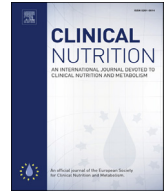




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Original article

Development of the Gastrointestinal Dysfunction Score (GIDS) for critically ill patients – A prospective multicenter observational study (iSOFA study)



Annika Reintam Blaser ^{a, b, *}, Martin Padar ^{a, c}, Merli Mändul ^{d, e}, Gunnar Elke ^f, Christoph Engel ^g, Krista Fischer ^{d, e}, Mikhael Giabicani ^h, Thomas Gold ⁱ, Benjamin Hess ^b, Michael Hiesmayr ^j, Stephan M. Jakob ^k, Cecilia I. Loudet ^l, Dennis M. Meesters ^{m, n}, Wasineenart Mongkolpun ^o, Catherine Paugam-Burtz ^{h, p}, Martijn Poeze ^{m, n}, Jean-Charles Preiser ^o, Mattias Renberg ^q, Olav Rooijackers ^q, Kadri Tamme ^{a, c}, Jan Wernerman ^q, Joel Starkopf ^{a, c}

^a Department of Anaesthesiology and Intensive Care, University of Tartu, Tartu, Estonia

^b Department of Intensive Care Medicine, Lucerne Cantonal Hospital, Lucerne, Switzerland

^c Department of Anaesthesiology and Intensive Care, Tartu University Hospital, Tartu, Estonia

^d Estonian Genome Center, Institute of Genomics, University of Tartu, Tartu, Estonia

^e Institute of Mathematics and Statistics, University of Tartu, Tartu, Estonia

^f Department of Anaesthesiology and Intensive Care Medicine, University Medical Center Schleswig-Holstein, Campus Kiel, Kiel, Germany

^g Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany

^h Department of Anaesthesiology and Critical Care, Beaujon Hospital, DMU Parabol, AP-HP Nord, Paris, France

ⁱ 2nd Medical Department, Cardiology, Hanusch Hospital, Heinrich Collinstr.30, 1140, Vienna, Austria

^j Division of Cardio-Thoracic-Vascular Surgical Anaesthesia and Intensive Care Medicine, Medical University of Vienna, Austria. Spitalgasse 23, Wien, 1090, Vienna, Austria

^k Department of Intensive Care Medicine, University Hospital (Inselspital) Bern, University of Bern, Bern, Switzerland

^l Department of Intensive Care Medicine, Hospital Interzonal General de Agudos San Martín de La Plata, La Plata, Argentina

^m Department of Surgery and Trauma Surgery, Maastricht University Medical Centre, Maastricht, the Netherlands

ⁿ NUTRIM School for Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, the Netherlands

^o Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium

^p INSERM UMR_S1149, Inserm et Université de Paris, Paris, France

^q Department of Clinical Science, Intervention and Technology, Division of Anaesthesiology and Intensive Care Medicine, Karolinska Institutet, Stockholm, Sweden

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SUMMARY

Background & aims: To develop a five grade score (0–4 points) for the assessment of gastrointestinal (GI) dysfunction in adult critically ill patients.

Methods: This prospective multicenter observational study enrolled consecutive adult patients admitted to 11 intensive care units in nine countries. At all sites, daily clinical data with emphasis on GI clinical symptoms were collected and intra-abdominal pressure measured. In five out of 11 sites, the biomarkers citrulline and intestinal fatty acid-binding protein (I-FABP) were measured additionally. Cox models with time-dependent scores were used to analyze associations with 28- and 90-day mortality. The models were estimated with stratification for study center.

Results: We included 540 patients (224 with biomarker measurements) with median age of 65 years (range 18–94), the Simplified Acute Physiology Score II score of 38 (interquartile range 26–53) points, and Sequential Organ Failure Assessment (SOFA) score of 6 (interquartile range 3–9) points at admission. Median ICU length of stay was 3 (interquartile range 1–6) days and 90-day mortality 18.9%.

A new five grade Gastrointestinal Dysfunction Score (GIDS) was developed based on the rationale of the previously developed Acute GI Injury (AGI) grading. Citrulline and I-FABP did not prove their potential for scoring of GI dysfunction in critically ill. GIDS was independently associated with 28- and 90-day

* Corresponding author. Department of Anaesthesiology and Intensive Care, University of Tartu, Puusepa 8, Tartu, 51014, Estonia.

E-mail address: annika.reintam.blaser@ut.ee (A. Reintam Blaser).

mortality when added to SOFA total score (HR 1.40; 95%CI 1.07–1.84 and HR 1.40; 95%CI 1.02–1.79, respectively) or to a model containing all SOFA subscores (HR 1.48; 95%CI 1.13–1.92 and HR 1.47; 95%CI 1.15–1.87, respectively), improving predictive power of SOFA score in all analyses.

Conclusions: The newly developed GIDS is additive to SOFA score in prediction of 28- and 90-day mortality. The clinical usefulness of this score should be validated prospectively.

Trial registration: NCT02613000, retrospectively registered 24 November 2015.

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1. Introduction

The clinical and prognostic relevance of gastrointestinal (GI) function in critically ill patients has been repeatedly recognized, but until now there is no validated clinical tool to monitor GI dysfunction as part of the multiple organ dysfunction syndrome [1,2]. There have been several attempts to create such a tool [3–5], but subjectivity of clinical assessment of GI function, as well as lack of uniform definitions and biomarkers have led to only limited success [2].

It has been shown that one single GI symptom is insufficient to predict outcome [4], as commonly requested for any variable considered for organ dysfunction scoring. However, complex assessment of different GI symptoms may allow identification of GI dysfunction/failure, related to adverse outcome [4,5]. In addition to GI symptoms, variables that show potential for assessment of GI dysfunction as part of multiple organ dysfunction syndrome include intra-abdominal pressure and the biomarkers citrulline and intestinal fatty acid-binding protein (I-FABP) [1,6–8].

In a consensus paper from 2012, simple definitions for GI symptoms were proposed, together with a definition of Acute Gastrointestinal Injury (AGI) using four grades of severity based upon the available evidence and expert opinion [9]. AGI grading was developed to rate malfunction of the GI tract in critically ill patients, occurring as a part of multiple organ dysfunction syndrome [9]. This concept is still valid, however, while the developed grading in its descriptive way can be used at bedside, it is not well applicable in clinical studies. AGI grading includes general subjective assessment of patient's condition and is focusing on feeding intolerance – a poorly defined entity that is dependent on local feeding practices – and its management [10]. Accordingly, observer-dependency is high, whereas at the same time more severely ill patients are likely to be given a higher grade of AGI compared to less severely ill patients presenting with similar GI symptoms.

Therefore, a clear score for GI dysfunction, readily available at bedside with minimized subjectivity and maximized reproducibility is warranted.

The aim of the present study was to explore the contribution of GI dysfunction to outcome in critical illness and develop a data-driven, verifiable score of GI dysfunction that can either stand on its own or complete the Sequential Organ Failure Assessment (SOFA) score [11].

2. Methods

We performed a multicenter prospective observational study endorsed by the European Society of Intensive Care Medicine (iSOFA study, [ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT02613000) enrolling consecutive adult patients admitted to the participating ICUs during the study period, irrespective of anticipated length of stay. Part A of the study was carried out in all ($n = 11$) study centers ([Supporting file 1](#)) and comprised of daily clinical data collection during patient's ICU stay for maximum 7 days, with an emphasis on

gastrointestinal and abdominal signs and symptoms, and measurement of intra-abdominal pressure and gastric residual volume (GRV). Part B was conducted in six centers, where in addition to clinical data collection plasma citrulline and intestinal fatty-acid binding protein (I-FABP) were measured once a day during patient's ICU stay for maximum 7 days. Initially per protocol planned measurements of D-lactate and ileal lipid binding protein were omitted due to insufficient funding.

2.1. Ethics

The study was approved by the Ethics Committee of the University of Tartu (approval 265/M–28). Approval from the local ethics committee was obtained at each study site. For Part A, informed consent was required in some countries and waived in the others ([Supporting file 1](#)), whereas for each patient included in Part B delayed informed consent was required. According to the local ethics approval, delayed informed consent was obtained from the patient or their next of kin. This allowed collection of blood samples immediately after admission to the ICU, necessary to study the dynamics of biomarkers. Patients or their next of kin were approached for informed consent at the first possibility. Patients were excluded from the study and their already collected data deleted, if patient or patient's next of kin denied participation in the study.

2.2. Patients

Enrolment period lasted for 2–4 consecutive weeks for each site with the aim to include at least 25 patients, and sites defined their study period individually between April 2015 and April 2018. All adult (18 years or older) patients without limitation of care at admission to the ICU were eligible for inclusion. Exclusion criteria were defined as no informed consent (including communication/language problems) and readmission of a patient to the ICU after having already completed the observation period.

2.3. Data collection

Gastrointestinal symptoms and abdominal signs (vomiting/regurgitation, absent bowel sounds, diarrhea, abdominal distension, GI bleeding, GI paralysis/dynamic ileus, defined according to [9]), GRV, intra-abdominal pressure (IAP), data on nutrition and prokinetics were all documented during patient's ICU stay for maximum 7 days and considered for the score without *a priori* exclusions. Additionally, severe diarrhea was defined as a Bristol scale 6–7 [12] for ≥ 5 times/day or ≥ 1000 mL/day when a stool collector was in place. SOFA subscores were recorded and the descriptive AGI grade [9] evaluated daily for maximum 7 days during the patient's ICU stay. Measurements of GRV and IAP were performed in all patients with respectively nasogastric tube or indwelling bladder catheter *in situ* (both inserted as a standard of care).

In centers participating in Part B of the study, plasma samples for levels of citrulline and I-FABP were obtained daily, with the first

samples taken immediately after ICU admission. Details on clinical data collection and biomarker measurements are presented in [Supporting file 1](#). Each site continued their standard of care in all aspects; no specific study interventions were applied.

2.4. Sample size calculation

Sample size calculation was based on previous studies [3,4] estimating the Area Under the Receiver Operating Characteristic (AUROC) curve of the SOFA score in prediction of 28-day mortality being 0.750 (SD 0.25). We aimed to detect a 5% absolute increase in the predictive capability of SOFA score with addition of the GI dysfunction score. We assumed a 28-day mortality in our study population of 20%. With a type I error of 5% and a power of 90%, 450 patients were needed for the analysis. We aimed to include at least 500 patients allowing for a drop-out rate of 10%.

2.5. Rationale for the score development

We used documented AGI grading as an existing graded approach to GI dysfunction to test its rationale and predictive power. We constructed a new score based on the same rationale but aiming minimization of subjective aspects in assessment.

Primary outcomes were 28- and 90-day mortality. For these outcomes daily data (SOFA, AGI, individual GI symptoms, and the new GID score) were analyzed as repeated measurements.

2.6. Analysis

Quantitative variables are presented as medians (interquartile ranges). Qualitative variables are summarized as absolute and relative frequencies.

For categorization, cut-off values for potentially useful continuous variables related to 28- and 90-day mortality were identified based on ROC-curve analyses.

All individual GI symptoms, abdominal signs, and biomarkers were compared daily between survivors and non-survivors using Wilcoxon-Mann-Whitney or Fisher's exact test. Cox models were fitted to see the effect of recorded variables as time-dependent covariates on 28- and 90-day mortality.

The main analysis began by investigating the effect of descriptive AGI grading on 28- and 90-day mortality. Thereafter, based on AGI logic, we defined a new score including all clinical symptoms and tested its predictive value for 28- and 90-day mortality. For mortality prediction AGI grading, SOFA (sub)scores and the new score were entered into the Cox model as time-dependent covariates. Cox models were estimated with stratification for study center.

The possible impact of the biomarkers to the new score (Gastrointestinal Dysfunction Score – GIDS) was tested by adding biomarkers at different cut-offs and evaluating each such test-score with Cox models.

C-statistic was used to describe predictive capability of the scores and their combinations.

Statistical analyses were performed with IBM SPSS Statistics for Windows Version 25.0 (IBM Corp, Armonk, NY) and with R statistical software [13].

2.7. Development of gastrointestinal dysfunction (GID) score

Step-by step process is presented in [Supporting file 2](#). In brief, to construct the guide for defining the new score, multiple models were fitted in order to understand how different symptoms discriminate between the AGI grades. Although the data consists of multiple observations per patient (one per each day spent in the

ICU), we preferred to use methods that ignore such dependence between observations, as no formal significance testing would be used at the modeling stage.

Logistic regression models were used for each AGI grade level to see how symptoms discriminate between the given AGI grade and all higher grades. For each model, only individuals assigned to the given or higher AGI grade were included in the analysis. Initially all symptoms were included as covariates. Stepwise logistic regression (both directions) was used thereafter, and the best model based on the Akaike information criterion (AIC) was chosen. These models provided insight for separating more severe from less severe symptoms, and the results were used to distinguish which symptoms were more relevant for higher AGI grade classification.

In addition, similar models for each specific AGI grade were fitted, by including all individuals (with either higher or lower grades), to identify symptoms that discriminate between specific AGI grade and all the other grades. As before, stepwise logistic regression was used, and the best model was chosen based on AIC.

Finally linear discriminant analysis (LDA) was performed, using the data on all recorded symptoms. This analysis also assists in separating more severe from less severe symptoms as all AGI grades can be looked at the same time.

Median number of symptoms with interquartile range with respect to the AGI grade was also investigated to see whether number of symptoms plays a role in defining a specific AGI grade in addition to severity of symptoms.

The modeling above guided us to define the principles for formation of the new score, where we considered also the clinical relevance and simplicity for the user. These principles were then used to define a test-score based on the symptoms for each study day. Thereafter, the performance of test-score as a time-dependent variable was evaluated in Cox models for 28- and 90-day mortality. This process was repeated testing several test-scores modified based on careful evaluation of the previous test-scores considering correlation with AGI grade, clinical applicability, and simplicity. The best performing test-score was named Gastrointestinal Dysfunction (GID) Score.

3. Results

3.1. Patients' characteristics

We included 540 patients from 11 sites, among them 224 patients from 5 sites (Stockholm, Bern, Vienna, Tallinn and Tartu) with biomarker measurements. Results of the biomarker values from one site (20 patients) were excluded due to major differences in timing of deproteinization of the samples. A flow diagram of the study is presented in [Fig. 1](#). Patient characteristics and outcomes are presented in [Table 1](#)

3.2. Mortality prediction by SOFA, AGI grading, GI symptoms and abdominal signs

Performance of descriptive AGI grading alone and in combination with SOFA score in prediction of 28- and 90-day mortality is presented in [Table 2](#). AGI grading was independently associated with mortality in our study population when added to SOFA total or to SOFA subscores. This led to a next analysis step aiming at developing a new score based on logics of AGI grading. In this analysis step, single GI symptoms and conditions were used to achieve better reproducibility compared to AGI grading ([Supporting file 2](#)).

Performance of GI symptoms and biomarkers in prediction of 28- and 90-day mortality are presented in [Supporting file 3](#). Daily and cumulative prevalence and unadjusted association with mortality of

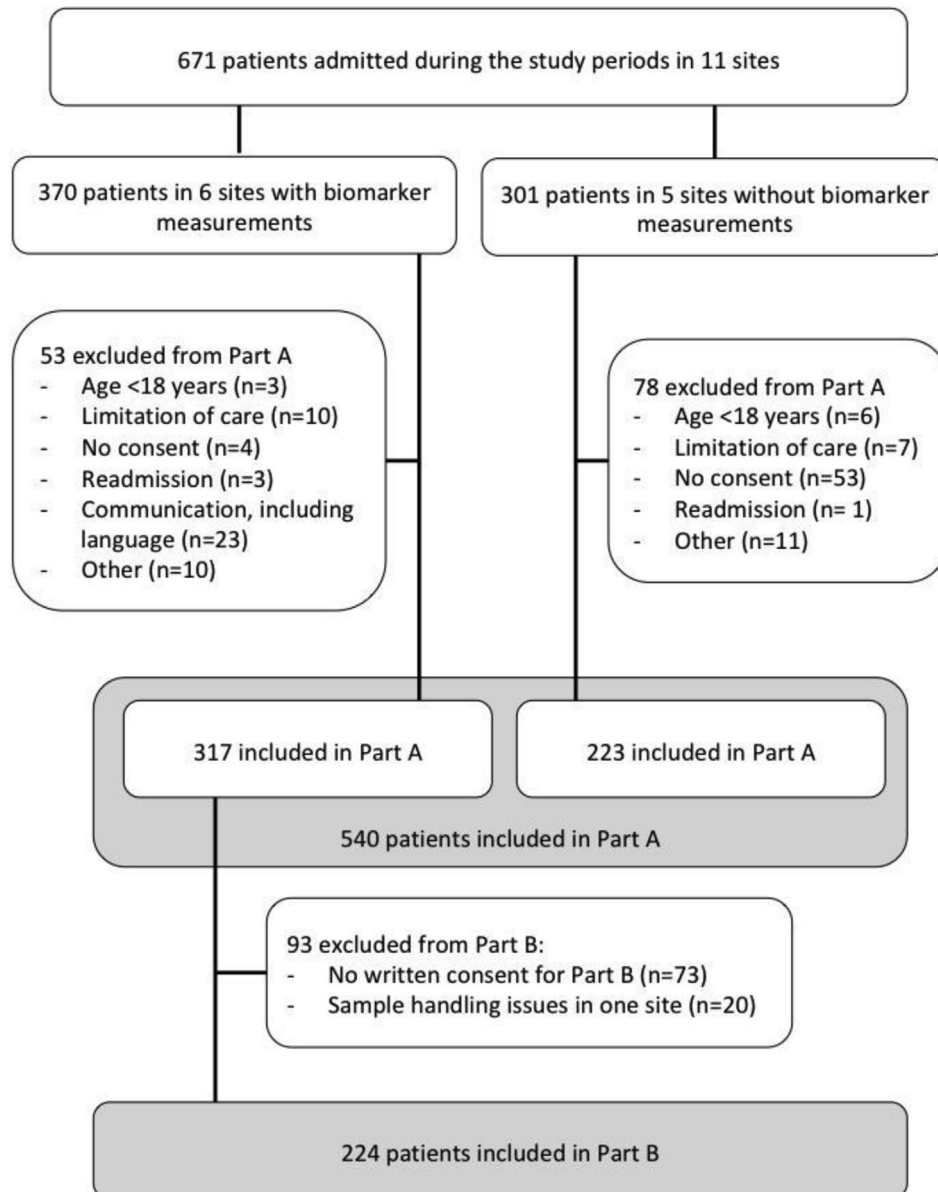


Fig. 1. Study flow chart.

GI symptoms, biomarkers, AGI grading, and GID score for 28- and 90-day mortality are presented in [Supporting file 3](#). Biomarkers were not associated with mortality in univariate or multivariate analyses with the exception of I-FABP above the reference in univariate analysis ([Supporting file 3, Tables S22 to S24](#)). Therefore, we primarily focused on GI symptoms as components for the new score, allowing inclusion of all study patients in this analysis.

The cut-off for prediction of both 28- and 90-day mortality for mean IAP was identified at 11.5 mmHg; therefore, in accordance with consensus definitions [14] we chose to use mean IAP of 12 mmHg or higher defining intra-abdominal hypertension (IAH) in further analyses. The cut-off for maximum GRV per one measurement was identified at 180 mL for 28-day mortality and at 225 mL for 90-day mortality; we chose 200 mL as our cut-off defining large GRV.

3.3. Mortality prediction by SOFA and GID score

The newly developed GID score is presented in [Table 3](#). The score has a significant impact on mortality prediction. The GIDS remained independently associated with mortality when tested in combination with SOFA score ([Table 4](#)).

Agreement between descriptive AGI grading and different test-scores (the same grade and score given to the same patient on this day) was approximately 60% in all tested models ([Supporting file 2](#)). The differences between the models stratified for center vs. non-stratified were small, with GIDS performing slightly better in stratified models.

Ninety-day survival according to maximum AGI grading and maximum GIDS is illustrated in [Fig. 2](#).

Table 1
Admission characteristics and outcome.

| | Total n = 540 |
|---|----------------|
| Male gender | 328 (60.7) |
| Age, years (range) | 65 (18–94) |
| Height, cm | 172 (165; 179) |
| Weight, kg | 78 (68; 88) |
| BMI, kg/m ² | 26 (23; 29) |
| APACHE II, points | 17 (11; 24) |
| SAPS II, points | 38 (26; 53) |
| SOFA, points | 6 (3; 9) |
| Profile | |
| Medical | 223 (41.3) |
| Elective surgical | 193 (35.7) |
| Emergency surgical | 124 (23.0) |
| Readmission ^a | 16 (3.0) |
| Main reason for ICU | |
| Postoperative care with MV | 165 (30.6) |
| Postoperative care without MV | 93 (17.2) |
| Respiratory failure | 69 (12.8) |
| Neurological deterioration | 61 (11.3) |
| Shock | 59 (10.9) |
| Cardiac failure | 38 (7.0) |
| Metabolic disorder | 10 (1.9) |
| Other organ failures | 15 (2.8) |
| Multiple organ failure | 9 (1.7) |
| Renal failure | 6 (1.1) |
| Other reason | 30 (5.6) |
| Principal pathology | |
| Cardiovascular | 172 (31.9) |
| Gastrointestinal/pancreatic/liver | 115 (21.3) |
| Neurological | 93 (17.2) |
| Pulmonary | 61 (11.3) |
| Renal | 21 (3.9) |
| Trauma/burns | 15 (2.8) |
| Other | 63 (11.7) |
| Any abdominal pathology | 161 (29.8) |
| Any specific abdominal condition ^b | 112 (20.7) |
| Abdominal surgery | 104 (19.3) |
| Laparotomy | 100 (18.5) |
| GI surgery | 62 (11.5) |
| Fluids >5 L before ICU | 48 (8.9) |
| Transfusion ≥5 pRBCs before ICU | 8 (1.5) |
| Fluids >5 L + ≥5 pRBCs before ICU | 15 (2.8) |
| Sepsis | 123 (22.8) |
| Severe sepsis or septic shock | 87 (16.1) |
| Invasive mechanical ventilation | 305 (56.5) |
| Noninvasive mechanical ventilation | 25 (4.6) |
| Vasopressor/inotrope | 311 (57.6) |
| SUMMARY NUTRITION | |
| EN/oral nutrition during ICU stay | 440 (81.5) |
| Early EN/oral nutrition during ICU stay | 371 (68.7) |
| OUTCOME | |
| Mortality during 28 days (in 539 patients) | 79 (14.6) |
| Mortality during 90 days (in 522 patients) | 102 (18.9) |
| ICU LOS (in 540 patients) | 3 (1; 6) |
| Hospital LOS (in 532 patients) | 12 (7; 22) |
| Duration of MV (in 540 patients) | 1 (0; 4) |
| Duration of vasopressors (in 539 patients) | 1 (0; 3) |

Legend: Data are presented as n (%) or median (25th percentile; 75 percentile) if not stated differently.

Abbreviations: APACHE II - Acute Physiology and Chronic Health Disease Classification System II GI; gastrointestinal; BMI - body mass index; EN - enteral nutrition; GRV - gastric residual volume; intensive care unit; ICU - intensive care unit; I-FABP - intestinal fatty acid binding protein; LOS - length of stay; MV - mechanical ventilation; pRBC - packed red blood cells; SAPS - The Simplified Acute Physiology Score; SOFA - sequential organ failure assessment.

^a Readmission = patient has been admitted to the ICU during current hospitalization before study start.

^b Any of the following: pancreatitis (at least two of three following: abdominal pain, serum amylase/lipase >3 times normal, and characteristic CT/MRI/US); peritonitis; mechanical ileus; liver failure (defined as INR > 1.5 and mental alterations related to acute or chronic liver disease); cirrhosis with ascites (clinically or radiologically); ruptured AAA; short bowel syndrome; other.

4. Discussion

In this international multicenter study, we developed a new clinical score for gastrointestinal dysfunction in critically ill patients – “GIDS”. The GIDS can be used as a stand-alone score or be combined with the SOFA score, whereas GIDS may improve the predictive power of SOFA score.

Compared to several previous attempts to construct respective scores [3–5,9] we included consecutive patients admitted to the ICU, and used prospective detailed daily data collection and step-wise statistical evaluation of the effect of individual GI symptoms and conditions alone and in different combinations.

Our study confirmed the previous findings that AGI grading [9] was associated with mortality [15–18]: the AGI was independently associated with 28- and 90-day mortality in models along with the SOFA (whether total or subscores). However, a complex evaluation in AGI grading is not based on clear symptoms but includes subjective assessment of the general development of a patient's condition. On one hand, this is probably appropriate at bedside when dealing with a patient with multiple organ dysfunction. On the other hand it allows assessment of GI function to be influenced by other organ dysfunctions. For example, a deteriorating patient will likely be given a higher AGI score compared to a patient in a stable condition presenting exactly the same GI symptoms, simply because it is frequently not possible to distinguish which organ failure led to a worsening of the other organ functions.

Two important observer-dependent variables, abdominal distension and GI paralysis, performed well as single symptoms in prediction of mortality (Supporting file 3, Table S24), suggesting their potential for classification as more severe symptoms. However, this potential was not confirmed in performance of the score. Our observations suggest that concomitant presence of several symptoms may be more important compared to occurrence of any single symptom at the time.

We chose mortality as an outcome variable to develop the new GID score. Validation of an organ dysfunction score against mortality is debatable, as organ dysfunction scores are expected to be inferior to illness severity scores in this regard [19]. However, today's golden standard of organ dysfunction assessment – SOFA score – is validated against mortality [20], and we aimed to follow a similar approach. The improved mortality prediction resulting from the addition of GIDS to SOFA underlines the limitation of the SOFA score, resulting from the absence of GI assessment.

Setting a mortality endpoint at 28 days may be a too short time period, whereas mortality beyond 90 days may be a more suitable outcome variable. Moreover, other outcome variables (e.g. restoration of the ability to orally consume an adequate diet) could be more specific GI endpoints and remain to be tested in future research.

Assessment of GI function in a critically ill patient is complicated. Probably, no clinical score can embrace all the functions of the GI tract including endocrine, immune, and barrier function. Likewise, the single organ subscores in SOFA score also do not cover all functions of respective organs and as alone-standing scores are far from perfect describing any single organ dysfunction. The strength of the SOFA score is in combining different organ systems in the assessment of multiple organ dysfunction syndrome in critically ill. The reason for exclusion of the GI system from original SOFA score, despite acknowledging its importance, was its complexity and difficulty to assess it [11]. Despite this difficulty still being present 25 years later, structured assessment of GI symptoms formulated in a score with minimized subjectivity to enhance reproducibility is necessary. The GIDS can be used as a stand-alone score or in combination with SOFA score.

In our score, we included some individual components that may be criticized. For example, IAP is not a measure of GI function. However,

Table 2

Descriptive AGI grading (9) in prediction of mortality alone and together with SOFA score and SOFA subscores as time-dependent (daily documented) variables in center-stratified Cox regression analysis.

| Unadjusted univariate analyses | | | | |
|--|---|---------|--|---------|
| Covariate | Mortality during 28 days n = 539; 79 died | | Mortality during 90 days n = 522; 101 died | |
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| AGI grade | 2.20 (1.82; 2.66) | <0.001 | 2.17 (1.82; 2.59) | <0.001 |
| Total SOFA score | 1.27 (1.21; 1.33) | <0.001 | 1.26 (1.20; 1.32) | <0.001 |
| SOFA cardiovascular | 1.68 (1.44; 1.96) | <0.001 | 1.64 (1.43; 1.87) | <0.001 |
| SOFA respiratory | 1.89 (1.48; 2.41) | <0.001 | 1.84 (1.51; 2.25) | <0.001 |
| SOFA hematological | 1.42 (1.12; 1.80) | 0.003 | 1.37 (1.10; 1.70) | 0.004 |
| SOFA renal | 1.69 (1.46; 1.95) | <0.001 | 1.55 (1.35; 1.78) | <0.001 |
| SOFA hepatic | 1.52 (1.21; 1.92) | <0.001 | 1.46 (1.17; 1.82) | <0.001 |
| SOFA neurological | 1.89 (1.61; 2.22) | <0.001 | 1.89 (1.64; 2.17) | <0.001 |
| Multivariate analyses | | | | |
| Covariates | Mortality during 28 days n = 539; 79 died | | Mortality during 90 days n = 522; 101 died | |
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Model 1: SOFA total + descriptive AGI grading | | | | |
| SOFA total | 1.22 (1.15; 1.29) | <0.001 | 1.22 (1.15; 1.28) | <0.001 |
| AGI grade | 1.39 (1.05; 1.84) | 0.020 | 1.42 (1.11; 1.82) | 0.005 |
| Model 2: SOFA subscores + descriptive AGI grading | | | | |
| SOFA cardiovascular | 1.15 (0.96; 1.38) | 0.116 | 1.13 (0.97; 1.34) | 0.110 |
| SOFA respiratory | 1.15 (0.89; 1.48) | 0.279 | 1.18 (0.96; 1.45) | 0.098 |
| SOFA hematological | 0.91 (0.66; 1.26) | 0.584 | 0.94 (0.71; 1.25) | 0.685 |
| SOFA renal | 1.44 (1.17; 1.77) | <0.001 | 1.32 (1.08; 1.60) | <0.001 |
| SOFA hepatic | 0.93 (0.65; 1.33) | 0.690 | 0.98 (0.70; 1.35) | 0.881 |
| SOFA neurological | 1.60 (1.32; 1.94) | <0.001 | 1.59 (1.34; 1.89) | <0.001 |
| AGI grade | 1.51 (1.16; 1.95) | 0.002 | 1.53 (1.21; 1.94) | <0.001 |

Abbreviations: AGI - acute gastrointestinal injury; CI - confidence interval; CIT - citrulline; GIDS - Gastrointestinal Dysfunction Score; HR - hazard ratio; SOFA - sequential organ failure assessment.

Table 3

Gastrointestinal Dysfunction Score (GIDS), grades of severity.

| 0 - No risk | 1 - Increased risk | 2 - GI dysfunction | 3 - GI failure | 4 - Life threatening |
|--|--|---|---|---|
| No symptoms OR one of the following with oral intake | Two of the following | Three or more symptoms of score 1 OR up to two of the following | Three or more of the following | One of the following |
| - Absent bowel sounds - Vomiting - GRV >200 mL - GI paralysis/dynamic ileus - Abdominal distension - Diarrhea (not severe) - GI bleeding without transfusion - IAP 12–20 mmHg | - No oral intake - Absent bowel sounds - Vomiting - GRV >200 mL - GI paralysis/dynamic ileus - Abdominal distension - Diarrhea (not severe) - GI bleeding without transfusion - IAP 12–20 mmHg | - Severe diarrhea - GI bleeding with transfusion - IAP >20 mmHg | - Prokinetic use - GI paralysis/dynamic ileus - Abdominal distension - Severe diarrhea - GI bleeding with transfusion - IAP >20 mmHg | - GI bleeding leading to hemorrhagic shock - Mesenteric ischemia - Abdominal compartment syndrome |

Legend: If some variables (e.g. GRV or IAP) have not been measured, the score can be calculated without considering these variables.

Abbreviations: GRV - gastric residual volume; GI - gastrointestinal; IAP - intra-abdominal pressure.

associations of IAP with GI symptoms, both of them being important for success of enteral nutrition, have been demonstrated in some studies [6,21,22]. Also based on the physiological rationale, IAP can be considered as a valuable additive to GI symptoms. For example, IAP may confirm or oppose the subjective assessment of abdominal distension. At the same time, it should be realized that IAH as an isolated temporary phenomenon without any GI symptoms and other organ dysfunctions may indeed occur without major effect on clinical outcome [23]. This is also reflected in our score where increased IAP alone does not suggest presence of GI dysfunction.

Furthermore, inclusion of oral intake as a component of the new score may be questioned. Whether ability to swallow belongs to GI function can be debated. Oral intake commonly refers to a better general condition of the patient and may add a component beyond GI function. Similarly, definition of the highest score (GIDS = 4) as a life-threatening condition differs from the lower

categories, containing a broader aspect than just GI symptoms. Considering limited performance of single GI symptoms discriminating between different categories of GI dysfunction (Supporting file 2), such approach identifying the life-threatening GI failure differently seems reasonable to date.

Because clinical assessment of GI symptoms is obviously observer-dependent and does not readily provide clear gradual discrimination between different grades of severity of GI dysfunction, it would be ideal to replace or complete it with one or two biomarkers. Our investigations on citrulline and I-FABP in this study do not support their usage in GI dysfunction score to date. Nevertheless, as our approach was based on association with/prediction of mortality, it does not exclude an association between citrulline and I-FABP and enterocyte function. Whether improvements in sampling methodology and improvement/unification of laboratory kits could bring any relevant progress in this field

Table 4

Gastrointestinal Dysfunction Score (GIDS) in prediction of mortality alone and together with SOFA score as time-dependent (daily documented) variables in center-stratified Cox regression analysis.

| Unadjusted univariate analyses | | | | |
|---------------------------------------|---|---------|--|---------|
| Covariate | Mortality during 28 days n = 532; 79 died | | Mortality during 90 days n = 516; 101 died | |
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| GIDS | 2.15 (1.76; 2.63) | <0.001 | 2.09 (1.72; 2.53) | <0.001 |
| Multivariate analyses | | | | |
| Covariates | Mortality during 28 days n = 532; 79 died | | Mortality during 90 days n = 516; 101 died | |
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Model 1: SOFA total + GIDS | | | | |
| SOFA total | 1.23 (1.16; 1.30) | <0.001 | 1.23 (1.16; 1.29) | <0.001 |
| GIDS | 1.40 (1.07; 1.84) | 0.014 | 1.40 (1.02; 1.79) | 0.005 |
| Model 2: SOFA subscores + GIDS | | | | |
| SOFA cardiovascular | 1.15 (0.95; 1.41) | 0.136 | 1.13 (0.95; 1.34) | 0.162 |
| SOFA respiratory | 1.20 (0.92; 1.56) | 0.167 | 1.25 (1.01; 1.54) | 0.036 |
| SOFA hematological | 0.88 (0.65; 1.20) | 0.422 | 0.89 (0.67; 1.18) | 0.425 |
| SOFA renal | 1.48 (1.22; 1.80) | <0.001 | 1.37 (1.14; 1.65) | <0.001 |
| SOFA hepatic | 1.00 (0.72; 1.40) | 0.994 | 1.05 (0.77; 1.43) | 0.758 |
| SOFA neurological | 1.59 (1.30; 1.94) | <0.001 | 1.58 (1.31; 1.89) | <0.001 |
| GIDS | 1.48 (1.13; 1.92) | 0.003 | 1.47 (1.15; 1.87) | 0.001 |

Legend: Values to calculate the scores were missing in 7 patients, 28-day mortality in 1 patient and 90-day mortality in 17 patients.

Abbreviations: AGI - acute gastrointestinal injury; CI - confidence interval; CIT - citrulline; GIDS - Gastrointestinal Dysfunction Score; HR - hazard ratio; SOFA - sequential organ failure assessment.

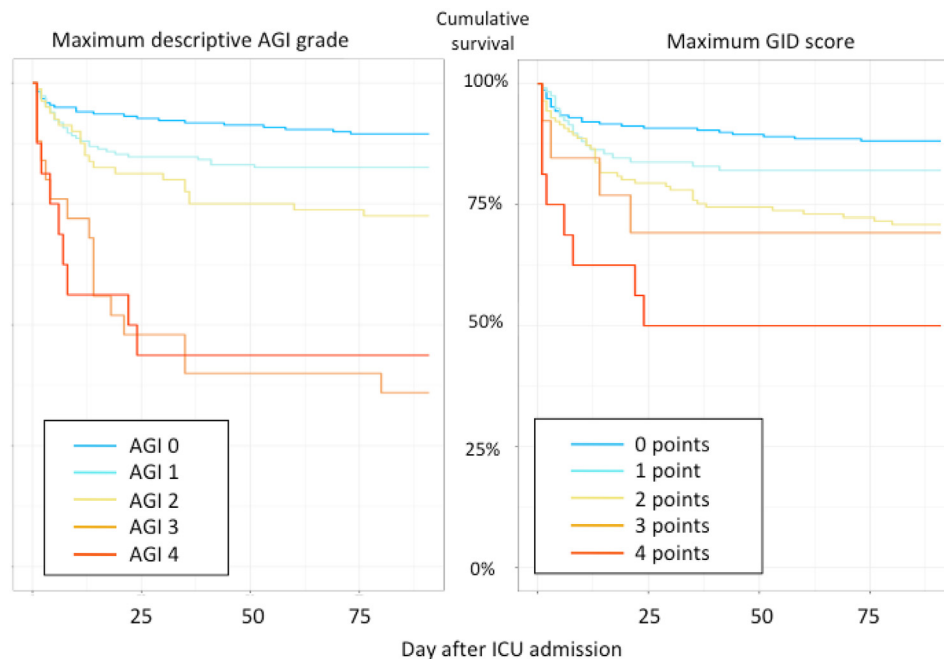


Fig. 2. Kaplan–Meier survival curves with cumulative 90-day survival based on maximum AGI grade and maximum GID score during the first week after ICU admission. Categories from 0 to 4 differed significantly ($P < 0.001$, Log rank test) in both the original AGI grading and the new GID score.

remains unclear. Detailed analysis of biomarkers dynamics and associations with different clinical conditions, including GI symptoms, will be undertaken, but is beyond the scope and volume of this manuscript.

Strengths of our study are the inclusion of consecutive patients and detailed prospective data collection during the first week in the ICU reflecting a real-world ICU setting across multiple sites. Important strength of the GIDS is its similarity to SOFA subscores,

which likely facilitates its application in both clinical practice and research.

Limitations of our study are that measurements of biomarkers were only performed in part of the study population and that some single GI symptoms (e.g. abdominal distension, absent bowel sounds) used for construction of the score still remain observer-dependent. Furthermore, for statistical analysis with repeated measurements, variables were not documented throughout the

whole study period used for outcome analysis (90 days). Additionally, we deviated from our initial plan using AUROC analysis to assess the predictive capability of scores, as this analysis does not allow a time-dependent assessment of the scores. Furthermore, data were collected over a relatively long time period - three years - and might be subject to variations in treatment.

Despite these limitations, we consider the GIDS a step towards a reliable clinical tool for GI dysfunction. Future studies should confirm its validity and reproducibility. However, given that there is no validated score for GI dysfunction in critically ill patients available at present, GIDS can be considered for quantification of GI dysfunction and may be preferred as a well-structured approach compared to available alternatives.

5. Conclusions

The GIDS enables the quantification of GI dysfunction in critically ill patients, and is additive to SOFA score in prediction of 28- and 90-day mortality. The proposed score follows the rationale of AGI grading, while using structured composition of symptoms instead of general subjective impression. Citrulline and I-FABP did not confirm their potential replacing observer-dependent clinical assessment. Future studies should validate the GIDS before it can be recommended for clinical use in critically ill patients.

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Author contributions

MPo and ARB drafted the study protocol. MH, SMJ, CL, JCP, OR, JW and JS participated in refinement of study project. ARB developed case report form and coordinated the study. MPa, KT, BH, GE, WM, TG, MR, OR, CL, DM, MG and CPB coordinated local data collection and responses to queries. MPa managed data cleaning and queries. ARB, GE, CE, KF, MM, MPa and JS developed the statistical analysis plan. MM performed the statistical analyses. MM, KF, ARB, MPa and JS developed the score. ARB and MM prepared the original draft of the manuscript. All authors critically reviewed and approved the final submitted version of the manuscript. All authors have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy and integrity of any part of the work, even ones in which the authors were not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Conflict of interest

ARB has received speaker fees from Nestlé and Fresenius Kabi. GE has received lecture fees and travel support from Fresenius Kabi, Abbott, and B. Braun Melsungen and advisory honoraria from Fresenius Kabi and Nutricia. MH reports grants and personal fees from Fresenius Kabi, and grants from Abbott. JS has received consulting fees from B. Braun Melsungen and Fresenius Kabi. JCP has received lecture fees from Fresenius, Nestlé and Danone/Nutricia. OR is a consultant for Fresenius Kabi and Nutricia and his institution received a research grant from Fresenius-Kabi. JW has received lecture fees and travel support from Nestlé, GE Health Care, and Nutricia. SMJ declares that the Department of Intensive Care Medicine has, or has had in the past, research & development/consulting contracts with Edwards Lifesciences Services GmbH,

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnu.2021.07.015>.

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