had only a minor impact. • AUC analysis revealed a strong correlation between citrulline and C-reactive protein ($r = 0.96$). Intestinal damage was associated with the occurrence of bacteraemia and acute lung injury, and influenced the kinetics of acute graft-versus-host disease
13	Onal, Kotek [121]	• Sample: 53 patients (36 prostate cancer, 17 endometrial cancer) who received 45 Gy pelvic radiotherapy using conventional fractionation • Patients with prostate cancer received an additional 25-30.6 Gy conformal boost. • Plasma citrulline levels were assessed on day 0, mid- (week 3) and post-radiotherapy (week 8), and four months post-radiotherapy. • Dose-volume histogram, citrulline concentration changes, and weekly intestinal toxicity scores were analysed.	• Citrulline concentrations were significantly reduced at week 3 (27.4 ± 5.9 μmol/L; $p < 0.0001$), treatment end (29.9 ± 8.8 μmol/L; $p < 0.0001$), and four months post-treatment (34.3 ± 12.1; $p = 0.01$). • The following factor pairs were significantly positively correlated: Citrulline concentration/mean bowel dose during, end of treatment, and four months post-radiotherapy; dose-volume parameters/citrulline change groups; cumulative mean radiation dose/intestinal toxicity at end and four months post-radiotherapy; citrulline changes/intestinal toxicity during and end of radiotherapy. • Citrulline concentration changes significantly differed during treatment according to radiotherapy oncology group intestinal toxicity grades ($p < 0.0001$)
14	Vokurka, Svoboda [122]	• Sample: prospective study in 11 adults (18 blood samples) with diarrhoea developed after allogeneic stem-cell transplant in between 2011-2012 compared to 20 healthy control samples	• Transplanted patients vs healthy controls: median (IQR) 9.3 (3.62-15.38) vs. 33.3 (26.82-36.23) μmol/L, $p<0.0001$ • Post-transplant toxic intestinal mucositis (n=8, days 1-22 post-transplant) vs. intestinal graft versus host disease (n=7, day 43-142) vs. other aetiology of diarrhoea (n=3, day 120-127): 9.55 (2.95-12.03) vs. 5 (3.85-9.05) vs. 15.6 (15.45-18.3) μmol/L ($p < 0.05$)
15	Gosselin, Feldman [123]	• Sample: Multicentre, prospective cohort study of 26 children to define time-related changes in serum citrulline during the course of hematopoietic cell transplantation. Markers of gastrointestinal function including oral energy intake, emesis, stool volume, presence of graft-versus-host disease, oral mucositis severity, and cytokine and neurohormone levels were measured. • Weekly serum citrulline concentrations were obtained from 10 days prior until 30 days after hematopoietic cell transplantation.	• Mean baseline citrulline concentration was 22.7 μmol/L (95% CI 17.7-27.6) on day -10, which decreased to a nadir of 7.5 μmol/L (95% CI 3.1-18.0, $p = 0.017$) on day 8 following hematopoietic cell transplantation before returning to baseline by day 30. • After adjustment for interleukin-6 level (1.0% lower citrulline per 10% increase in interleukin-6, $p = 0.004$), presence of acute graft-versus-host disease (27% lower citrulline, $p = 0.025$), and oral energy intake (2.1% lower citrulline per 10% decrease in energy intake, $p = 0.018$), the nadir shifted to day 10, when mean citrulline concentration was lower in patients with severe oral mucositis (6.7 μmol/L, 95% CI 3.4-13.1) than in those without severe mucositis (11.9 μmol/L, 95% CI 5.8-24.4, $p = 0.003$). • Change in citrulline was not correlated with stool volume, C-reactive protein, tumour necrosis factor-alpha, leptin, or ghrelin.
16	Karlik, Kesavan [124]	• Aim: To determine whether citrulline levels correlate with clinical markers of intestinal injury in children undergoing a myeloablative allogeneic transplant regimen	• For every 1 μmol/L increase in citrulline, the odds of developing mucositis were 0.88 (95% CI 0.79-0.99, $p = 0.036$) • The odds of developing diarrhoea were 0.70 times less for every 1 μmol/L increase in citrulline (95% CI=0.59-0.84, $p < 0.0001$)

No	Authors	Settings (sample and design)	Main Results
17	Brady, Horn [125]	• Sample: 15 patients treated with external beam radiation therapy to either prostate only (n=6) or prostate and pelvis (n=9). • Plasma citrulline levels were measured prior to radiotherapy and weekly during treatment and at 6 weeks, 3 months and 6 months post external beam radiation therapy • Bowel toxicity was assessed at the same time points using EPIC bowel summary scores.	• The strongest correlation between the fall in plasma citrulline levels from baseline and greatest bowel toxicity was observed after 3 weeks of radiotherapy (p=0.03). • A strong predictive trend was noted with positive correlations at 6 weeks post radiotherapy ($r = 0.594$, $p = 0.025$), 3 months post radiotherapy ($r = 0.534$, $p = 0.060$), 6 months post radiotherapy ($r = 0.606$, $p = 0.037$), 9 months post radiotherapy ($r = 0.618$, $p = 0.019$) and 1 year post radiotherapy ($r = 0.358$, $p = 0.345$). • No significant correlation was found between changes in plasma citrulline levels or EPIC reported toxicity
18	Kong, Wang [126]	• Sample: 42 patients with gastric or colorectal cancer underwent chemotherapy • Patients were asked to grade and record their symptoms of gastrointestinal toxicity daily • The urinary lactulose-mannitol ratio was measured to assess the intestinal permeability. • Plasma levels of citrulline, diamine oxidase, D-lactic acid, and endotoxin were also measured	• The urinary lactulose-mannitol ratio and plasma citrulline levels increased on the third and sixth post-chemotherapy days, respectively • There were no significant differences in the plasma levels of D-lactic acid, endotoxin or diamine oxidase activity compared to their levels before chemotherapy
19	Wang, Ling [127]	• Aim: To investigate the correlations between fatigue, diarrhoea, and alterations in gut microbiota induced by pelvic radiotherapy. •	• During the 5-week treatment of pelvic radiotherapy in 11 cancer patients, the general fatigue score significantly increased and was more prominent in the patients with diarrhoea. • The fatigue score was closely correlated with the decrease of serum citrulline and the increases of systemic inflammatory proteins, including haptoglobin, orosomucoid, alpha-1-antitrypsin and tumour necrosis factor-alpha.
20	Zezulová, Bartoušková [128]	• Design: Plasma citrulline, serum neopterin and urinary neopterin were measured weekly in 49 patients with rectal carcinoma during chemoradiation	• Citrulline significantly ($p < 0.05$) decreased while serum and urinary neopterin concentrations increased during therapy. • Irradiated gut volume correlated significantly inversely with citrulline and positively with urinary neopterin. • Statistically significant inverse correlations were also observed between urinary neopterin and plasma citrulline concentrations during the treatment. • Urinary neopterin concentrations were significantly higher and citrulline concentrations were lower in patients who experienced grade ≥ 3 gastrointestinal toxicity

Supplementary Table 6. Studies regarding citrulline levels in critical illness or other conditions.

No	Authors	Settings (sample and design)	Main Results
1	Backman, Hallberg [129]	• Design: The amino acid pattern in plasma was studied in a reference group (n=26) and in three groups of massive obese subjects (n=9, 8, and 9 respectively) before and at intervals after jejuno-ileostomy.	• The concentrations of lysine, tyrosine, cystine, and glutamic acids were higher, and aspargin, glutamine, serine, and glycine were lower than in the reference group. • During the post-operative period the amino acid pattern changed significantly with serine, glycine, and taurine increased and valine, lysine, leucine, tryptophan, thyrosine, cystine, and citrulline decreased. • The amino acid pattern in the obese group with the longest post-operative observation time and a stable body weight differed significantly from that in the reference group only with regard to a low valine concentration and high concentration of taurine and glutamic acid.
2	Müller, Cüppers [130]	• Sample: 6 patients - infusing 0.3 mg/24 h of exogenous glucagon	• In six normal subjects the same infusion reduced significantly ($p < 0.05$) plasma alanine, asparagine, glutamate, glutamine, glycine, proline, serine, threonine, arginine, ornithine, lysine and tyrosine • This particular glucagon sensitivity of duodenopancreatectomized patients suggests that glucagon deficiency is the cause of their hyperaminacidaemia.
3	Jeevanandam, Ramias [131]	• Sample: 10 obese and 10 non-obese traumatized patients • Plasma levels of free amino acids in the early flow phase of injury when subjects were receiving maintenance fluids without calories or nitrogen	• Obese controls showed an increase in valine, leucine, isoleucine, and glutamic acid levels, and a decrease in glycine, tryptophan, threonine, histidine, taurine, citrulline, and cystine levels compared with lean controls. • Hypoaminoacidemia was equally seen in traumatized obese and non-obese patients, and it was mainly due to a 24% decrease in nonessential amino acids. • Essential amino acid levels were the same in all groups.
4	Sandstrom, Gasslander [132]	• Sample: Serum L-arginine and L-citrulline and urinary nitrite/nitrate concentrations 1 to 3 days after the onset of symptoms in 11 patients with gallstone pancreatitis, 10 patients with alcoholic pancreatitis, and 6 patients with idiopathic pancreatitis. 13 healthy control blood donors, 9 patients fasting before hernia operations, 8 patients with acute cholecystitis, and 9 alcoholic subjects but no pancreatitis. • Serum arginine and citrulline concentrations were measured with high performance liquid chromatography, and urinary nitrite/nitrate spectrophotometrically.	• Patients with acute pancreatitis had lower serum L-arginine and L-citrulline concentrations than controls
5	Sandstrom, Trulsson [133]	• Design: Serum amino acid spectrum was measured daily for five days and after recovery six weeks later in 19 patients admitted to the hospital for acute pancreatitis.	• These patients had abnormal levels of most amino acids including arginine, citrulline, glutamine and glutamate. • Phenylalanine and glutamate were increased, while arginine, citrulline, ornithine and glutamine were decreased compared to levels after recovery
6	Thibault, Avallone [134, 135]	• Sample: 20 morbidly obese patients operated by Roux-en-Y gastric bypass (17 women, 47 ± 12 years, BMI, 53.3±11.3 kg/m^2) • Body composition determined by single-frequency bioelectrical impedance analysis. Blood testing, • Plasma concentrations of 20 amino acids including citrulline were available for only 7 patients.	• Plasma citrulline (53.6 ± 16.0 μmol/L) and other amino acids, except cysteine, did not differ from normal values
7	Luiking, Poeze [42]	• Aim: To compare arginine and citrulline metabolism in septic patients and nonseptic control patients in an intensive care unit and in healthy control subjects. • Sample: 10 patients with septic shock, 7 critically ill control patients, and 16 healthy elderly subjects	• Whole-body citrulline production was significantly lower in septic patients (4.5 ± 2.1 μmol/kg/h) than in intensive care control patients (10.1 ± 2.9 μmol/kg/h, $p < 0.01$) and in healthy control subjects (13.7 ± 4.1 μmol/kg/h, $p < 0.001$) • Citrulline production is severely low in patients with sepsis and is related to diminished de novo arginine and nitric oxide production
8	Peters, Dobrowolski [136]	• Aim: To assess citrulline generation test reference values in 14 stable intensive care patients with respiratory failure with normal renal function and able to tolerate enteral nutrition • Amino acid analysis was performed using reverse phase high performance liquid chromatography • 8 females, 6 males, mean age 60.2 years and BMI 27.2 kg/m^2	• The incremental area under the curve at 90 minutes during the test following enteral glutamine was 5,807,437 mmol/L.min for venous and 6,807,507 mmol/L.min for arterial citrulline sampling • Performing the test with intravenously administered glutamine resulted in an area of 7,707,235 mmol/L.min for venous and 9,297,223 mmol/L.min for arterial citrulline sampling • Positive correlation between venous and arterial citrulline sampling in enteral ($r = 0.96$, $p < 0.0001$) and intravenous glutamine ($r = 0.91$, $p < 0.0001$)

No	Authors	Settings (sample and design)	Main Results
9	Crenn, Neveux [137]	• Aim: To investigate in septic shock patients with multi-organ failure plasma citrulline pharmacokinetics, associated parameters and pro tumour necrosis factor alpha /anti–interleukin-10–inflammatory plasma cytokines • Two groups (n = 16 ,7 males, age 63 ± 12 years) were selected: survivors (n = 8), deceased patients (n = 8)	• Citrulline decreased during day 0 (29 ± 10 vs18 ± 6 μmol/L, p < 0.05) in most patients • Citrulline remained < 10 μmol/L in 2 patients of the deceased group whereas a transient citrulline <10 μmol/L was noted in 2 survivors. Citrulline normalised on day 7 in 5 survivors and 1 deceased patient (p = 0.10) • Citrulline was negatively correlated with C-Reactive protein (r = 0.31, p< 0.01) but positively with glutamine, arginine and creatinine (r = 0.95, 0.92, 0.25, p< 0.05) • No significant correlation was found between citrulline and albumin, tumour necrosis factor alpha, and interleukin-10
10	Pan, Wang [138]	• Sample: 32 patients with acute pancreatitis onset within 7 days • Severity of disease and gut dysfunction on admission, on day 7, and day 3 of enteral nutrition • Serum levels of intestinal fatty acid binding protein, citrulline, and C-reactive protein (CRP) and the lactulose and mannitol absorption ratio in urine were measured in parallel	• Intestinal fatty acid binding protein increased on admission and in severe attacks • All patients: ↑ gut dysfunction score, C-reactive protein, urine level of lactulose and mannitol absorption ratio; ↓ citrulline • Positive correlation noted between intestinal fatty acid binding protein and gut dysfunction score, Acute Physiology and Chronic Health Evaluation II score, C-reactive protein and intensive care stay • Negative correlation noted between intestinal fatty acid binding protein and citrulline
11	Piton, Manzon [139]	• Design: Prospective observational pf 67 patient without small bowel disease and without chronic renal failure consecutively admitted to a single intensive care unit • Plasma citrulline concentrations were studied at admission, 12, 24, 48 hours, and the 7th day after admission	• 1st day: mean citrulline decreased from 18.8 to 13.5 μmol/L • Low plasma citrulline at 24 hours was associated with low plasma glutamine (p = 0.01) and arginine (p = 0.04), high plasma C-reactive protein (p = 0.008), nosocomial infection rate (p = 0.03), and 28-day mortality (p = 0.02) • Multivariate analysis: plasma citrulline ≤ 10 μmol/L at 24 hours and Sequential Organ Failure Assessment score ≥ 8 at 24 hours had higher 28-day mortality (odds ratio 8.7, 15.1, respectively)
12	Través, García-Arumí [140]	• Sample: 28 patients who underwent subtotal gastrectomy or hemicolectomy and were placed on short-term parenteral nutrition • Design: Assigned on a Parenteral-Oral (4-day parenteral nutrition and 4-day oral, n = 8) or a Parenteral-Only (7-day parenteral nutrition, n = 20ts) nutritional regime	• Pre-operative citrulline values were within range with those of a western population. • On day 4 in the Parenteral-Oral regime, citrulline levels were 60% lower than pre-operative levels • When enteral feeding was resumed, citrulline rose and was close to pre-operative values on day 8 • In the Parenteral-Only regime the parenteral nutrition solution composition had no influence on the citrulline
13	van Noord, Mensink [141]	• Sample: Consecutive patients suspected of chronic gastrointestinal ischaemia (n = 40), healthy subjects (n = 9) • Blood samples for analysis of intestinal fatty acid-binding protein, D-dimer, lactate dehydrogenase, leucocyte counts, C-reactive protein, and L-lactate were drawn before and after a standard meal. • Intestinal mucosal injury was assessed with glutamine, citrulline and arginine in blood samples and compared to a sugar absorption test	• Ischaemia diagnosed in 32 patients • No difference noted in any parameter between patients with and without ischaemia • L-lactate was increased in ischaemia patients compared to non-ischaemia patients. • In ischaemia patients, D-dimer levels showed a significant elevation post-prandially compared to baseline.
14	Verdam, Greve [142]	• Aim: To investigate the relation between plasma markers of small intestinal function and chronic hyperglycaemia • Sample: Cross-sectional observational study of 40 severely obese subjects with chronic hyperglycaemia and 30 severely obese subjects without chronic hyperglycaemia who were indicated for bariatric surgery. • Measurement of plasma levels of citrulline, intestinal fatty acid binding protein, glucagon-like peptide-2, glycated haemoglobin HbA1c	• Plasma citrulline and intestinal fatty acid binding protein levels were significantly elevated in chronic hyperglycaemia compared to normal HbA1c (Citrulline: 35 ± 2.1 vs 26 ± 1.4 μmol/L, p = 0.001; intestinal fatty acid binding protein: 140 ± 22 vs 69 ± 14 pg/mL, p = 0.001 • Plasma citrulline and intestinal fatty acid binding protein correlated with HbA1c (r = 0.30, 0.33, p < 0.05, respectively). • Intestinal fatty acid binding protein to citrulline ratio was higher in subjects with elevated HbA1c (4.0 vs 3.1, p = 0.03) • Glucagon-like peptide-2 was not related to citrulline or intestinal fatty acid binding protein (p > 0.05)
15	Lundy, Chung [143]	• Design: Observations of serial plasma citrulline levels in a severely burned adult who ultimately died from non-occlusive mesenteric ischaemia leading to full-thickness small bowel necrosis	• Decrease of citrulline around settings of ischaemia and increase of lactate
16	Noordally, Sohawon [144]	• Aim: Prospective observational single-centre controlled study (n = 91, 31 females, mean 69.3 years) • Inclusion criteria: intensive care stay over 48 hours • Plasma citrulline: low (0-15 μmol/L), medium (16-35 μmol/L), and high (> 36 μmol/L)	• Mean citrulline: 21.7 ± 13.1 μmol/L • Patients with intestinal dysfunction had low plasma citrulline level < 15 μmol/L (p = 0.014) • No correlations noted between C-reactive protein, albumin, prealbumin, renal failure, inotrope use, Sequential Organ Failure Assessment score, Acute Physiology and Chronic Health Evaluation II score and citrulline

No	Authors	Settings (sample and design)	Main Results
17	Grimaldi, Guivarch [145]	• Sample: 21 patients following resuscitation after cardiac arrest • Urinary intestinal fatty acid-binding protein, plasma citrulline, whole blood endotoxin were measured at admission, days 1-3 and 6 • Kinetics of release and the relationship between intestinal fatty acid-binding protein, citrulline and endotoxin values	• Lowest median of citrulline was attained at day 2 (11 vs 24 μmol/L at admission, p = 0.01) and normalised at day 6 (21 μmol /L) • Highest endotoxin level was negatively correlated lowest plasma citrulline levels (r^2 =0.55, p < 0.001)
18	Kao, Hsu [146]	• Aim: To investigate how sepsis affects glutamine metabolism, including its conversion to citrulline, by measuring glutamine and citrulline flux, fractional splanchnic extraction of glutamine and leucine, and the contribution of glutamine nitrogen to citrulline in septic patients and healthy controls • Sample: 8 patients with severe sepsis and 10 healthy controls were given primed, constant intravenous infusion of [$^2H_2$]citrulline and sequential administration of intravenous and enteral [α-^{15}N]glutamine and [^{13}C]leucine in the post-absorptive state	• Compared with healthy controls, septic patients had a significantly lower whole body citrulline flux and plasma concentration, higher endogenous leucine flux, and higher glutamine clearance • The majority of the ^{15}N label transferred from glutamine to citrulline was found at the α-position • Lower glutamine plasma concentrations in sepsis were a result of increased glutamine clearance • Despite adequate splanchnic uptake of glutamine, there is decreased production of citrulline, suggesting a defect in the metabolic conversion of glutamine to citrulline, decreased uptake of glutamine by the enterocyte but increased uptake by the liver, and/or shunting of glutamine to other metabolic pathways
19	Piton, Belon [147]	• Design and Sample: 103 intensive care patients, prospective observational study • Inclusion criteria: 18 years old or older; expected intensive care stay over 48 hours, without pregnancy, chronic small bowel disease, or chronic renal failure • Plasma intestinal fatty acid-binding protein, citrulline concentrations, and variables relating to prognosis and treatment, were measured on admission	• Intestinal fatty acid-binding protein elevation on admission was associated with catecholamine support, higher lactate concentration, higher Sequential Organ Failure Assessment score, and higher international normalized ratio (p < 0.001) • Plasma citrulline concentration ≤ 10 μmol/L on admission was associated with higher intra-abdominal pressure, higher plasma C-reactive protein concentration, and more frequent antibiotic use (p < 0.005) • No correlation between plasma levels of intestinal fatty acid-binding protein and citrulline • On admission, Sequential Organ Failure Assessment score ≥ 12, plasma citrulline ≤ 12.2 μmol /L, and plasma intestinal fatty acid-binding protein concentration ≥ 355 pg/mL were associated with higher 28-day mortality (odds ratio 4.39, 5.17, 4.46, respectively)
20	Ware, Magarik [148]	• Sample: Plasma citrulline, arginine and ornithine levels and nitrate/nitrite were measured at baseline in 135 patients with severe sepsis • Acute respiratory distress syndrome was diagnosed by a consensus definition	• Plasma citrulline levels: • Below normal in all patients: median 9.2 (5.2-14.4) μmol/L • Acute respiratory distress syndrome vs non-acute respiratory distress syndrome: 6.0 (3.3-10.4) vs 10.1 (6.2-16.6) μmol/L, p = 0.002 • The rate of acute respiratory distress syndrome was 50% in the lowest citrulline quartile compared to 15% in the highest citrulline quartile (p = 0.002) • In multivariable analyses, citrulline levels were associated with acute respiratory distress syndrome after adjustment for covariates including illness severity
21	Alekseeva and Sal'nikov [149]	• Sample: 27 critical condition patients (15 females, age 70 ± 14 years • On admission to intensive care, plasma glutamine, citrulline, glutamic acid (liquid chromatography), relative duodenal and jejunum electrical activity were measured	• No increase noted in plasma glutamine, citrulline or glutamic acid • Worst prognosis was observed when citrulline was ≤ 10 μmol/L and signified decrease in proximal small intestine relative electrical activity
22	Carswell, Vincent [150]	• Sample: obese controls (BMI > 30 kg/m^2, n = 7), adjustable gastric banding (n = 6), Roux-en-Y gastric bypass (n = 7), biliopancreatic diversion with duodenal switch (n = 5). • Measurements: oro-caecal transit time, fasting plasma citrulline, 3 days of faecal elastase 1, calprotectin, fatty acids	• No difference in oro-caecal transit time (p = 0.935) or citrulline levels (p = 0.819) • Faecal calprotectin was elevated post- Roux-en-Y gastric bypass vs obese (p = 0.016) and faecal elastase 1 was decreased post- Roux-en-Y gastric bypass vs obese (p = 0.002)
23	Piton, Belin [151]	• Sample: 69 patients with cardiac arrest of both cardiac and hypoxic origin admitted to intensive care • Design: Prospective, observational, single-centre study, evaluating plasma citrulline and intestinal fatty acid-binding protein concentrations on admission and after 24 hours • Comparison of the variables according to 28-day Cerebral Performance Category score of 1-2 (good neurological outcome) vs 3-5 (poor neurological outcome)	• On admission, citrulline was low in 65 % and plasma intestinal fatty acid-binding protein was high in 82 % • At 24 hours, citrulline was low in 82 % and intestinal fatty acid-binding protein was normal in 60 % • Patients with a poor neurological outcome had a lower plasma citrulline concentration and a higher intestinal fatty acid-binding protein on admission • Multivariate analysis: plasma citrulline levels ≤ 13.1 μmol/L and intestinal fatty acid-binding protein > 260 pg/mL were independently associated with a poor neurological outcome (odds ratio 21.9, 13.6, respectively)

No	Authors	Settings (sample and design)	Main Results
24	Piton, Cypriani [152]	• Aim: To examine whether catecholamines in critically ill patients may be associated with enterocyte damage • Design: Prospective observational study. • Sample: Critically ill patients requiring epinephrine and/or norepinephrine on admission to intensive care (n = 60). Controls not receiving catecholamines (n = 27) • Measurement on admission: plasma intestinal fatty acid-binding protein, plasma citrulline, abdominal perfusion pressure, and variables relating to prognosis and treatment	• Plasma intestinal fatty acid-binding protein was higher among patients receiving catecholamine vs controls • In patients receiving catecholamines, a dose of 0.48 γ/kg/min or more on admission was associated with a higher intestinal fatty acid-binding protein concentration • Sepsis-related Organ Failure Assessment score > 11 and plasma intestinal fatty acid-binding protein more than 524 pg/mL on admission were independently associated with 28-day mortality • Citrulline was not associated with catecholamine dose but was generally low: median 14.7 (8.8-27.9).
25	Poole, Deane [153]	• Sample: Prospective observational study, 15 healthy, 20 critically ill subjects • Fasting plasma citrulline concentrations were assayed in blood samples immediately prior to the administration of a liquid test meal (1 kcal/ml; containing 3 g of 3-O-methylglucose) that was infused directly into the small intestine • Serum 3-O-methylglucose concentrations were measured over the following 4 hours, with the area under the 3-O-methylglucose concentration curve calculated as an index of glucose absorption	• Healthy subjects vs critically ill patients: citrulline 26.5 vs 15.2 μmol/L, $p < 0.01$; glucose absorption 79.7 vs 61.0 mmol/L/240 min, $p = 0.05$ • No relationship between fasting citrulline concentration and subsequent glucose absorption was noted ($r = 0.28$; $p = 0.12$)

Supplementary Table 7. Meta-regression results of the correlation of citrulline with small bowel length with four potential sources of heterogeneity.

Variable	Coefficient (95% CI)	SE	*p*-value
Male %	-0.0196 (-0.1155, 0.0763)	0.03	**0.562**
Age	0.0500 (-0.1267, 0.2268)	0.06	**0.434**
BMI	-0.0088 (-0.1593, 0.1416)	0.05	**0.864**
Mean citrulline concentration	-0.0779 (-0.3997, 0.2439)	0.10	**0.497**
Mean small bowel length	-0.0266 (-0.1043, 0.0510)	0.02	**0.355**
Constant	3.7196 (-5.4980, 12.9372)	2.90	**0.289**
Restricted maximum likelihood estimate of between-study variance: $\tau^2 = 0.8593$			
% residual variation due to heterogeneity: $I^2 = 98.9\%$			
Proportion of between-study variance explained: Adjusted $R^2 = 0\%$			
Joint test for all covariates: Model $F(5,3) = 0.34$			
With Knapp-Hartung modification: $p > F = 0.862$			

Supplementary Table 8. Diagnostic accuracy characteristics from studies investigating short bowel syndrome.

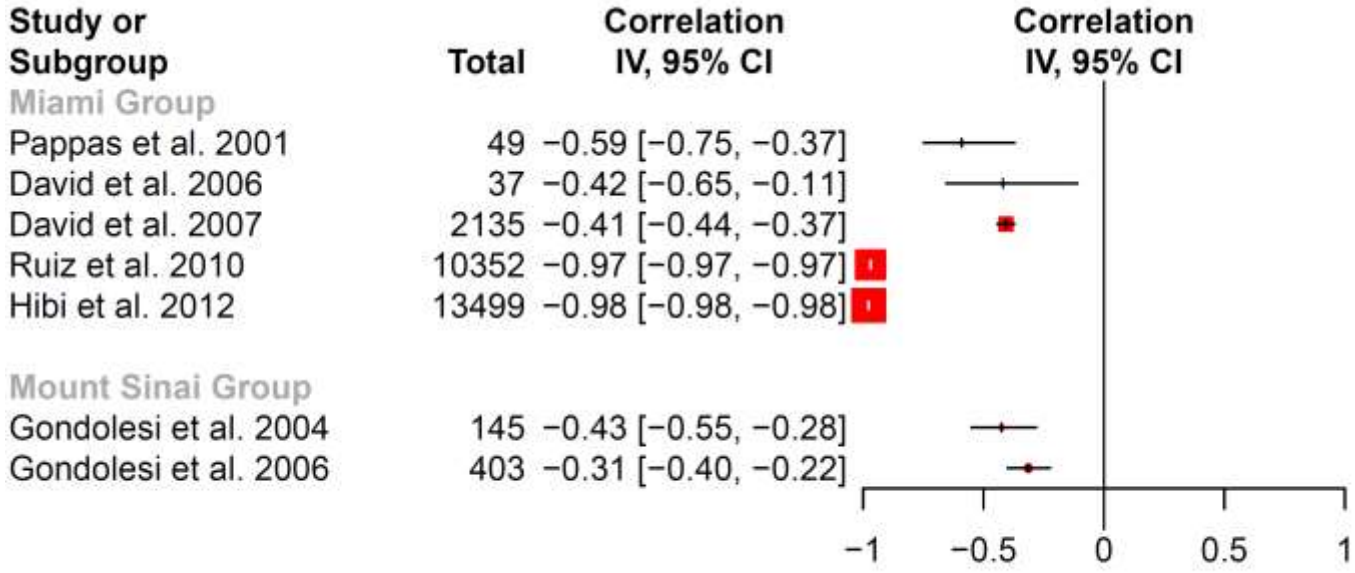
Study	TP	FP	FN	TN	Citrulline cut-off level (µmol/L)	AUC (ROC) (95% CI)	Sensitivity	Specificity	Groups under comparison
Crenn, Coudray-Lucas [67]	34	2	3	18	20		92 %	91 %	HPN dependency
Rhoads, Plunkett [49]	13	0	3	5	20	0.91 (0.79, 1.00)	81 %	100 %	HPN dependency
Peters, Wierdsma [53]	8	4	22	14		0.50 (0.30, 0.71)	25 %	77 %	SBS vs Controls
Papadia, Sherwood [40]	22	4	5	24	21	0.87	83 %	87 %	HPN dependency
Parekh, Natowicz [78]	30	21	0	28	20	0.82 (0.71, 0.93)	100 %	57 %	SBS vs Controls
Santarpia, Catanzano [79]	15	1	0	9	10	0.65 (0.43, 0.88)	100 %	9 %	HPN dependency
Fitzgibbons, Ching [50]	16	2	2	7	15	0.88 (0.75, 1.00)	89 %	78 %	HPN dependency
Bailly-Botuha, Colomb [80]	20	9	1	3	20	0.46 (0.25, 0.67)	95 %	25 %	HPN dependency
Diamanti, Noto [83]	11	1	1	10	20		91 %	89 %	HPN dependency
Pironi, Guidetti [86]	25	25	2	20	20		50 %	91 %	HPN dependency
Raphael, Nurko [88]	5	1	3	1	20		63 %	50 %	HPN dependency
Diamanti, Panetta [51]	9	1	5	13	10	0.90 (0.70, 1.00)	64 %	93 %	HPN dependency
Pironi, Guidetti [87]	33	0	34	26	14		49 %	100 %	HPN dependency
Suzuki, Kanamori [89]	2	1	0	3	15		100 %	75 %	HPN dependency
Amiot, Messing [90]	38	10	86	134	20	0.85 (0.78, 0.92)	31 %	93 %	HPN dependency
Pinto Costa, Serodio [91]	6	4	5	20	25.5	0.67 (0.46, 0.88)	55 %	83 %	SBS vs Controls

Supplementary Table 9. Results of diagnostic meta-analysis regarding sensitivity and specificity in patients with all conditions and only short bowel syndrome.

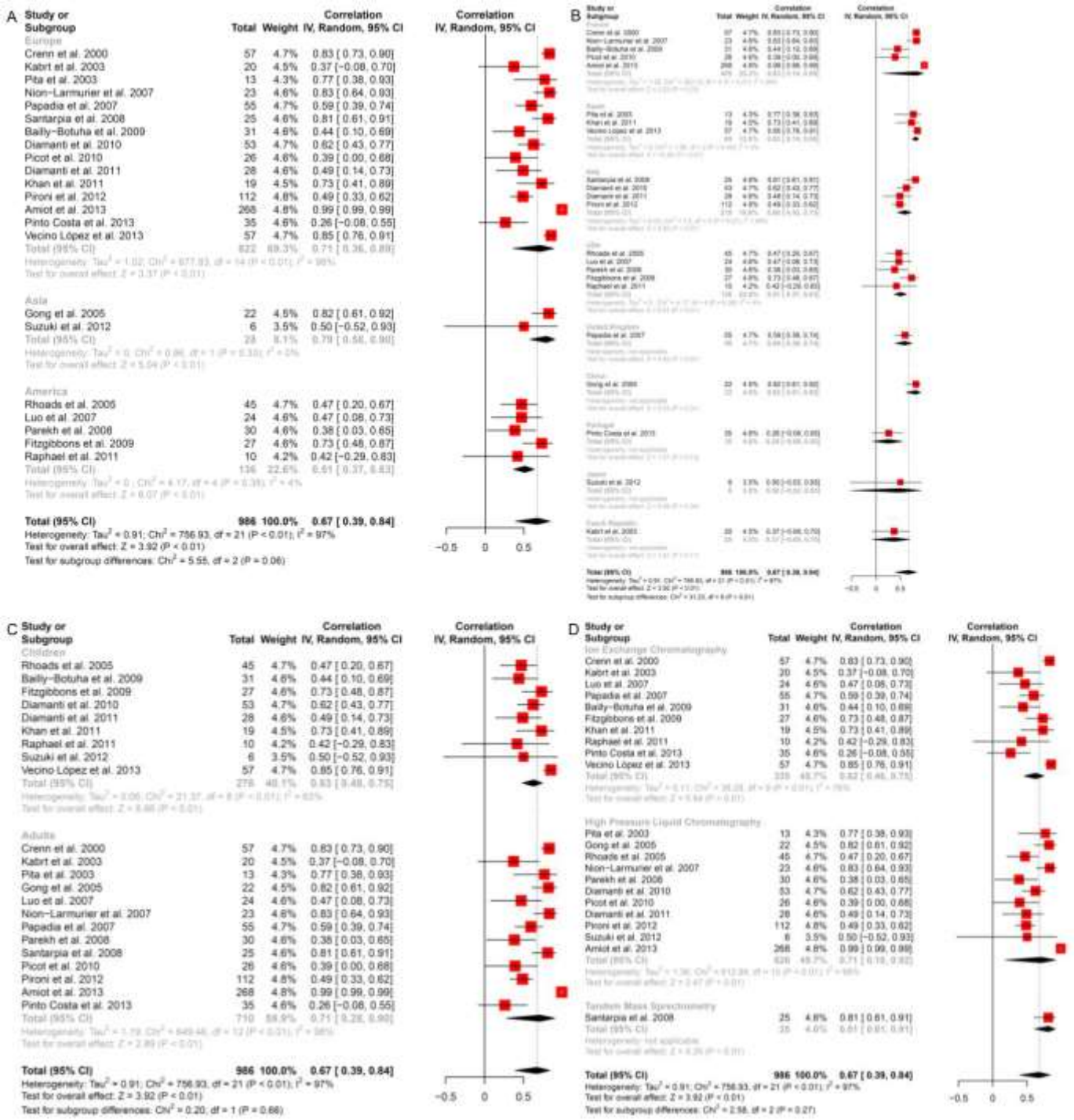
	All conditions (26 studies)				**Short bowel syndrome (16 studies)**			
	Coefficient (95% CI)	**SE**	***z***	***p* > *z***	**Coefficient (95% CI)**	**SE**	***z***	***p* > *z***
Bivariate Model								
Expected value of logit[Sensitivity]	1.37 (0.82, 1.92)	0.28			1.55 (0.70, 2.40)	0.43		
Expected value of logit[Specificity]	1.63 (1.19, 2.06)	0.22			1.52 (0.86, 2.17)	0.33		
Variance of logit[Sensitivity]	1.57 (0.77, 3.19)	0.57			2.22 (0.89, 5.57)	1.04		
Variance of logit[Specificity]	0.82 (0.37, 1.85)	0.34			1.13 (0.41, 3.12)	0.58		
Correlation between logits	-0.55 (-0.84, -0.02)	0.21			-0.64 (-0.92, 0.06)	0.25		
HSROC								
λ	3.08 (2.51, 3.64)	0.29			3.10 (2.31, 3.90)	0.41		
θ	-0.37 (-0.89, 0.14)	0.26			-0.24 (-0.96, 0.47)	0.36		
β	-0.32 (-0.82, 0.17)	0.25	-1.27	0.204	-0.34 (-0.94, 0.27)	0.31	-1.10	0.272
σ_α^2	1.03 (0.37, 2.82)	0.53			1.15 (0.26, 5.06)	0.87		
σ_θ^2	0.88 (0.45, 1.72)	0.30			1.30 (0.56, 2.98)	0.55		
Summary								
Sensitivity	**80 % (69%, 87%)**	**0.05**			**82 % (67%, 92%)**	**0.06**		
Specificity	**84 % (77%, 89%)**	**0.03**			**82 % (70%, 90 %)**	**0.05**		
Diagnostic odds ratio	**20.03 (11.55, 34.72)**	**5.62**			**21.43 (9.58, 47.90)**	**8.80**		
Positive likelihood ratio	**4.85 (3.47, 6.80)**	**0.84**			**4.58 (2.82, 7.44)**	**1.13**		
Negative likelihood ratio	**0.24 (0.16, 0.37)**	**0.05**			**0.21 (0.11, 0.41)**	**0.07**		
Inverse negative likelihood ratio	**4.13 (2.72, 6.25)**	**0.87**			**4.68 (2.43, 9.01)**	**1.56**		
Model characteristics	Covariance between estimates of Expected value of logit[Sensitivity] and Expected value of logit[Specificity]: -137.82452 Log likelihood = -0.0247892				Covariance between estimates of Expected value of logit[Sensitivity] and Expected value of logit[Specificity]: -0.06415 Log likelihood = -79.102622			

Supplementary Figures

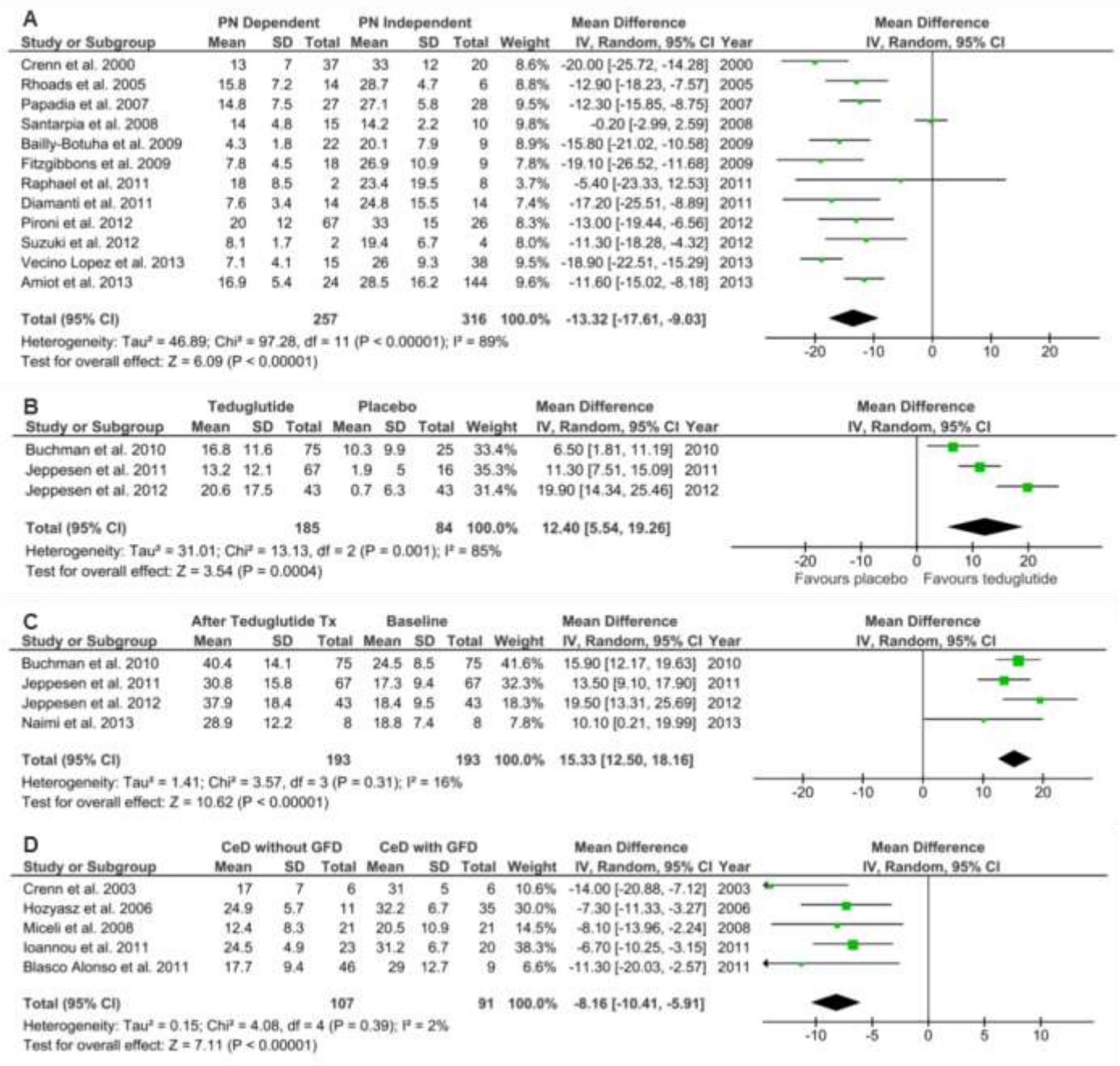
Supplementary Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



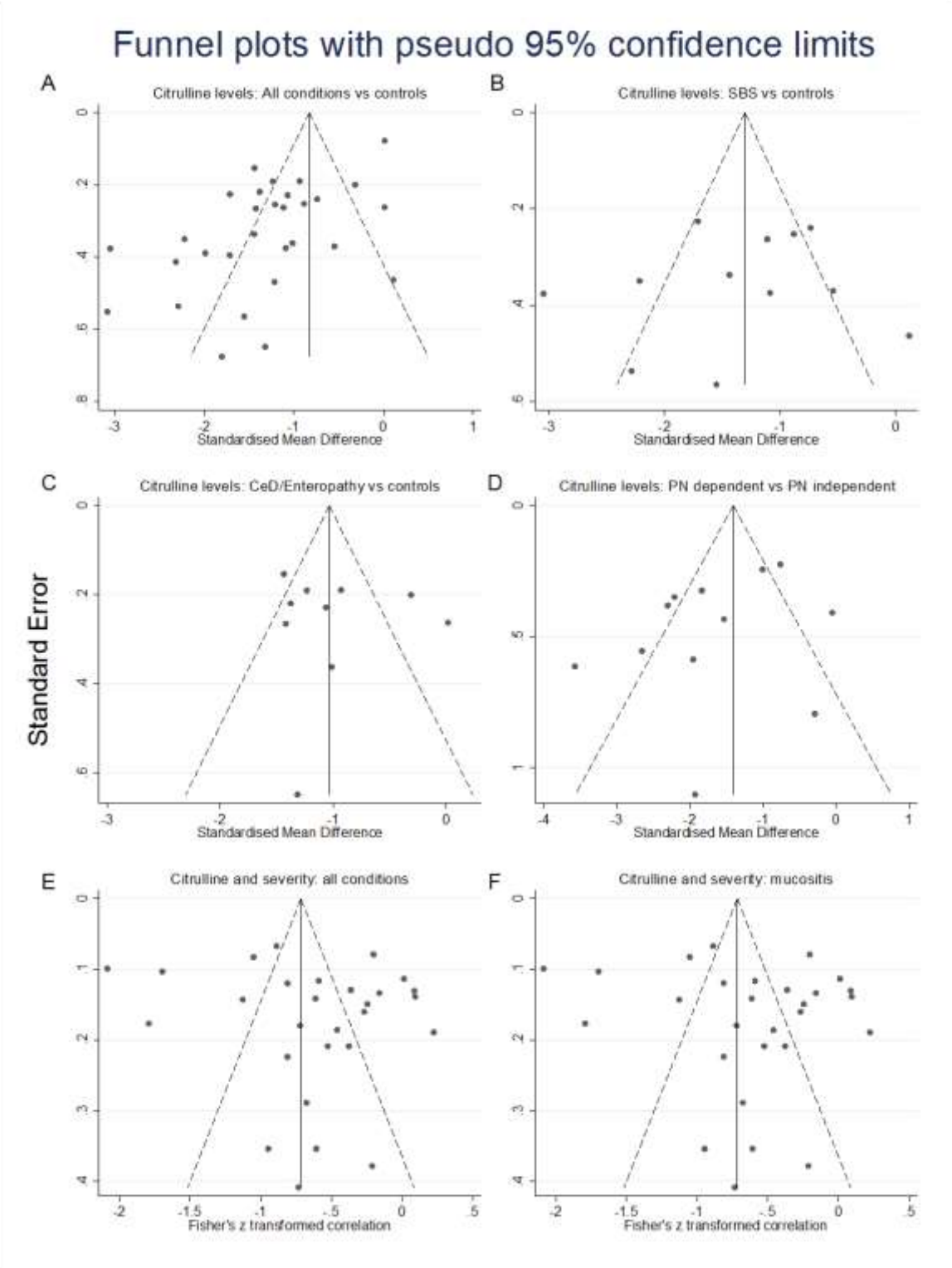
Supplementary Figure 2. Forest plot of Intestinal Transplantation (citrulline concentrations with rejection) – without meta-analysis.



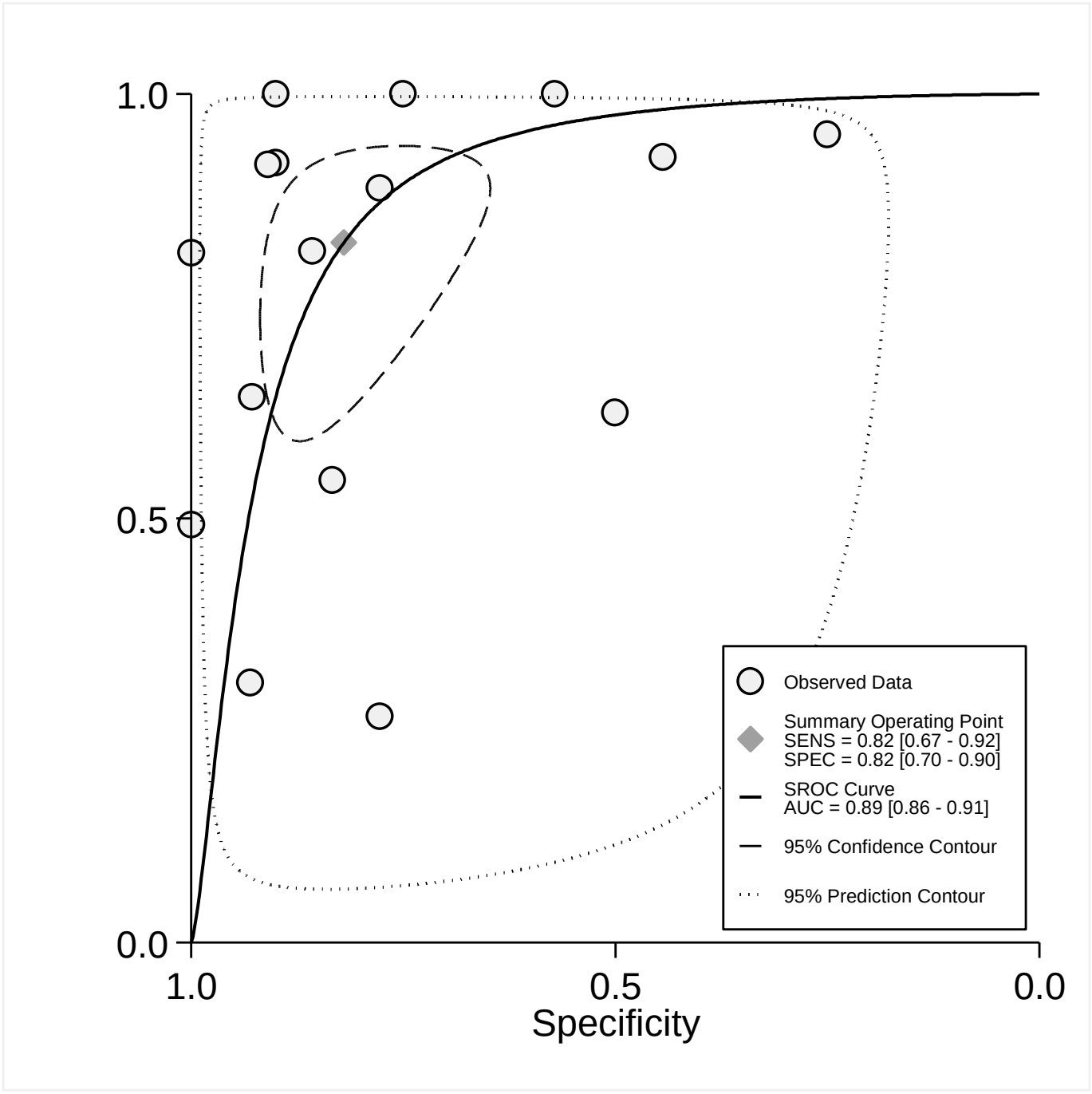
Supplementary Figure 3. Forest plots of short bowel syndrome correlations with small bowel length – subgroup analyses by (A) continent, (B) country, (C) patient type, and (D) citrulline measurement method.



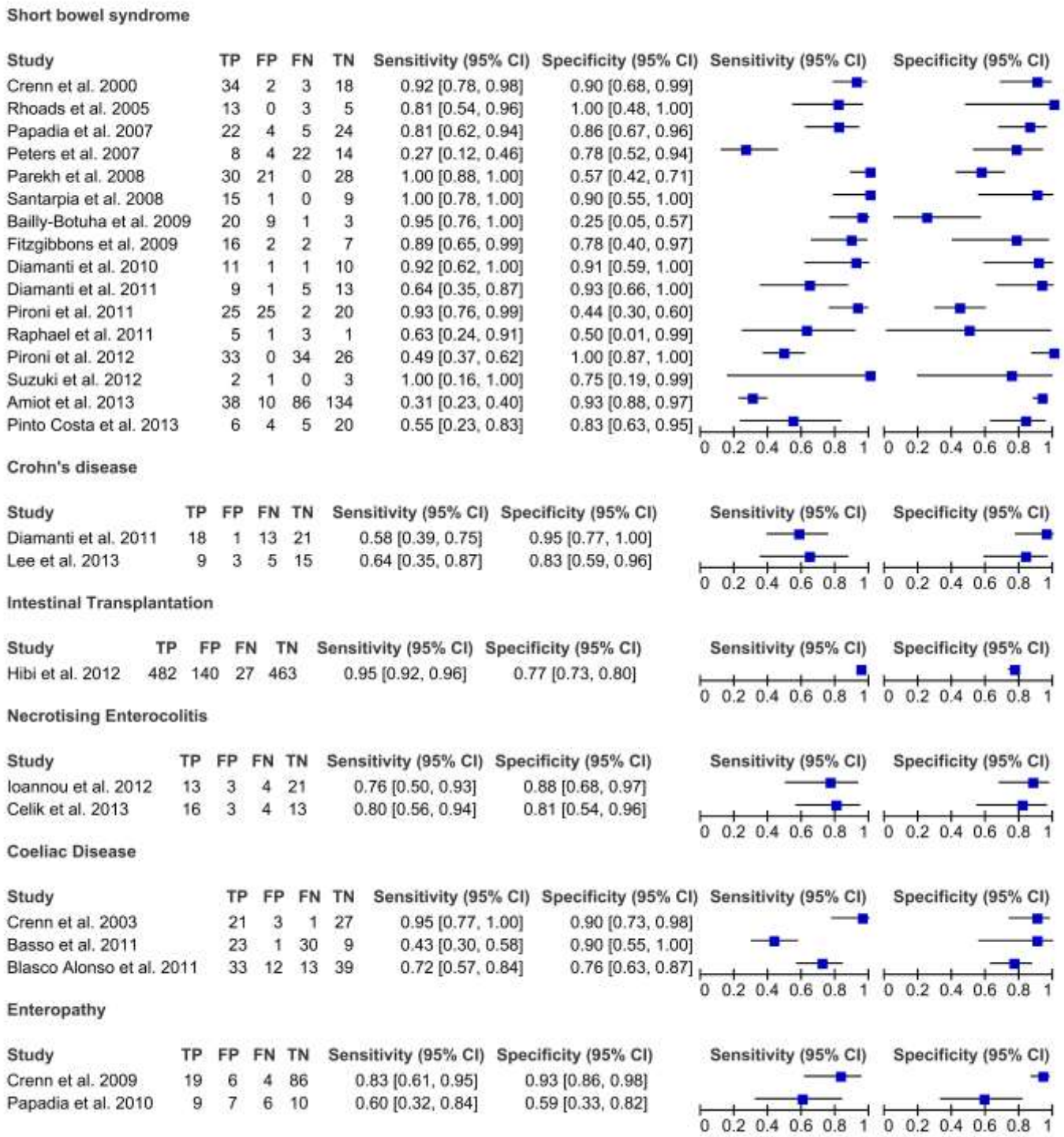
Supplementary Figure 4. Forest plots. (A) Mean differences of citrulline levels between PN dependent and independent SBS patients. (B) Mean increase of citrulline levels after treatment with teduglutide vs placebo in SBS patients. (C) Mean increase of citrulline levels after treatment with teduglutide vs baseline in SBS patients. (D) Mean difference of citrulline levels in coeliac disease patients who had received GFD treatment vs those who had not.



Supplementary Figure 5. Funnel plots. A. Mean citrulline levels: All conditions vs controls (30 studies). No asymmetry seen. B. Mean citrulline levels: SBS vs controls. No asymmetry observed. C. Mean citrulline levels: CeD/Enteropathy vs controls. No asymmetry observed. D. Mean citrulline levels: PN dependent vs PN independent patients. No asymmetry observed. E. Citrulline levels with disease severity in all conditions (28 studies). No asymmetry seen. F. Citrulline levels with disease severity in mucositis after chemoradiation. No asymmetry observed.



Supplementary Figure 6. Summary ROC curve for diagnostic accuracy in SBS patients.



Supplementary Figure 7. Forest plots of sensitivity and specificity in all patient conditions (26 studies)**.**

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