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Protocol

Prospective multicenter study to validate the gastrointestinal dysfunction score (GIDS) in intensive care patients: Study protocol for Part A of the international GUTPHOS study

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SUMMARY

Background: While gastrointestinal (GI) dysfunction is commonly encountered among critically ill patients, a uniform prospectively validated scoring system is lacking. The present study aims to validate the recently developed Gastrointestinal Dysfunction Score (GIDS) in a multicenter, prospective cohort of consecutive adult patients admitted to intensive care units (ICU).

Methods: GUTPHOS is a prospective, multicenter, non-interventional cohort study in which at least 1400 consecutive adult patients (age ≥18 years) admitted to the ICU will be monitored daily for abdominal signs and symptoms of GI dysfunction. The previously developed GIDS constructed from these signs and symptoms will be tested in relation to mortality and duration of ICU dependency and parenteral nutrition (PN) dependency. Between January and June 2024, each participating clinical site will include 50–120 consecutive patients over an eight-week period. Study data will be collected in three phases: baseline data upon ICU admission, daily observations throughout a maximum of 7 days in ICU or until discharge, and a follow-up period of 90 days. The primary outcomes are 28- and 90-day all-cause mortality. Secondary outcomes include ICU and hospital mortality, ICU and hospital length of stay,

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days alive and free of ICU by day 28 and day 90, days alive and free of hospital by day 28 and day 90, and days alive and free of organ support and PN dependency by day 28.
Discussion: The GUTPHOS study will be the first worldwide, multicenter, prospective, observational cohort study to validate the GIDS in adult patients admitted to ICUs against 28- and 90-day mortality. The availability of a validated tool will allow its use in interventional studies that are currently hindered by the lack of a validated measurement tool for GI dysfunction.
Clinical trial registry: NCT05909722.

Abbreviations

ACS	Abdominal compartment syndrome
AGI	Acute gastrointestinal injury
APACHE	Acute Physiology and Chronic Health Evaluation
APP	Abdominal perfusion pressure
eCRF	Electronic Case Report form
DNR-code	Do-not-resuscitate-code
EN	Enteral nutrition
ESICM	European Society of Intensive Care Medicine
FREM	Feeding, Rehabilitation, Endocrinology, and Metabolism
GI	Gastrointestinal
GIDS	Gastrointestinal Dysfunction Score
IAH	Intra-abdominal hypertension
IAP	Intra-abdominal pressure
ICU	Intensive Care Unit
KDIGO	Kidney Disease Improving Global Outcomes
MELD	Model for End-Stage Liver Disease
PN	Parenteral nutrition
rMSPE	Root mean square percentage error
RRT	Renal replacement therapy
REDCap	Research Electronic Data Capture
SAPS	Simplified Acute Physiology Score
SOFA	Sequential Organ Failure Assessment

1. Background

Gastrointestinal (GI) dysfunction is frequently encountered in critically ill patients worldwide and is associated with worse clinical outcomes and increased mortality [1]. While GI dysfunction is most widely assessed by clinical assessment and monitoring, there is no universal accepted scoring system to prospectively identify or classify GI dysfunction in clinical practice [2].

The Gastrointestinal Dysfunction Score (GIDS) has been recently developed as a five-grade score (0–4 points) for the assessment of GI function [3] in the intensive care unit (ICU), similar to sequential organ failure assessment (SOFA) sub-scores that are used for the assessment of other organ systems [4]. This original study (iSOFA) showed that among a cohort of 540 critically ill patients, GIDS was an independent predictor of 28- and 90-day mortality when added to the total SOFA score or all the SOFA sub-scores, thereby improving the performance of the SOFA score in predicting mortality. Additionally, assessing potential biomarkers citrulline and intestinal fatty acid-binding protein were not proven as valuable elements of the score in mortality prediction. Despite including observer-dependent GI signs and symptoms in the GIDS, the score currently represents the most promising effort to date and, therefore, requires validation in a prospective study to fulfill the current missing gap for a uniform GI dysfunction scoring tool. The presence of a validated score will allow its use in interventional studies to monitor GI function that are currently hindered by the lack of a tool for measurement of GI dysfunction.

The GUTPHOS study aims to validate the GIDS in predicting mortality, duration of ICU stay, and parenteral nutrition (PN) dependency among a large, multicenter cohort of consecutive adult patients admitted to ICUs worldwide. We hypothesize that GIDS can independently predict 28- and 90-day all-cause mortality, days alive and free of organ support, and PN dependency by day 28 and thereby improve the predictive capability of the SOFA score in patients admitted to the ICU.

2. Methods and analysis

2.1. Study design

The GUTPHOS study is an investigator-initiated collaboration between the steering committee members of the GUTPHOS investigators. The GUTPHOS investigators are active members of the Feeding, Rehabilitation, Endocrinology, and Metabolism (FREM) section of the European Society of Intensive Care Medicine (ESICM). The GUTPHOS study is a combined, prospective, multicenter, non-interventional cohort study that will include at least 1400 consecutive adult patients (age $\geq$18 years) admitted to the participating ICUs, that consists of two parts. The main part (Part A) will validate the GIDS in the entire patient cohort. In addition, the epidemiology, management, and outcomes of phosphate abnormalities will be investigated in a subset that includes at least 1000 patients with daily phosphate measurements available (Part B). Due to similarities in study protocols and common interest (both studies emerging from the FREM section of ESICM), these two studies are combined in one multicenter, prospective, observational cohort study of consecutive adult ICU patients. The study is registered on ClinicalTrials.gov under the clinical trial registry number NCT05909722 and endorsed by the ESICM.

2.2. Setting

This multicenter cohort study aims to recruit at least 20 ICUs from the global network of the ESICM FREM section and principal investigators' contact networks. ICUs are eligible when they anticipate admitting at least 50 eligible patients during eight

weeks. All study sites can choose the start of the eight-week study period within six months from the global study start on January 8th, 2024. To avoid bias from different sample sizes of study sites, all participating sites will recruit all consecutive adult patients during the recruitment period of eight weeks or up to 120 patients, whichever comes first.

2.3. Participants

All consecutive patients during the study period will be screened and enrolled in the study when eligible according to inclusion and exclusion criteria (Table 1). Eligible patients will be included in the study, irrespective of the predicted or expected duration of ICU stay or primary pathology, to reduce the risk of selection bias. This approach is based on the rationale that all patients (including those without GI dysfunction = scoring 0) must be included to test and validate an organ dysfunction score constructed in categories 0–4, similar to the SOFA score. This approach was also used to develop GIDS in the original iSOFA study [3].

2.4. Study procedures

All study sites will collect observational data during three phases: baseline data upon ICU admission, an observational study period of a maximum of 7 days or until ICU discharge, and a follow-up period of 90 days (Table 2). A complete detailed overview of study parameters that will be collected is provided in the Appendix. Study site characteristics will be collected from each participating site, including ICU size and type, average number of ICU admissions per year, type of hospital, and description of current practice of the method of intra-abdominal pressure (IAP) measurements.

Upon ICU admission, patient data will be collected on demographics (age, sex, body mass, and height), comorbidities, and ICU-admission characteristics (admission diagnosis, principal pathology, time in hospital before ICU admission, do-not-resuscitate order, history of any previous major GI surgery, disease severity expressed as the acute physiology and chronic health evaluation (APACHE II) score [5], simplified acute physiology (SAPS II) score

Table 1
In- and exclusion criteria for the study.

Inclusion criteria	Exclusion criteria
- Admission to ICU during the study period - Age ≥18 years	- Restrictions of ICU-related care, including no intubation or ICU admission except for patients with a do-not-resuscitate order only (without other limitations) - Admitted to the ICU for treatment as a potential organ donor - Continuous chronic home ventilation (i.e., for neuromuscular disease) - Declined participation or informed consent - Readmission to the ICU during the study period

Table 2
Table of workflow and study- and outcome parameters obtained during the study.

	ICU Day 1	ICU Day 2	ICU Day 3	ICU Day 4	ICU Day 5	ICU Day 6	ICU Day 7	ICU discharge	Hospital discharge	Day 28	Day 90
Enrolment											
Screening	•										
Informed consent	•										
Baseline characteristics[1]	•										
Study period											
GI symptoms	•	—	—	—	—	—	•				
IAP measurements[2]	•	—	—	—	—	—	•				
GIDS and AGI	•	—	—	—	—	—	•				
Nutritional intake details[3]	•	—	—	—	—	—	•				
GI-influencing medications	•	—	—	—	—	—	•				
SOFA score	•	—	—	—	—	—	•				
Follow-up											
Organ-free support days[4]										•	
All-cause mortality	•	—	—	—	—	—	—	—	—	—	•

Abbreviations: ICU = Intensive Care Unit; GI = Gastro-Intestinal; IAP = Intra-Abdominal Pressure; GIDS = Gastro-Intestinal Dysfunction Score; AGI = Acute Gastrointestinal Injury.
[1] includes demographics, ICU admission details, disease severity scores, and comorbidities. A complete list of baseline characteristics is provided in Appendix 1; [2] if available as part of routine care; [3] includes the route of nutrition, total daily energy (nutritional and non-nutritional) and protein intake, and additional administration of vitamins and trace elements; [4] total calendar days with the absence of any of the following organ support modalities: ventilation, vasopressor, inotrope, RRT, ICU, or parenteral nutrition support.

[6], and presence and severity of sepsis based on Sepsis-3 criteria [7]).

Daily assessments will be taken in the first seven days of ICU admission or until ICU discharge if earlier, including GI signs and symptoms (as determined from previous iSOFA study [3]), GIDS (Table 3), Acute Gastrointestinal Injury (AGI) grade (Table 4) [2], IAP (when available and recorded by site), underlying pathology or putative mechanism for GI dysfunction if considered present, nutrition intake details (total daily intake and route, including enteral nutrition (EN) and PN), GI motility-influencing medication, SOFA (total and sub-) score with underlying variables [4].

During the follow-up period, which lasts until the 90th day after enrolment, data on ICU, hospital, 28- and 90-day all-cause mortality, hospital and ICU length of stay, duration of mechanical ventilation, and days alive and free of organ support and PN nutrition by day 28 will be collected.

2.5. Study outcomes

The primary outcomes are 28- and 90-day all-cause mortality. Secondary outcomes include ICU and hospital mortality, days alive and free of ICU by day 28 and day 90, days alive and free of hospital by day 28 and day 90, and days alive and free of organ support and PN by day 28.

2.6. Ethical considerations

Primary ethical approval was provided by the University of Tartu Ethics Committee on May 29th, 2023 (approval number 377/T-15). Each participating site will apply for local ethics committee approval according to local site country and institutional regulations. If informed consent is deemed necessary for this observational study according to the approval of the local ethics committee,

Table 3
Gastrointestinal dysfunction score (GIDS).

0 points	1 point	2 points	3 points	4 points
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

Abbreviations: GRV=Gastric residual Volume; GI=Gastrointestinal; IAP=Intra-Abdominal Pressure If GRV or IAP is not measured, the score will be calculated without these variables.

Table 4
Acute gastrointestinal injury (AGI) Grades.

AGI 0	Definition: GI system appears to function normally, no signs of GI dysfunction
AGI I	Definition: GI symptoms related to a known cause and perceived as transient. Rationale: Condition is clinically seen as occurrence of GI symptoms after an insult, which expectedly has temporary and self-limiting nature. Examples: - Postoperative nausea or vomiting during the first days after abdominal surgery - Postoperative absence of bowel sounds - Diminished bowel motility in the early phase of shock
AGI II	Definition: GI symptoms requiring therapeutic interventions for achievement of nutrient and fluid requirements. Rationale: This condition occurs without previous GI interventions or is more severe than might be expected concerning the course of preceding abdominal procedures. No changes in the general condition of the patient related to GI problems. Examples: - Gastroparesis with high gastric residuals or reflux - Paralysis of the lower GI tract - Diarrhea - Intra-abdominal hypertension (IAH) grade I (intra-abdominal pressure (IAP) 12–15 mmHg) - Visible blood in gastric content or stool
AGI III	Definition: restoration of GI function is not achieved despite interventions, and the general condition is not improving. Rationale: sustained intolerance to enteral feeding without improvement after treatment (e.g., erythromycin, postpyloric tube placement), leading to persistence or worsening of MODS. Examples: - Despite treatment, feeding intolerance is persisting and possibly associated with the persistence or worsening of Multiple Organ Dysfunction Score (MODS): - High gastric residuals - Persisting GI paralysis - Occurrence or worsening of bowel dilatation - Progression of IAH to grade II (IAP 15–20 mmHg) - Low abdominal perfusion pressure (APP) together with IAH (below 60 mmHg)
AGI IV	Definition: AGI has progressed to become directly and immediately life-threatening, with worsening MODS and shock. Rationale: AGI has led to an acute critical deterioration of the general condition of the patient with distant organ dysfunction(s). Examples: - Bowel ischemia with necrosis - GI bleeding leading to hemorrhagic shock - Ogilvie's syndrome - Abdominal compartiment syndrome (ACS)

delayed informed consent will be obtained from the patient or the patient's next of kin, representative, or proxy at the first possibility. If the patient's condition precludes personal consent to participate in this initial decision, but the next of kin or representative agrees with participation, the patient will be asked secondarily during recovery. All patient data and any data already collected will be excluded from the study if the patient or the patient's next of kin declines participation, except for screening data with the reason for exclusion. If the patient declines participation after being included in the study based on the consent by the patient's next of kin or proxy, already collected data will be handled (kept until declined or all deleted) based on local ethical rules at the site.

2.7. Data management

Patient data are collected as part of routine clinical care. National death registries, where available, or direct patient contact by site investigators will be used to obtain data on mortality. All data will be recorded in an electronic case report form (eCRF) using Research Electronic Data Capture (REDCap) in a pseudonymized way. Patients are identifiable only at the site via coded patient logs, accessible only to the investigators at each site. Anonymous data in the database will be kept until 15 years after the end of the study. Patient log sheets and informed consent forms will be saved at least until the end of the study or according to local practice.

2.8. Sample size

A sample size of the study was calculated according to the recent guidance for calculating sample size for the clinical prediction model [8]. For all-cause 28- and 90-day mortality, events documented in the previous iSOFA study (14 and 18%, respectively) were used [3]. Using a root mean square percentage error (rMSPE) of 0.05 and seven predictor values (GIDS and six SOFA sub scores), a sample of $n = 470$ for 28-days mortality and $n = 510$ for 90-days mortality outcome was calculated. Accordingly, we aim for a larger sample size for validation of the GIDS than the iSOFA study to better describe higher GI dysfunction categories [3,4]. However, an uneven distribution in GIDS grading is anticipated by including all consecutive patients in study sites with a high turnover and short average ICU stay. The full scale of consecutive patients is essential for validating a score that can be applied to all patients. Intending to observe at least ten events in each category of the GIDS, 1350 patients will need to be included (with a rMPSE of 0.03) to reach statistical power for the 90-day mortality outcome. We aim to include at least 1400 patients to allow our primary study objective to be tested.

2.9. Data analysis

Continuous values will be reported as means (SDs), or medians [interquartile ranges], and discrete variables will be presented as numbers (%). Differences between sub-cohorts will be assessed using independent samples t-tests for continuous data or chi-squared tests for categorical data. Mann–Whitney U tests or Fisher's exact tests will be used instead if test assumptions are not met. The quantile-quantile plots will be visually assessed for the normality of the distribution of continuous data. When inconclusive, a significant Kolmogorov–Smirnov test will be performed. Non-dichotomous categorical data are compared using an analysis of variance. Levene's test will be used for the homogeneity assumption. Normality will be checked as previously described. Missing values for scores will be replaced with the previous documented value or standard reference value (0 points) in the absence of the previous measurement. This approach is in line with practical use of the SOFA score, not requesting measurements of all values every day for calculation of the score. For individual daily data (GI signs and symptoms, and IAP), we will perform complete case analysis. For variables where measurements are not performed in all patients (e.g. IAP and GRV), we will perform additional sensitivity analyses using imputation. Respectively, we will replace unmeasured cases by “no IAH” and “no elevated GRV”. This approach is needed to enable calculating the score also in patients where measurements of GRV or IAP were not indicated or not possible. Time-to-event type data will be analyzed using Cox proportional hazards model. If necessary, variables will be used as time-dependent covariates. Predictions of the scores will be compared using Area Under the Receiver Operating Characteristics (AUROC). Event-free days will be analyzed using Fine-Gray competing risk models. Only two-sided analyses will be used, and $P < 0.05$ will be considered statistically significant. For all analyses, IBM SPSS statistics 29.0 (I.B.M. Corp, Armonk, NY, USA; 2022) and R Statistical Software 4.3.2 (R Core Team, Vienna, Austria, 2023) will be used for all analyses.

2.10. Demographics and comorbidities

Patient demographics, disease severity, comorbidities [9], and the main reason for ICU admission will be used to describe the patient population characteristics. Descriptive statistics will be performed for all patients' demographic and clinical data.

2.11. GI signs and symptoms and IAP measurements

All individual GI symptoms, abdominal signs, IAP values, categories of intra-abdominal hypertension (IAH) [10], and AGI grades between survivors and non-survivors will be compared. Comparisons are performed daily and summarized over all days of observation. This comparison will be done separately by day 28 and day 90, using the t-test and chi-square test or, if the assumptions are violated, the Mann-Whitney U test or Fisher's exact test, respectively.

2.12. GIDS performance (primary outcome)

Performance of the GIDS will be evaluated with Cox models, including GIDS and total SOFA score (and separately all SOFA subscores) as time-dependent scores and using 28- and 90-day mortality as outcome variables in separate models. AUROC will be used to compare the prediction of total SOFA and SOFA sub-scores with and without GIDS.

2.13. Secondary outcomes

Analysis of the association of GIDS with days alive and free of ICU and days alive and free of PN by day 28 will be performed with adjustment for total SOFA score and SOFA sub-scores using Fine–Gray competing risk model with death treated as a competing risk. ICU and hospital mortality and days alive and free of organ support will be presented and compared in categories based on the patient's maximum GIDS during the observation period.

3. Discussion

This study will be the first multicenter, prospective, observational cohort study to validate the GIDS score in a multicenter cohort of consecutive adult patients admitted to ICUs worldwide against 28- and 90-day mortality, with secondary endpoints being the duration of ICU and PN dependency.

3.1. GI dysfunction as a part of multiple organ dysfunction

The importance of GI dysfunction as a part of multiple organ dysfunction has been recognized already for a long time. However, it was not included in the most widely used multiple organ dysfunction score, the SOFA score, due to its complexity and being at risk of subjectivity [4,11]. Indeed, the GI tract performs multiple functions. However, there is no gold standard to measure GI function, it is relatively impossible to confirm "normal" GI function in critically ill patients, there are no validated biomarkers able to capture GI dysfunction, and most of the symptoms and signs used for clinical assessment are subjective and/or observer-dependent. Initial hope to identify biomarkers qualifying for a score reflecting GI dysfunction has unfortunately not been confirmed so far [3]. Several attempts have been made to create a tool to monitor GI (dys)function in recent decades [1,12]. These studies commonly predefined a GI dysfunction score and tested it in prospective patient cohorts [13,14]. In contrast, a more recent study used machine learning to refine and modify a previously predefined score [15]. The GIDS is, to our knowledge, the only score that is created based on real data and has been shown to be independently associated with mortality when used together with SOFA scores reflecting other organ dysfunctions [3]. However, several limitations of GIDS and its development need to be acknowledged. The GIDS includes all available signs and symptoms reflecting GI dysfunction or processes in the abdominal compartment instead of presenting a continuum from normal to most abnormal GI function. Moreover, oral intake is the only variable potentially supporting but certainly not confirming "normal" GI function. As oral intake is not possible in sedated and mechanically ventilated patients, other organ dysfunctions are inevitably reflected in the GIDS. Due to the absence of a gold standard to measure GI function in critically ill patients, validating GIDS in this aspect is impossible. Additionally, the number of patients in the categories of more severe dysfunction was low in the original study, making it difficult to draw firm conclusions regarding the predictive value in these patients [3]. The present study aims to correct the limitation by including a larger sample size.

3.2. Validation and use of organ dysfunction scores

Multiple organ dysfunction scores are commonly validated against mortality outcomes despite the prediction that mortality is not the main aim of these scores. Instead, the scores should describe organ dysfunction dynamics in repeated daily assessments. Searching for an optimal balance between simplicity and precision is a great challenge in developing organ dysfunction scores. As summarized by the authors of the SOFA score, organ dysfunction should be described as a continuum that can be objectively graded, with a low number of variables included, can be repeated daily, and is applicable in every institution [11]. Obviously, the GIDS only fulfils 2/4 of these conditions. However, several stand-alone organ dysfunction scores (e.g., Kidney Disease Improving Global Outcomes (KDIGO) and Model for End-Stage Liver Disease (MELD)) are more complex than respective sub-score within the SOFA score (creatinine and bilirubin, respectively). Accordingly, the search for a more straightforward score for GI dysfunction should continue independent of the results of the current planned study. However, simplification should, in our opinion, take place secondarily based on data and not primarily before obtaining and analyzing all available information comprehensively. We hope that beyond validating the GIDS, this study will help in the process of providing future directions for the most optimal score regarding simplicity and precision.

3.3. Future research

One possible approach for a more straightforward score within the multiple organ dysfunction score could be based on the application of interventions, following the rationale of the cardiovascular SOFA score mainly based on the application and dose of vasopressors and inotropes instead of signs of cardiovascular dysfunction. On the other hand, a validated GI score may be used for evaluating the effectiveness of interventions to attenuate GI dysfunction and a threshold to initiate evidence-based therapies to treat GI dysfunction, such as prokinetics, post-pyloric feeding, and PN.

4. Conclusions

This prospective, observational, multicenter cohort study will be the first to validate the GIDS as an organ dysfunction score in a multicenter cohort of consecutive adult patients admitted to ICUs worldwide. The availability of a validated tool will allow its use in interventional studies that are currently hindered by the lack of a validated measurement tool for GI dysfunction.

Ethical approval

The medical ethics committee from the University of Tartu Ethics Committee has approved this study (number 3 77/T-15 from May 15th, 2023).

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Author's contributions

IWKK contributed to the conception of the research, writing, and revision of the final manuscript. MaxM contributed to the writing and revision of the manuscript. MerliM contributed to the development of statistical analysis plan. ARB contributed to the conception of the research, writing, and revision of the manuscript and has the principal investigator's role. ARHvZ contributed to the conception of the research, writing, and revision of the manuscript and has the co-principal investigator's role. The steering committee members contributed to the conception of the research and revised and approved the final version of the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study will be available upon reasonable request.

Consent for publication

Not applicable.

Study status

The study's recruitment started in January 2024. Inclusion of the last patient is expected in June 2024.

Declaration of competing interest

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The other authors declare no competing interests.

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Appendix A. Supplementary data

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