Title: A scoping review considering potential biomarkers or functional measures of gastrointestinal dysfunction and enteral feeding intolerance in critically ill adults

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What we know:

- Gastrointestinal dysfunction in critically ill adults is common leading to enteral feeding intolerance.
- Enteral feeding intolerance in critically ill adults is poorly defined and can lead to suboptimal nutritional delivery.
- There are no validated measures of enteral feeding intolerance increasing the risk of hospital acquired malnutrition.

What this study adds:

- Markers of gastrointestinal dysfunction and enteral feeding intolerance in critical care can be categorised as:

  1) Serum biomarkers,

  2) Physiological markers,

  3) Functional markers
- There are some associations between enteral feeding intolerance and biomarkers, but more research is required.

Abstract

Background & Aim: Enteral feeding intolerance (EFI) as a result of gastrointestinal (GI) dysfunction in critically ill adults can lead to suboptimal nutritional delivery, increasing the risk of hospital acquired malnutrition. There are no validated measures of EFI or consensus as to which measures could be used to define EFI. The aim of this scoping review is to explore the validity of biomarkers, physiological or functional measures of GI dysfunction and EFI in critically ill adults characterising their use in routine clinical practice to identify those with GI dysfunction to better guide nutritional support.

Methods: Database searches were completed in Ovid MEDLINE, Embase, CINAHL and Web of Science using the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines. The search was performed until June 2022. Articles were included if they reported original studies that identify potential biomarkers or functional measures of EFI in critically ill adults. A nine-stage process was completed to extract and complete data synthesis.

Results: 139 unique articles were identified. Following review of titles and abstracts, 114 of these articles were excluded, three further articles were excluded after full text review and 22 articles met the inclusion criteria. A thematic analysis of the articles included identified three overarching themes of GI dysfunction: 1) Serum biomarkers, 2) Physiological markers, and 3) Functional markers. Within the category of serum biomarkers, a further three sub-categories were identified: i) enterohormones, ii) markers of enterocyte function, and iii) cytokines and neurotransmitters. Some associations were seen between EFI and heparin binding protein, intra-abdominal pressure, cholecystokinin and acetylcholine levels but no markers are currently suitable for daily clinical use.

Conclusions: Further larger studies are required to characterise the relationships between serum biomarkers, physiological and functional makers of GI dysfunction in critically ill adults. A robust definition of GI dysfunction should be included in any future research.

Background

Gastrointestinal (GI) dysfunction is a common occurrence during critical illness and is associated with poorer clinical outcomes (1). GI dysfunction is made up of a spectrum of functional impairments throughout the GI tract including delayed gastric emptying, reduced GI absorption, intestinal dysmotility, diarrhoea, GI bleeding and intra-abdominal hypertension (2). These functional impairments contribute to increased levels of morbidity including increased duration of mechanical ventilation, prolonged intensive care unit (ICU) length of stay, increased multi-organ failure and increased mortality (2, 3). A systematic scoping review of GI dysfunction in critically ill adults identified a core set of research priorities relating to monitoring of GI dysfunction: 1) How to monitor GI function at the bedside; 2) How to define enteral feeding intolerance (EFI); 3) What is the reference method for measuring of gastric emptying in studies; 4) What is the best abdominal ultrasound protocol for GI dysfunction; 5) What is the reference method to be used to measure absorption of nutrients in research; 6) What is the reference method to be used to measure barrier dysfunction in research (3).

GI dysfunction is a key cause of EFI leading to inadequate provision of optimal nutrition during the ICU admission (4). The majority of critically ill adult patients admitted to an ICU rely on artificial nutrition support to meet their nutritional needs. Early enteral nutrition (EN) is recommended for critically ill patients who are unable to maintain oral intake (5,6). Adequate nutritional support has been associated with improvements in infection, wound healing, sarcopenia and length of hospital stay (7,8,9). However, many critically ill patients fail to reach nutritional targets (10,11,12), often due to GI dysfunction (1).

Many ICUs rely on routine measurements of gastric residual volume (GRV) to assess GI dysfunction and EFI, but these have been shown to poorly correlate with gastric emptying, regurgitation, incidence of aspiration and pneumonia (13,14). As a result, the routine measurement of GRV is no longer recommended by the American Society of Enteral and Parenteral Nutrition (ASPEN) to determine tolerance to EN (5). Various other symptoms of GI function are used in clinical practice to assess GI dysfunction but there is no single marker of GI function and nutrient absorption currently recommended for use at the bedside (15). For

these reasons there is growing interest in establishing a biomarker or other functional measure to monitor GI dysfunction and tolerance of EN.

The aim of this scoping review is to explore aspects relating to areas of uncertainty in GI dysfunction of critically ill patients related to EFI, including the validity of currently available biomarkers, physiological and functional measures of GI dysfunction and EFI in critically ill adults, characterising their suitability for use in routine clinical practice to better guide nutritional support.

Methods

Search strategy and eligibility criteria

The Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) was used to develop and report the evidence reviewed for this study (Supplementary table 1) (16).

Potentially eligible studies were identified by searching the following databases: Ovid MEDLINE, Embase, CINAHL and Web of Science (Supplementary table 2). Medical Subject Headings (MeSH) were used to expand the search to ensure inclusion of all appropriate articles. The following limits were applied: (1) written in the English language; (2) adults ($\geq$ 18 years); (3) full text article available. Databases were searched until June 2022. Additional citations were included following hand searching of reference lists of included articles. Studies were included if they had an interventional, observational cohort or case-control study design. Review articles, case reports, case series < 10 patients, conference abstracts and letters or editorials were excluded.

Inclusion criteria

Titles and abstracts of identified articles were screened for inclusion by a single reviewer (BJ), with full texts of potentially eligible articles (based on the abstract) then retrieved and screened. Articles were included if they reported original studies that identify potential biomarkers, physiological or functional measures of EFI or GI dysfunction in critically ill adults – names of potential biomarkers and functional measures were identified by an initial scoping search of the literature and included citrulline, intestinal fatty acid binding protein (I-FABP), heparin binding protein (HPB), growth-differentiation factor-15 (GDF15),

acetylcholine, enterohormones and ultrasound. Studies must have been conducted in an ICU setting; surgical, medical and trauma patients were all eligible for inclusion.

Data extraction

The following data were extracted from each included article: (1) study design, (2) objective, (3) inclusion criteria, (4) population, (5) sample size, (6) name of biomarker, (7) name of physiological/functional measure, (8) study findings and (9) limitations to applying finding to clinical practice.

Quality appraisal

The methodological quality of the studies was reviewed using the critical appraisal tools of the Joanna Briggs Institute (17).

Data synthesis

Data synthesis was completed using a thematic analysis approach to collate common issues reported in the data (18). Studies were screened and initially coded into groups based on the biomarker, physiological or functional measure reported. Where appropriate, these groups were then divided into sub-categories. Overarching themes were then developed into a conceptual framework.

Results

139 unique articles were identified. Following review of titles and abstracts, 114 of these articles were excluded. A further three articles were excluded after full text review. 22 articles met the inclusion criteria (Figure 1).

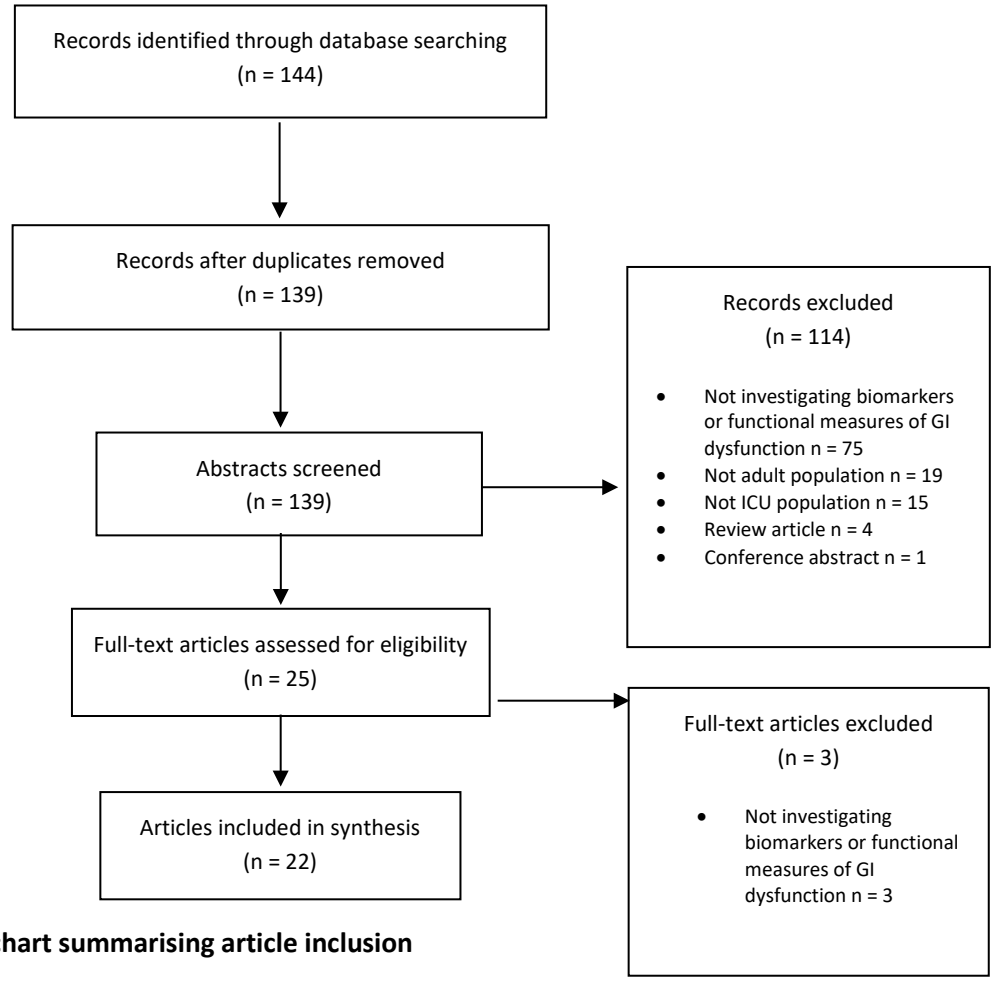

Figure 1: PRISMA flowchart summarising article inclusion

Characteristics of the included studies

The majority of studies (n=17; 77%) were in a mixed ICU population (1, 19-34). Three studies (14%) were conducted in surgical/trauma patients (35-37) and the remaining two studies (9%) in medical ICU patients (38,39). 10 (45%) studies investigated the use of biomarkers (19-26,35,38), with 11 individual biomarkers examined. Four (18%) studies investigated physiological markers (1,28,29,36) and seven (32%) studies investigated the use of a functional measure (ultrasound) (30-34,37,39) (Table 1).

Quality appraisal

Twenty (91%) of the included articles reported observational studies (1,20-23, 25-39) while two (9%) were post-hoc analyses of previous studies (19,24). There was a high variation in the methodological quality of included studies and high levels of heterogeneity between study participants. 18 of the 22 (82%) studies were deemed to be of good or excellent quality according to the Joanna Briggs checklists (1,20-32,34-36,38)

(Supplementary table 3). One study (4.5%) was deemed of satisfactory quality (19) and three (14%) studies were judged to be of poor methodological quality (33,37,39) (Supplementary table 3). They have however still been included in this narrative review with the limitations of the studies discussed in further detail below.

Thematic analysis

A thematic analysis identified three overarching themes: 1) Serum biomarkers of EFI, 2) Physiological markers of EFI, and 3) Functional markers of EFI. Within the category of serum biomarkers, a further three sub-categories were identified: i) enterohormones, ii) markers of enterocyte function, and iii) cytokines and neurotransmitters (Figure 2).

Serum biomarkers

11 individual biomarkers were examined (Figure 2). Crona et al. (19) found patients with EFI demonstrated significantly higher concentrations of total ghrelin, lower concentrations of acyl ghrelin, and lower ratios of acyl ghrelin to des-acyl ghrelin. However, Santacruz et al. (21) failed to find an association between ghrelin and EFI. Matsumoto et al. (35) found increased levels of I-FABP in patients with shock bowel and that patients with shock bowel had significantly increased rates of EFI. Greis et al. (38) also linked increased levels of I-FABP in addition to ileal bile acid binding protein (I-BABP) and zonulin with delayed gastric emptying. However, 2 further studies (25,26) failed to link I-FABP with EFI or GI dysfunction. Tao et al. (22) in their study of 113 mixed ICU patients showed patients tolerant to EN to have a significant increase in acetylcholine and CCK, whilst Sun et al. (23) in their study of 221 patients demonstrated links between HBP and EFI. No significant associations were found between citrulline (20,25,26), peptide YY (PYY) (21), motilin (19) or GDF15 (24) and EFI.

Physiological markers

2 physiological markers of EFI were investigated in studies included in this review. Wiedsma et al. (28) in an observational study of 48 mixed ICU patients concluded that a faecal weight of greater than 350g per day could be used as a marker for malabsorption and fat, protein and carbohydrate losses. 5 studies (1,26,27,29,36) utilised IAP as a marker of EFI. All studies found correlations between increased IAP and EFI.

Functional markers

Ultrasound was investigated as a measure of EFI in 7 studies (30-34,37,39). 2 studies (33,39) noted strong correlation between ultrasonographic measurement of gastric antral cross-sectional area (usCSA) and aspirated GRV, whilst one study (30) noted a moderate correlation between usCSA and gastric volume measured by computerised tomography and one study found a poor correlation (32) with GRV. Jahreis et al. (37) measured gastric volume using a miniaturized ultrasound device, but no comparison was made with any other method of measuring gastric volume. Liu et al. (31) found improved EN compliance and intake when measuring EN tolerance with ultrasound rather than GRV with less incidence of complications in the ultrasound group. Finally, in a study of 43 mixed ICU patients Wang et al (34) measured gastric antrum echodensity, demonstrating an increase in echodensity as GI dysfunction and EFI levels increased. Ability to visualise the gastric antrum with ultrasound varied between the studies with successful measurement in 58-100% of cases.

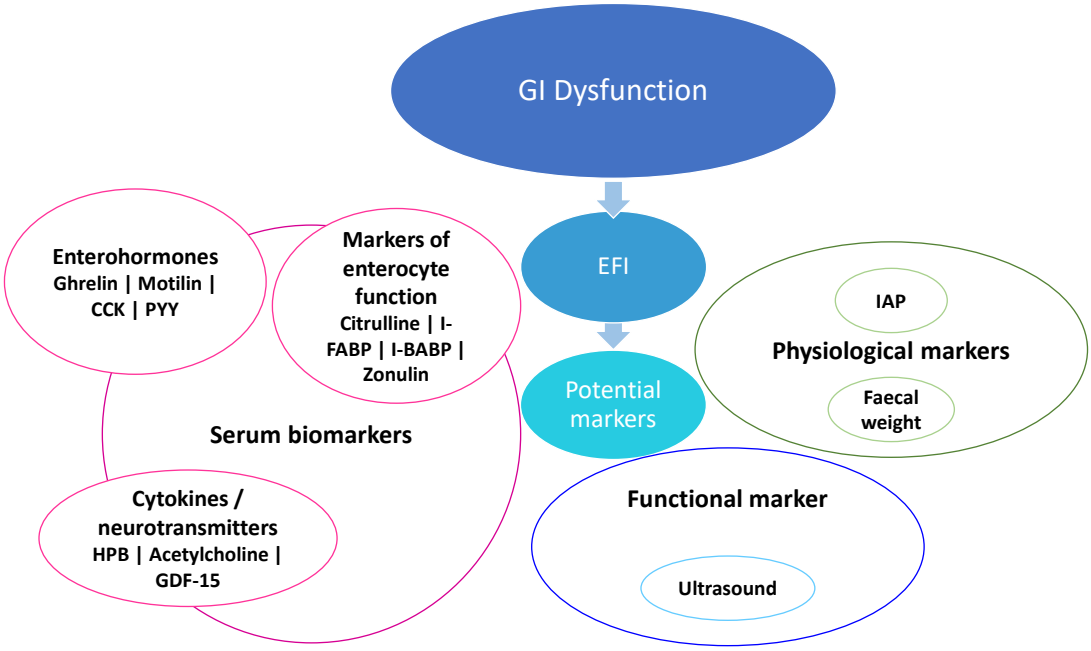

Figure 2: Framework of potential biomarkers, physiological and functional measures of GI dysfunction and EFI

Table 1: Summary of studies investigating biomarkers, physiological and functional measures as predictors of EFI in critically ill patients

Author, year	Marker	Population	Sample size	Study type	Results
Serum biomarkers					
Crona, 2012 (19)	CCK, ghrelin, motilin	Mixed ICU	30	Posthoc analysis	Patients with intolerance demonstrated significantly ↑ total ghrelin, ↓ acyl ghrelin, ↓ ratios of acyl ghrelin to des-acyl ghrelin. Des-acyl ghrelin, motilin, CCK similar between groups. No association between gastrointestinal hormone concentrations and gastric emptying measured by acetaminophen absorption test.
Poole, 2015 (20)	Citrulline	Mixed ICU	35	Prospective observational	No relationship seen between fasting citrulline concentration and subsequent glucose absorption.
Matsumoto, 2017 (35)	I-FABP	Trauma	92	Retrospective observational	Rate of EFI significantly ↑ in patients with shock bowel than in patients without (75.0% vs. 22.4%, OR 10.1, 95% CI 2.63–48.6, P < 0.001). Median plasma I-FABP levels were significantly ↑ in patients with shock bowel than in patients without (18.3 ng/mL [13.1–25.6] vs. 8.16 ng/mL [2.4–16.6], p=0.036).
Greis, 2017 (38)	Zonulin, I-BABP, I-FABP	Medical ICU	50	Prospective observational	↑ levels of zonulin, I-BABP, I-FABP in patients with delayed gastric emptying as measured by paracetamol absorption test prior to initiation of feeding. Significantly ↑ CD4, alpha4beta7, CCR9 and T lymphocytes in patients with delayed gastric emptying than normal gastric emptying.
Santacruz, 2017 (21)	PYY, ghrelin	Mixed ICU	22	Prospective observational	No significant differences in PYY or ghrelin levels between high and low GRV groups.
Tao, 2019 (22)	Acetylcholine, CCK	Mixed ICU	113	Prospective observational	Patients tolerant to early EN demonstrated a significant ↑ in plasma acetylcholine and CCK levels and significant ↓ in TNF-α and IL6. A positive correlation between acetylcholine levels and amount of EN was observed.

Sun, 2020 (23)	Heparin binding protein	Mixed ICU	221	Retrospective cross-sectional	Patients divided into 4 groups based on worst HBP values: HBP ≤ 20 ng/mL (group A), 20 < HBP ≤ 50 ng/mL (group B), 50 <HBP ≤ 100 ng/mL (group C), HBP > 100 ng/mL (group D). EFI incidence in group A was significantly ↓ than in group C (p=0.014) or group D (p=0.001). No differences in EFI incidence were found between groups A and B or B and C. The AUC of EFI was 0.729 (p=0.001). The optimal cut-off point for EFI was 48.28 ng/mL; with sensitivity of 64.7% and specificity of 56.6%.
Van Dyck, 2020 (24)	Growth-differentiation factor-15 (GDF15)	Mixed ICU	1383	Posthoc analysis	Serum GDF15 concentrations on ICU day 4 were inversely but weakly associated with tolerance of EN/oral nutrition (ON) in the following 24 h (OR for risk of intolerance per ng/ml GDF15 ↑: 1.027 [1.012; 1.042], p<0.0001, R^2=0.008), with limited sensitivity and specificity (area under receiver operating curve (AUROC) 0.57). These associations were independent of baseline risk factors.
Padar, 2021 (25)	Citrulline, I-FABP	Mixed ICU	60	Prospective observational	↑ citrulline values from day 4 in patients with successful EN/ON; patients failing to achieve 80% of caloric intake by day 4 had a slight ↓ in citrulline levels after day 4 (not significant). Abdominal distension was associated with ↓ citrulline values on day 1 and 3 (p=0.002 and 0.049). No association between other GI symptoms and citrulline levels. I-FABP levels were not different between those with EN/ON tolerance or intolerance.
Reintam Blaser, 2021 (26)	IAP, citrulline, I-FABP	Mixed ICU	540 (224 with biomarker measurements)	Multicentre prospective observational	Citrulline and I-FABP did not predict score of GI dysfunction. The cut-off for prediction of both 28- and 90-day mortality for mean IAP was identified at 11.5 mmHg.
Physiological markers					
Reintam, 2008 (27)	IAP	Mixed ICU	264	Prospective observational	EFI observed in 154 patients (58.3%); developed predominantly during the first 3 days of admission (144/154 [93.5%]). 72 patients (27.3%) developed IAH.

Weidsma, 2011 (28)	Faecal weight	Mixed ICU	48	Observational pilot	21% patients classified as having diarrhoea (> 350 g/day faeces) & therefore classified to be at ↑ risk for energy malabsorption. Patients with normal stools had a significantly ↓ total daily faecal energy loss (kcal/d) compared with patients with diarrhoea (P<0.001). Faecal fat, protein, carbohydrate losses significantly ↑ in the patients with diarrhoea (p<0.001) and energy-absorption capacity was significantly ↓ (p<0.001). Patients with > 350 g faeces/day had a significantly ↑ negative energy balance compared with patients with < 350 g/day faeces (loss of 627 kcal/day versus neutral balance; p=0.012).
Reintam Blaser, 2013 (1)	IAP	Mixed ICU	377	Observational	Incidence of IAH 42.7 % (mortality rate 31.1 %). EFI occurred in 140patients (37.1 %). None of the GI symptoms alone norIAH or caloric intake <80 % independently predictedmortality. The best GIF score with respect to mortality predictionincluded all six GI symptoms, but not IAH, EFI and/orcaloric intake.
Bejarano, 2013 (36)	IAP	Surgical ICU	72	Prospective observational	Baseline IAP and APACHE II score could predict EFI with a sensitivity of 92.2% and specificity of 52.4%. Using the ROC area under the curve they demonstrated an accuracy of 80.3% (95% CI, 68.7%-92%) for their formula.
Bordejé, 2019 (29)	IAP	Mixed ICU	247	Prospective observational	Mean daily IAP was similar, but maximum daily IAP was higher in the intolerant group (p < 0.001). An IAP value of 14 mmHg identified in sensitivity versus specificity curves as the best cut-off to predict EFI, but it had low sensitivity (58.6%) and low specificity (48.7%).
Functional marker					
Hamada, 2014 (30)	Ultrasound	Mixed ICU	55	Prospective observational	A moderate correlation (r=0.39) was seen between gastric antral cross-sectional area & CT. Adequate measurements were only obtained in 65% of cases.
Sharma, 2017 (39)	Ultrasound	Medical ICU	19	Prospective observational	Gastric cross-sectional area using IVC as a landmark (R^2 = 0.92, p<0.0001) and aorta as a landmark (R^2 = 0.86, p<0.0001) correlated with GRV. The gastric antrum could not be visualised in 21-42% of cases (depending on if aorta or IVC used as landmark).

Liu, 2017 (31)	B-ultrasound	Mixed ICU	30 healthy volunteers; 64 critically ill patients	Prospective observational	Modified B-ultrasound had a better effect in guiding EN with ↑ EN duration, EN compliance and calorie intake compared to the gastric withdrawal method ($p<0.05$). ↓ incidence of GI complications and pneumonia in the B-USS group ($p=0.031$).
Bouvet, 2020 (32)	Ultrasound	Mixed ICU	61	Prospective observational	Gastric suctioning did not provide an accurate estimate of residual gastric volume compared with ultrasound, with a mean bias of 66.6 ml and a 95% agreement band ranging from 218 ml to 351 ml.
Taskin, 2021 (33)	Ultrasound	Mixed ICU	56	Prospective observational	Antral cross-sectional area correlated significantly with aspirated GRV; antral cross-sectional area ↑ linearly with ↑ aspirated GRV ($R^2=0.73$, $p<0.0001$).
Jahreis, 2021 (37)	Ultrasound	Surgical ICU	18	Prospective observational	Ultrasound examination was possible in all 217 cases. Measurements could be performed without pausing EN. The GRV was significantly ↑ with sparsely auscultated bowel sounds than with normal and excited bowel sounds ($p<0.01$). Significantly ↑ GRV was present when using a high-caloric/low-protein nutritional product compared to an isocaloric product ($p=0.02$).
Wang, 2022 (34)	Ultrasound	Mixed ICU	43	Prospective observational	Gastric antrum echodensity measurements had sufficient intra- and inter-investigator reliabilities. Echodensity showed significant ↑ trend as AGI severity ↑. Patients with EFI had ↑ echodensity at EN initiation.

Discussion

Several articles investigating the use of biomarkers, physiological or functional measures of GI dysfunction and EFI were appraised in this scoping review. The results of this review suggest that there are currently no suitable biomarkers, physiological or functional measures available as a surrogate measure of GI dysfunction or EFI. However, some associations have been noted and warrant further investigation. Future work should assess suitability for use in clinical practice alongside practical and financial implications for use.

Enterohormones

Several enterohormones have been suggested as potential biomarkers of EFI in critically ill patients. Ghrelin levels have been shown to be altered in patients with delayed gastric emptying (40). Motilin, a 22-amino-acid peptide synthesised in the duodeno-jejuno mucosa that regulates interdigestive migrating contractions in the GI tract (41) has been widely studied alongside ghrelin for it's role in appetite regulation and food intake in health and disease (42).

Two further hormones, PYY and CCK were also studied in papers included in this review. PYY and CCK are released from the enteroendocrine cells of the small intestine in response to the presence of nutrients (43,44). In health exogenous administration of PYY and CCK is associated with slowed gastric emptying (43,45) but their value in critical illness related delayed gastric emptying is yet to be determined.

Studies investigating the use of ghrelin as a potential marker of EFI showed somewhat conflicting results. Whilst Crona and MacLaren (19) concluded that the concentrations of various ghrelin moieties differ in patients tolerant and intolerant to gastric EN, Santacruz et al. (21) found no correlation between ghrelin and EFI measured by GRV. The complexities of ghrelin metabolism add challenges to using it as a biomarker and several moieties of ghrelin are present in the human body. Acyl ghrelin was previously thought to be the active hormone; however recent evidence suggests that des-acyl ghrelin also possesses activity, and the enzyme ghrelin-O-acyl transferase regulates their interconversion (46). Crona and MacLaren (19) measured levels of total ghrelin, acyl ghrelin, and des-acyl ghrelin and the acyl:des-acyl ghrelin ratio, while Santacruz et al. (21) only measured acyl ghrelin therefore not taking into account the possible effect of des-acyl ghrelin on gastric motility.

In addition to ghrelin levels, Crona and MacLaren (19) also investigated serum motilin and CCK, and Santacruz et al. (21) also measured plasma PYY levels; whilst Tao et al. (22) measured CCK in addition to plasma cytokine and acetylcholine levels. The studies included in this review were not able to demonstrate any associations between serum motilin and PYY levels and EFI. However, Tao et al. (22) observed a significant increase in plasma CCK levels in patients tolerant to EN. The authors speculate that early EN promotes recovery of gastrointestinal endocrine function leading to increased CCK levels with downstream effects on gastric motility. Further work in larger patient groups is required to confirm these results.

Markers of enterocyte function

Citrulline has been proposed as marker of GI dysfunction in critical illness due to the correlation between citrulline levels and enterocyte mass and function in chronic GI diseases (47). I-FABP and I-BABP are released into the circulation when the enterocyte membrane is damaged (48,49). Zonulin regulates intestinal tight junctions and can be used as a biomarker of intestinal function in several diseases (50). Poole et al. (20), Padar et al. (25) and Reintam Blaser et al. (26) were all unable to demonstrate a significant association between citrulline or I-FABP and EFI and GI dysfunction. However, Greis et al. (38) noted a significant association between I-FABP and I-BABP levels and delayed gastric emptying and Matsumoto et al. (35) demonstrated increased levels of I-FABP in patients with shock bowel, with significantly increased rates of EFI in these patients. Furthermore, Greis et al. (38) demonstrated a significant association with zonulin and delayed gastric emptying, noting that zonulin increases intestinal permeability of the small intestine related to immune activated mucosal barrier impairment and linked this to gastric dysmotility.

The study by Poole et al. (20) investigating citrulline as a marker of absorptive capacity, measured only glucose absorption to assess tolerance. Citrulline concentration has been shown to have some correlation with fat and nitrogen absorption in short bowel syndrome (51) and therefore the association between citrulline and absorption of other macronutrients in the critical care setting may warrant further investigation. The dynamics of citrulline metabolism are complex and depend on glutamine availability, renal function and inflammation (52). Three separate metabolic pathways exist for citrulline synthesis and conversion. Citrulline is synthesised in the liver where it is then metabolised for urea production. Secondly

citrulline is converted to arginine for nitric oxide production in most tissues that produce nitric oxide and lastly citrulline is synthesised in the gut from glutamine (53). As many critically ill patients demonstrate glutamine deficiency (54), and arginine, which is normally a conditionally essential amino acid in health, becomes an essential amino acid during metabolic stress (55), it is clear that citrulline levels are likely to be altered in critical illness independently of levels of EFI. It is therefore possible that patients who are more unwell have lower citrulline levels due to their increased organ dysfunction, and as patients who are more unwell are more likely to experience EFI this accounts for any correlation seen between citrulline and EFI. These additional factors influencing citrulline levels may make interpretation of citrulline as a biomarker of GI dysfunction and EFI in clinical practice challenging.

Levels of I-FABP and I-BABP are known to increase in the circulation upon damage to the enterocyte membrane (50), however they are cleared rapidly from the circulation via the renal system with a half-life of 11 minutes (56). It may therefore be necessary to include measures of urinary fatty acid binding proteins in addition to serum levels in future studies in order to prove their usefulness as biomarkers of EFI and GI dysfunction.

Cytokines and neurotransmitters

Acetylcholine is an anti-inflammatory transmitter in the cholinergic pathway (57). The primary aim of the study by Tao et al. (22) was to explore whether early EN affected acetylcholine levels and inflammation by modulation of the CCK-acetylcholine pathway. The authors observed that patients who tolerated EN presented higher acetylcholine and CCK levels and lower inflammation. It could be postulated that the anti-inflammatory action of early EN improves GI endocrine function and leads to a subsequent rise in CCK and acetylcholine in those tolerant to EN and these biomarkers could prove to be useful in monitoring EFI. Further research to better understand these relationships is required.

HPB is a neutrophil-derived granule protein, that has been shown to be a useful biomarker for predicting organ dysfunction in sepsis (58). In primary acute GI injury, such as abdominal trauma, the neutrophils of the damaged intestinal barrier release HBP. This led Sun et al. (23) to hypothesise that HBP

levels may be associated with GI dysfunction in the critically ill. However, the exact mechanisms linking GI function and HBP have not been elucidated and further work is required to understand this relationship.

Van Dyck et al. (24) hypothesised that GDF15 may be a driver of GI intolerance in the critically ill. Levels of GDF15, have been shown to increase during critical illness (59,60). Van Dyck et al. (24) concluded that the use of GDF15 as a biomarker for EFI is limited. However, this work included patients receiving ON as well as EN and it therefore could be argued that this study did not represent EFI as not all patients were being enterally fed. A cut off of intake of 100 kcal per day was used to indicate GI tolerance. This cut off for oral caloric intake is very modest and is unlikely to be a true reflection of tolerance.

Physiological markers of EFI

Increased IAP has been associated with GI dysfunction (27). Five studies included in this review investigated the link between IAP and GI dysfunction (1,26,27,29,36). Bejarano et al. (36) and Bordeje et al. (29) investigated correlations between IAP and EFI, producing mixed results. Both studies found IAP to be higher in patients with EFI. Bejarano et al. (36) were able to predict EFI with a combination of IAP and APACHE II score with a sensitivity of 92% and specificity of 52.4%. However, Bordeje et al. (29) noted IAP to have low sensitivity and specificity in predicting EFI. Reintam Blaser et al. conducted three prospective observational studies investigating links between IAP, EFI, GI dysfunction and mortality (1,26,27). The group identified that a large proportion of critically ill patients had symptoms of GI dysfunction; however none of these symptoms alone nor raised IAP or EFI predicted outcome independently. From this work, new clinical scores for GI dysfunction in the critically ill have been developed enabling the quantification of GI dysfunction and decreasing reliance on subjective measures. An IAP value of 12mmHg was identified as a predictive cut off for both 28 and 90 day mortality and this value was therefore included within the score. EFI and GI dysfunction are clearly complex and multifactorial problems in the critically ill and development of a grading system is key to better understanding and treating these issues.

Faecal weight was suggested as a marker of malabsorption of enteral nutrition in the work by Weidsma et al. (28). This study differed from most included in this review in that it focused on lower GI malabsorption rather than delayed gastric emptying. Many studies of EFI have focused on upper GI function

and delayed gastric emptying due to better understanding and easier detection of upper GI symptoms (15). However, as demonstrated by Weidsma at al. (28) significant energy may be lost as a result of diarrhoea and further work is necessary to ensure this is accounted for in assessment of feed tolerance.

Functional markers of EFI

Ultrasound has been used to measure gastric emptying in healthy populations for some time but its use in critically ill, enterally fed patients has not been validated (61). The studies examined in this review produced conflicting results regarding the suitability for use of ultrasound as a marker of gastric emptying in critical care. Four (32,33,37,39) of the 7 studies investigating the use of ultrasound to measure gastric emptying used GRV as the sole comparator to validate the findings from the ultrasound scans. However, GRV does not accurately reflect gastric emptying (13,14) and as such cannot be used to validate a measure of gastric emptying. Only Hamada et al. (30) used CT as a reference measure of gastric volume, although they noted a delay between ultrasound and CT measurements, which may have impacted the measured gastric volume. If ultrasound is to be validated as a technique for measuring gastric emptying and used as a surrogate for EFI then this must be measured against a reliable measure of gastric volume.

Limitations

A major limitation of this review is the lack of agreed definitions of GI dysfunction and EFI as previously highlighted (3). Further limitations include aspects of the design of the included studies such as being observational, having small sample sizes and including a heterogeneity of critical care patients.

Several potential markers of GI dysfunction and EFI have been identified in this review but larger adequately powered studies are required before they can be validated for use (Figure 3).

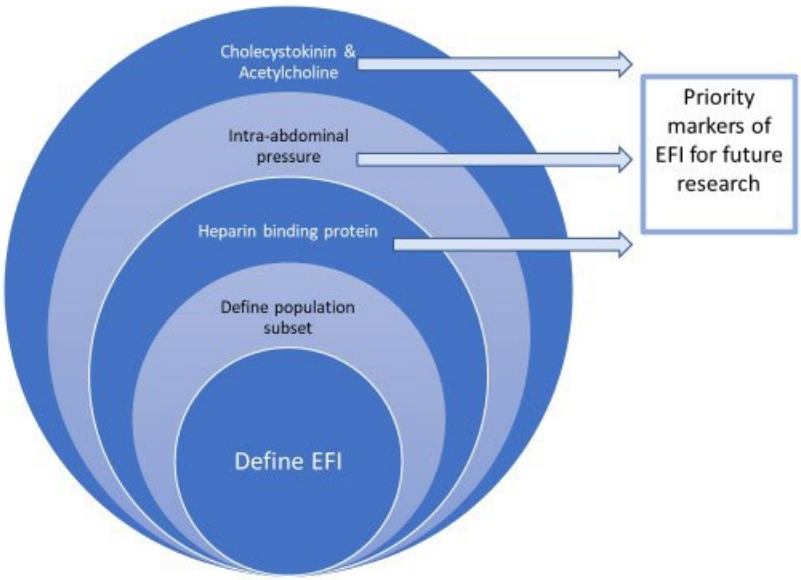

Figure 3: Future research priorities for markers of GI dysfunction and EFI

Conclusion

The findings of this scoping review suggest there are no suitable biomarkers or functional measures of GI dysfunction or EFI available for immediate use in a clinical setting. However, there are some potential markers of interest including HPB, IAP, CCK and acetylcholine levels. To validate their use as surrogate measures of GI dysfunction, further larger studies are required to characterise these relationships in critically ill adults. Future work should assess suitability for use in clinical practice alongside practical and financial implications for use.

Authorship statement

Authors made the following contribution to the manuscript [1]: BJ, LVM and PCC formulated the question for the scoping review [2], BJ conducted the literature search [3], BJ reviewed articles for inclusion [4], BJ conducted the analysis and drafted the manuscript [5], BJ, LVM and PCC critically reviewed and revised the manuscript [6], BJ, LVM and PCC provided final approval of the manuscript.

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Conflicts of interest

None of the authors has any conflict of interest to declare.

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