Intensive Care Med (2013) 39:899–909
DOI 10.1007/s00134-013-2831-1

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Gastrointestinal symptoms during the first week of intensive care are associated with poor outcome: a prospective multicentre study

Received: 26 September 2012
Accepted: 4 January 2013
Published online: 31 January 2013

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Abstract *Purpose:* The study aimed to develop a gastrointestinal (GI) dysfunction score predicting 28-day mortality for adult patients needing mechanical ventilation (MV). *Methods:* 377 adult patients from 40 ICUs with expected duration of MV for at least 6 h were prospectively studied. Predefined GI symptoms, intra-abdominal pressures (IAP), feeding details, organ dysfunction and treatment were documented on days 1, 2, 4 and 7. *Results:* The number of simultaneous GI symptoms was higher in nonsurvivors on each day. Absent bowel sounds and GI bleeding were the symptoms most significantly associated with mortality. None of the GI symptoms alone was an independent predictor of mortality, but gastrointestinal failure (GIF)—defined as three or more GI symptoms—on day 1 in ICU was independently associated with a threefold increased risk of mortality. During the first week in ICU, GIF occurred in 24 patients (6.4 %) and was associated with higher 28-day mortality (62.5 vs. 28.9 %, $P = 0.001$). Adding the created subscore for GI dysfunction (based on the number of GI symptoms) to SOFA score did not improve mortality prediction (day 1 AUROC 0.706 [95 % CI 0.647–0.766] versus 0.703 [95 % CI 0.643–0.762] in SOFA score alone). *Conclusions:* An increasing number of GI symptoms independently predicts 28 day mortality with moderate accuracy. However, it was not possible to develop a GI dysfunction score, improving the performance of the SOFA score either due to data set limitations, definition problems, or possibly indicating that GI dysfunction is often secondary and not the primary cause of other organ failure.

Keywords Gastrointestinal symptoms · Gastrointestinal dysfunction · Intensive care · Outcome

Introduction

Gastrointestinal (GI) problems in critically ill patients are common and associated with impaired outcome [1–4]. The hypothesis of the gut as a motor of multiple organ failure (MOF) has repeatedly been proposed in the past [5, 6]. Despite this, the pathophysiological role of GI dysfunction in the clinical course of MOF has not been sufficiently investigated. In a recent consensus statement, the working group on abdominal problems (WGAP) of the European Society of Intensive Care Medicine proposed a terminology aiming to provide clinical definitions, although evidence-based criteria for these definitions were limited [7].

The sequential organ failure assessment (SOFA) score, widely used to assess organ dysfunction in critically ill patients, does not take GI dysfunction into account [8]. A previous single-centre study demonstrated that the addition of a GIF score based on the combination of feeding intolerance (FI) and intra-abdominal hypertension (IAH) to the original SOFA score improved the predictive power of the latter [9].

The primary aim of this multicentre study was to develop a GI dysfunction score predicting 28-day mortality, among adult mechanically ventilated patients. A secondary aim was to study the possible additive value of GI dysfunction score to SOFA score on outcome prediction. Thus, the hypothesis tested was that symptoms of GI dysfunction could be used as predictors of outcome separately and/or as part of the SOFA score.

Methods

General

In this prospective, observational, multicentre study, 40 ICUs around the world participated. Study units were asked to include consecutive adult patients (18 years and older) with expected duration of MV of at least 6 h. Patients who were spontaneously breathing on admission day were not included, even if they required MV later during their ICU stay. Patients in whom transvesical intra-abdominal pressure (IAP) measurements were not possible for any reason, such as previous cystectomy, were excluded. The inclusion period ranged from two to four weeks in the different sites between October and December 2009. Local Ethics Committees for each country approved the study. Informed consent was obtained from next of kin or waived (due to the observational design) according to local ethical rules. The study protocol was endorsed by the clinical trials working group of the World Society of Abdominal Compartment Syndrome (WSACS trial number 013, www.wsacs.org) as well as by the WGAP and ECCRN of the ESICM.

Power analysis based on earlier single-centre study [9] indicated that 343 patients should be analyzed to detect a 5 % increase in the predictive capability between SOFA and GIF score (based on the AUC of the ROC curve of the SOFA score of 0.840 (SD 0.25)). However, as the GIF score for current study was not predefined, but had to be developed during the study, we aimed to enroll 500 patients.

Demographic and base-line clinical data (clinical profile, previous surgery, presence/absence of sepsis [10], APACHE II—acute physiology and chronic health evaluation II—score [11] and blood lactate concentration) were collected on the day of ICU admission.

Predefined GI symptoms, IAP (minimum, maximum and mean daily values), feeding details, SOFA score with all its sub-scores, urine output, fluid balance, positive end-expiratory pressure, as well as serum albumin and C-reactive protein levels were documented on days 1, 2, 4 and 7 in the ICU. Caloric needs were calculated as 20 kcal/kg/day for day one and as 25 kcal/kg/day the following study days. Survival data were collected on day 28 after ICU admission. An electronic case report file was used for data collection.

Definitions

The following definitions were used for uniform data collection:

Patient category: medical = no surgery within 4 weeks preceding ICU admission; elective surgical = surgery within 4 weeks preceding admission, scheduled >24 h in advance; emergency surgical = surgery within 4 weeks preceding admission, scheduled within 24 h of operation.

GI symptoms were defined as follows:

High gastric residual volumes (GRV) = maximum GRV above 500 ml at least once. Absent bowel sounds (BS) = BS were not heard on careful auscultation. Vomiting/regurgitation = visible vomiting or regurgitation in any amount. Diarrhoea = loose or liquid stool three or more times per day. Bowel distension = suspected or radiologically confirmed bowel dilatation in any bowel segment. GI bleeding = visible appearance of blood in vomits, nasogastric aspirate, or stool.

Feeding intolerance (FI) was considered present when less than 20 % of the calculated caloric needs were administered with enteral nutrition (EN) and at the same time GI symptom(s) were documented being a reason for withholding or reducing the EN.

Intra-abdominal hypertension (IAH) = mean IAP of the day ≥12 mmHg [12] and abdominal compartment syndrome (ACS) = mean IAP >20 mmHg with new organ dysfunction or failure [12], with IAP measured in the supine position with zero-point at mid-axillary line with a maximal instillation volume of 25 ml.

Statistical analysis

Statistical Package for the Social Sciences (IBM SPSS Statistics 20.0, Somers, NY, USA) software was used for statistical analysis. Data are presented median (interquartile range) if not stated otherwise. Kolmogorov–Smirnov test with Lilliefors correction was used to test normality of distribution. To compare groups, Student's *t*-test (normal distribution) and Mann–Whitney *U* test (non-Gaussian distribution) were used for continuous variables, and Chi-square test for categorical variables.

Univariate analyses of admission parameters were applied to identify the risk factors for 28-day mortality. Parameters with $P < 0.2$ in univariate analysis were entered stepwise into a multiple logistic regression model to identify the best combination for prediction of 28-day mortality. Single variables or subscores were preferred against the total SOFA score. Kaplan–Meier curves and log-rank tests were used to compare survival of patients with and without GI symptoms.

GI symptoms were entered separately into a regression model predicting mortality to evaluate the importance of individual GI symptoms.

Receiver operating characteristic (ROC) curves were used to determine the likelihood ratios of different versions of possible gastrointestinal failure (GIF) scores, the SOFA score and the SOFA with GIF scores combined to predict the ICU mortality. The optimal cut-off value was calculated from the ROC curve analysis as the point with the greatest combined sensitivity and specificity. A P value <0.01 was considered significant, adjusting for multiple comparisons.

Results

377 patients from 40 ICUs were included. The study flowchart is presented in Fig. 1. Admission and day 1 characteristics with $P < 0.2$ for associations with mortality in univariate analyses are presented in Table 1.

Admission diagnosis was gastrointestinal in 27.3 %, (including hepatopancreatic pathology in 6.6 %), pulmonary 19.1 %, cardiac 17.2 %, neurological 15.9 % and polytrauma in 8.7 %. Other admission diagnoses included renal and vascular pathologies, burns and others. Most common reasons for admission were respiratory failure (22.5 %), shock (18.3 %), postoperative MV after major surgery (17.8 %) and neurological deterioration (16.2 %).

Median duration of MV was 4.0 (2–13), ICU stay 7.0 (3–17) and hospital stay 19.0 (10–28) days. Mean APACHE II score on admission was 19.0 (SD 8.0) points, 278 patients (73.7 %) were treated with vasoactive/inotropic agents. The overall 28 day mortality was 31.0 %. 142/377 patients (37.7 %) had a medical profile, 78 (20.7 %) were elective and 157 (41.6 %) emergency surgery patients; respective mortality rates were 40.8, 17.9 and 28.7 %. One-third of the elective surgery patients underwent cardiovascular, one-third GI, and one-third other surgical procedures.

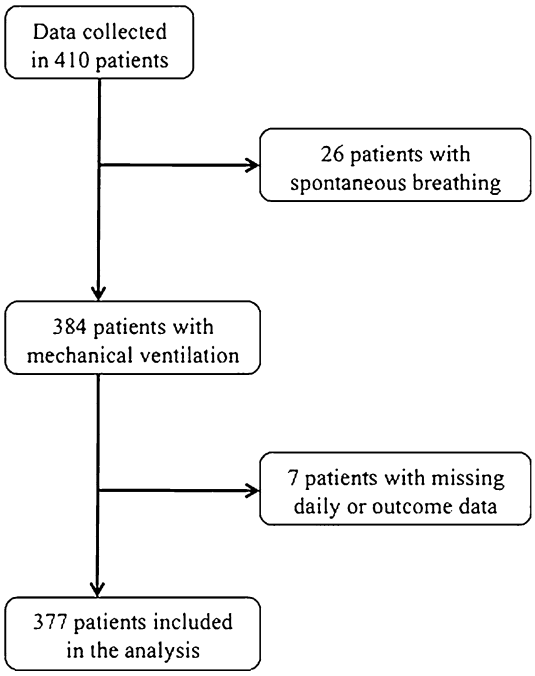

Fig. 1 Enrolment flow-chart

Daily and global incidences of GI symptoms and IAH for all patients, and for survivors and non-survivors separately are presented in Table 2. The number of coincident GI symptoms was higher in non-survivors on each day. None of the patients had more than four GI symptoms simultaneously.

The incidence of absent BS was 37.7 % (mortality rate 38.0 %), of overt GI bleeding 6.4 % (mortality rate 54.2 %), of IAH 42.7 % (mortality rate 31.1 %) and of ACS 3.6 % (mortality rate 38.5 %). FI occurred in 140 patients (37.1 %). Prepyloric route for EN was common, postpyloric route was used in 4.3 % on day 1, increasing to 12.9 % on day 7.

Multivariate regression analyses for 28 day mortality including the different GI symptoms, caloric intake <80 % and IAH are presented in Table 3. The occurrence of absent BS on day 1, GI bleeding during the first two days and bowel distension on day 7 were independently associated with 28 day mortality, while vomiting, high GRV, diarrhoea and the presence of IAH were not predictive.

The reasons for withholding/stopping EN were not documented in 58 % of the cases, and therefore in these cases the presence or absence of FI could not be assessed. EN < 80 % of caloric needs on day 1 and 2 was associated with better survival.

Table 1 Patient characteristics on admission and day 1 among survivors and nonsurvivors

Characteristics	All ($n = 377$)	Survivors ($n = 260$)	Nonsurvivors ($n = 117$)	P value
Admission				
Age, years, median (range)	62 (18–98)	61 (18–98)	64 (22–91)	0.082
Body mass index	26 (23–29)	26 (23–29)	25(22–29)	0.086
Medical profile, *n* (%)	142 (37.7)	84 (32.3)	58 (49.6)	0.001
Abdominal surgery, *n* (%)	118 (31.3)	90 (34.6)	28 (23.9)	0.042
Day 1				
APACHE II score, points	18 (13–24)	17 (12–22)	21 (17–30)	<0.001
Sepsis, *n* (%)	137 (36.3)	82 (31.5)	55 (47.0)	0.005
SOFA score (points)	8 (5–10)	7 (5–10)	10 (7–14)	<0.001
Vasopressors, *n* (%)	263 (69.8)	172 (66.2)	91 (77.8)	0.029
pO_2/FiO_2 (mmHg)	188 (108–322)	193 (115–347)	177 (97–292)	0.151
Creatinine (μmol/L)	99 (72–164)	91 (69–139)	126 (80–188)	<0.001
Glasgow coma scale (points)	13 (6–15)	14 (7–15)	10 (4–15)	<0.001
Fluid balance (L/24 h)	+1.4 (0.4–2.9)	+1.1 (0.2–2.7)	+2.0 (1.0–3.5)	0.001
Urine output (L/24 h)	1.6 (0.9–2.6)	1.8 (1.0–2.7)	1.2 (0.4–2.3)	<0.001
Mean IAP (mmHg)	9.8 (7.0–12.7)	10.0 (7.3–12.8)	9.0 (5.9–12.6)	0.066
Minimal APP (mmHg)	62 (52–71)	62 (53–72)	60 (46–70)	0.033
Number of GI symptoms	0 (0–1)	0 (0–1)	1 (0–1)	0.013
Three or more GI symptoms, *n* (%)	18 (4.8)	7 (2.7)	11 (9.4)	0.008

Data are median (interquartile ranges) if not stated otherwise
APACHE II score acute physiology and chronic health evaluation II (11), *SOFA score* sequential organ failure assessment (8), pO_2/FiO_2 partial oxygen pressure in blood/content of oxygen in inspired air, *IAP* intra-abdominal pressure, *APP* abdominal perfusion pressure, *GI* gastrointestinal

Based on daily comparisons of survivors and nonsurvivors with different number of GI symptoms (Table 2) as well as Kaplan–Meier curves with maximum number of GI symptoms, the cut-off point for GIF was defined as three or more coincident GI symptoms listed above.

Gastrointestinal failure (three or more coincident GI symptoms) occurred in 24 patients (6.4 %) and was associated with higher 28-day mortality (62.5 vs. 28.9 %) (Fig. 2).

Prediction of 28 day mortality in a statistical model including demographic data and admission day variables identified in univariate analyses, GI symptoms and SOFA sub-scores on admission day is presented in Table 4. The occurrence of GIF on day 1 was associated with a threefold increased mortality, being an independent predictor of mortality together with renal and neurological SOFA sub-score. None of the GI symptoms alone nor IAH or caloric intake <80 % independently predicted mortality.

Regression analyses including daily SOFA sub-scores and the number of GI symptoms revealed increasing number of GI symptoms as an independent predictor of mortality on day 2 and 7 with a tendency towards statistical significance on admission and day 4 (Table 5). Only the neurological SOFA score predicted mortality on all study days, renal SOFA score was predictive at three of the 4 days, haematologic SOFA on one day, while none of the other SOFA sub-scores predicted mortality.

The best GIF score with respect to mortality prediction included all six GI symptoms, but not IAH, FI and/or caloric intake, giving points as follows: 0 = no GI symptoms; 1 = 1 GI symptom; 2 = 2 GI symptoms; 3 = 3 GI symptoms and 4 ≥ 4 GI symptoms.

Receiver operating characteristic curve analyses for SOFA score alone, for the GIF score based on the number of GI symptoms and their combination are presented in Table 6. ROC curves including GIF score were not significantly different from the ROC curves of the SOFA score alone.

Discussion

The current prospective worldwide multicentre study including critically ill patients with an expected duration of mechanical ventilation of more than 6 h demonstrated that a large proportion of these patients had GI symptoms during the first week of admission. Some specific symptoms, including absent BS, GI bleeding and bowel distension, as well as the total number of GI symptoms, were associated with 28 day mortality. Furthermore, an increasing number of GI symptoms predicted outcome independently. However, the study failed to develop an additional dysfunction score that significantly improved mortality prediction of the SOFA score.

The total incidence, as well as the occurrence of the individual GI symptoms, was comparable to earlier observations [1–4], despite the fact that the definitions for these symptoms differ somewhat between studies. The proportion of patients with two or more simultaneous GI symptoms was lower in the present study (20 %) than in a

Table 2 Daily and global incidence of gastrointestinal (GI) symptoms, intra-abdominal hypertension and gastrointestinal failure among survivors and non-survivors

	Day 1	Day 2	Day 4	Day 7	Cumulative
Total number of patients	377	352	264	200	377
Survivors	260	244	194	147	260
Nonsurvivors	117	106	70	53	117
Median (IQR) number of GI symptoms					Cumulative maximum[#]
Total	1 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	1 (0–2)
Survivors	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	1 (0–1)
Nonsurvivors	1 (0–1)	1 (0–1)	1 (0–1)	1 (0–1)	1 (0–2)
P value*	<0.001	<0.001	<0.001	<0.001	<0.001
Absent bowel sounds					
Total (%)	125 (33.2)	82 (23.3)	42 (15.9)	29 (14.9)	142 (37.7)
Survivors (%)	76 (29.2)	45 (18.4)	25 (12.9)	15 (10.3)	88 (33.8)
Nonsurvivors (%)	49 (41.9)	37 (34.9)	17 (24.3)	14 (28.6)	54 (46.2)
P value*	0.018	<0.001	0.033	0.009	0.022
Diarrhoea					
Total (%)	26 (6.9)	40 (11.2)	46 (17.4)	39 (19.5)	81 (21.5)
Survivors (%)	16 (6.2)	20 (8.2)	31 (16.0)	26 (17.7)	53 (20.4)
Nonsurvivors (%)	10 (8.5)	20 (18.9)	15 (21.4)	13 (24.5)	28 (23.9)
P value*	0.388	0.006	0.270	0.314	0.498
Bowel distension					
Total (%)	54 (14.3)	53 (15.1)	32 (12.9)	19 (9.5)	78 (20.7)
Survivors (%)	33 (12.7)	34 (13.9)	21 (11.5)	10 (6.8)	48 (18.5)
Nonsurvivors (%)	21 (17.9)	19 (17.9)	11 (16.7)	9 (17.0)	30 (25.6)
P value*	0.202	0.325	0.275	0.049	0.129
Vomiting/regurgitation					
Total (%)	18 (4.8)	11 (3.1)	5 (1.9)	7 (3.5)	31 (15.5)
Survivors (%)	11 (4.2)	7 (2.9)	3 (1.5)	5 (3.4)	22 (8.5)
Nonsurvivors (%)	7 (6.0)	4 (3.8)	2 (2.9)	2 (3.8)	9 (7.7)
P value*	0.445	0.738	0.611	1.000	1.000
High gastric residual volume					
Total (%)	13 (3.4)	8 (2.3)	8 (3.0)	8 (4.0)	28 (7.4)
Survivors (%)	8 (3.1)	5 (2.4)	5 (2.6)	5 (3.4)	15 (5.8)
Nonsurvivors (%)	5 (4.3)	3 (2.8)	3 (4.3)	3 (5.7)	13 (11.1)
P value*	0.556	0.706	0.712	0.697	0.086
Gastrointestinal bleeding					
Total (%)	16 (4.2)	13 (3.7)	5 (1.9)	4 (2.0)	24 (6.4)
Survivors (%)	7 (2.7)	4 (1.6)	2 (1.0)	2 (1.4)	11 (4.2)
Nonsurvivors (%)	9 (7.7)	9 (8.5)	3 (4.3)	2 (3.8)	13 (11.1)
P value*	0.049	0.003	0.116	0.270	0.020
At least 1 GI symptom					
Total	168 (44.6)	146 (41.7)	109 (41.3)	81 (40.5)	227 (60.2)
Survivors	105 (40.4)	88 (33.8)	71 (27.3)	51 (19.6)	148 (56.9)
Nonsurvivors	63 (53.8)	58 (49.6)	38 (32.5)	30 (25.6)	79 (67.5)
P value*	0.019	0.001	0.011	0.009	0.054
2 or more GI symptoms					
Total	62 (16.4)	46 (13.1)	21 (8.0)	20 (10.0)	76 (20.2)
Survivors	39 (15.0)	24 (9.2)	13 (5.0)	10 (3.8)	44 (16.9)
Nonsurvivors	23 (19.7)	22 (18.8)	8 (6.8)	10 (8.5)	32 (27.4)
P value*	0.293	0.009	0.203	0.017	0.026
3 or more GI symptoms = GI failure					
Total (%)	18 (4.8)	11 (3.1)	6 (2.3)	3 (1.5)	24 (6.4)
Survivors (%)	7 (2.7)	2 (0.8)	1 (0.5)	1 (0.7)	9 (3.5)
Nonsurvivors (%)	11 (9.4)	9 (8.5)	5 (7.1)	2 (3.8)	15 (12.8)
P value*	0.008	0.001	0.006	0.172	0.001
4 or more GI symptoms					
Total	4 (1.1)	11 (3.1)	0	1 (0.5)	16 (4.2)
Survivors	2 (0.8)	2 (0.8)	0	1 (0.4)	5 (1.9)
Nonsurvivors	2 (1.7)	9 (7.7)	0	0	11 (9.4)
P value*	0.591	0.001			0.002
Intra-abdominal hypertension					
Total (%)	109 (28.9)	96 (27.4)	68 (25.8)	40 (20.0)	161 (42.7)
Survivors (%)	77 (29.6)	71 (29.1)	55 (28.4)	32 (21.8)	111(42.7)
Nonsurvivors (%)	32 (27.4)	25 (23.6)	13 (18.6)	8 (15.1)	50 (42.7)
P value*	0.713	0.421	0.105	0.305	1.000

* *P* values refer to comparisons between survivors and nonsurvivors

[#] Maximal daily sum of GI symptoms

Table 3 Multivariate regression analyses with GI symptoms, failure of enteral nutrition, and intra-abdominal hypertension predicting 28 day survival

Day 1	*P* value	OR	Lower CI 95 %	Upper CI 95 %
Absent bowel sounds	**0.007**	**2.457**	1.285	4.700
Vomiting/regurgitation	0.877	0.903	0.25	3.258
Maximum GRV > 500 ml	0.888	0.910	0.244	3.397
Diarrhoea	0.387	1.700	0.511	5.659
Bowel distension	0.916	0.954	0.398	2.289
GI bleeding	**0.042**	**4.404**	**1.058**	**18.333**
EN < 80 % of caloric needs	**0.032**	**0.325**	**0.116**	**0.906**
IAH	0.316	0.708	0.361	1.390
DAY 2				
Absent bowel sounds	0.425	1.368	0.633	2.957
Vomiting/regurgitation	0.887	1.120	0.234	5.352
Maximum GRV > 500 ml	0.673	1.392	0.300	6.469
Diarrhoea	0.408	1.640	0.508	5.289
Bowel distension	0.759	1.162	0.445	3.030
GI bleeding	**0.008**	**19.093**	**2.153**	**169.336**
EN < 80 % of caloric needs	**0.040**	**0.355**	**0.132**	**0.952**
IAH	0.062	0.461	0.204	1.041
DAY 4				
Absent bowel sounds	0.192	1.793	0.746	4.310
Vomiting/regurgitation	0.366	3.147	0.263	37.699
Maximum GRV > 500 ml	0.398	1.995	0.402	9.901
Diarrhoea	0.361	1.642	0.567	4.758
Bowel distension	0.829	1.122	0.396	3.173
GI bleeding	0.150	5.595	0.538	58.177
EN < 80 % of caloric needs	0.440	1.437	0.573	3.605
IAH	0.127	0.512	0.217	1.210
DAY 7				
Absent bowel sounds	0.162	2.157	0.735	6.332
Vomiting/regurgitation	0.230	0.162	0.008	3.158
Maximum GRV > 500 ml	0.636	1.490	0.285	7.790
Diarrhea	0.793	1.181	0.342	4.083
Bowel distension	**0.036**	**7.070**	**1.140**	**43.859**
GI bleeding	0.249	3.822	0.392	37.281
EN < 80 % of caloric needs	0.951	0.970	0.364	2.582
IAH	0.153	0.428	0.134	1.372

The variables entered into the multivariate analysis were exclusively those listed above
Significant findings are marked in bold
GRV gastric residual volume, *GI* gastrointestinal, *EN* enteral nutrition, *IAH* intra-abdominal hypertension

previous single-centre study (36 %) [4]. An increasing number of GI symptoms was related to increased mortality in both studies [4]. In the present study, absent BS, GI bleeding and bowel distension were the symptoms and signs associated with mortality, similar to earlier findings [4]. Another previously reported finding that a combination of IAH and FI predicted outcome [9] could not be confirmed in this study, as unfortunately there was a high rate of missing data for the reasons to withhold or reduce EN. Thus, although a final GIF score is still not formulated, occurrence of GIF is, independently of its exact formulation, associated with adverse outcome in all studies.

A major limitation of assessment of GI symptoms is that some of the symptoms are subjective and poorly defined, the most questioned being absent BS. There is a consensus not using absent BS as a reason to withhold enteral nutrition [13]. Absence of BS still should be considered pathological, however. Consistent association of absent BS (despite the obvious limitations of this symptom) with mortality is an important finding of our study. An explanation might be that absence of BS reflects severity of inflammation and hypoperfusion, but also deeper sedation and immobilisation often required for artificial organ support (cardiac assist devices, ECMO, CVVH etc.). The exact doses of sedation and analgesia were not recorded in the present study. There is one previous observation that absent or abnormal BS are associated with higher mortality in univariate analysis [4].

A high incidence of IAH was observed in the study population (42.7 % compared to 27–30 % in some previous studies [9, 14]). The possibility to measure IAP was an inclusion criterion, the reason being that previous studies have shown a relation between IAH and mortality

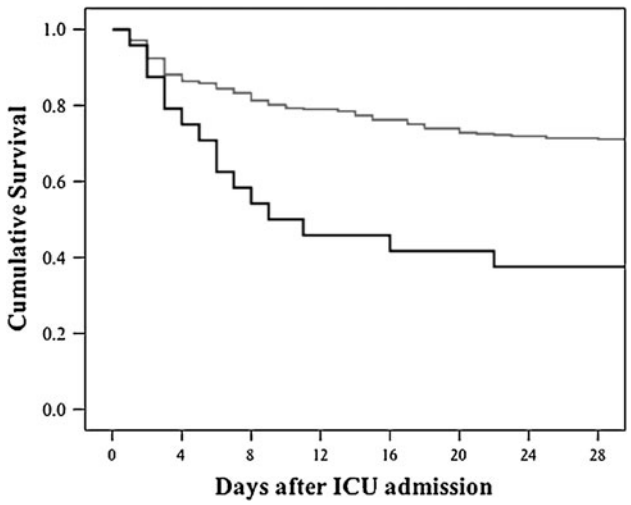

Fig. 2 Kaplan–Meier survival plot for patients with GIF versus without GIF. *Grey line* shows less than three GI symptoms concomitantly during the first week in ICU. *Black line* shows at least three GI symptoms concomitantly during the first week in ICU. $P < 0.001$ between the groups (Log-rank test)

Table 4 Multivariate regression analysis with admission day variables predicting 28-day mortality

	P value	Odds ratio	95 % CI
Age	0.542	1.005	0.990–1.019
Body mass index	0.207	0.971	0.929–1.016
Medical profile	0.083	1.598	0.940–2.716
Sepsis	0.223	1.400	0.815–2.406
Fluid balance day 1	0.859	1.000	1.000–1.000
Three or more GI symptoms day 1	**0.035**	**3.189**	**1.082–9.396**
Renal SOFA sub-score	**<0.001**	**1.423**	**1.169–1.733**
Neurological SOFA sub-score	**<0.001**	**1.444**	**1.231–1.694**
Haematologic SOFA sub-score	0.073	1.277	0.977–1.668
Respiratory SOFA sub-score	0.311	1.113	0.905–1.368
Hepatic SOFA sub-score	0.804	0.962	0.710–1.305
Cardiovascular SOFA sub-score	0.859	0.982	0.808–1.195

Nagelkerke *R*-square 0.253
The table presents the final model of multivariate analysis after removal of clearly correlated variables
Significant findings are marked in bold
GI gastrointestinal, *SOFA* sequential organ failure assessment

[9, 15]. Furthermore, the IAP value is numerical and reproducible, and as such could be considered as a parameter for a SOFA GI sub-score [12]. The proportion of patients in whom transvesical pressure measurement is not possible (mainly post-cystectomy patients) is extremely small in a general ICU population. In the present study, IAH was not associated with increased mortality, confirming the findings of a recently published study [16].

There are several possible reasons for failure to improve the predictive value of the SOFA score by including a GI dysfunction score. First, there might be a type-II statistical error, since we did not meet our enrolment goal. The goal was based on expected enrolment rates for a fixed study period, but on retrospect the actual enrolment control could have improved our study design. With inclusion of patients on MV for at least 6 h we aimed to minimize the inclusion of "recovery room patients" and concentrate on "real" ICU patients. Exclusion of spontaneously breathing patients was planned because of different pathophysiological patterns of IAP during MV. Unfortunately, selection bias must have occurred, as in some centres patient enrolment was unexpectedly low and at the same time severity of illness and associated mortality were higher than expected. In a previous study on GI dysfunction enrolling all MV patients staying in ICU for 24 h and showing that GIF score increased the predictive power of the SOFA score [9] mean APACHE II score (14 vs. 19) and therefore also predicted mortality (19 vs. 32 %) [11] were lower than in the present study. Compared to earlier studies in unselected ICU patients, we also observed a rather limited performance of SOFA score predicting mortality [17, 18]. In particular, the cardiovascular subscore of SOFA, usually the best-performing subscore [9, 19], had a low power in our study. The relative high proportion of patients receiving vasoactive drugs, resulting in high cardiovascular subscores, additionally confirms that the sickest patients were included. The inclusion of more severely ill patients and associated lower diversity of patients might explain that both SOFA and GI score poorly predicted mortality. Moreover, the fact that addition of GI dysfunction did not improve the predictive power of the SOFA score may actually be an important finding of the study. It leads us to the hypothesis that in this general ICU population of severely ill patients not "primary GI failure" due to abdominal pathology is the main problem, but rather "secondary GI failure" due to systemic inflammation and/or hypoperfusion.

The majority of the patients did not reach their caloric needs via the enteral route, but in many cases the exact reasons were not documented. This may reflect daily practice in study units. These missing data made it impossible to identify the impact of FI on outcome in this study. Former studies have defined FI as <80 % of caloric needs achieved after 48–72 h in the ICU [20] or as withholding EN for any GI reason [9]. In both cases, this highly depends on the local feeding strategy and nutritional goals, which remain controversial for critically ill patients during the initial phase of critical illness [21–23]. Our observation of EN < 80 % being associated with better survival is likely biased by not initiating enteral nutrition in patients with an expected oral intake within a couple of days [24].

Several biomarkers reflecting intestinal function have been suggested recently (I-FABP, citrulline, D-lactate) [25, 26]. Future studies should establish their place in clinical practice and establish their correlations with clinical GI signs and symptoms, as well as with prognosis [27].

Table 5 Regression analyses with daily SOFA sub-scores and the number of GI symptoms as an additional sub-score predicting 28-day mortality

SOFA sub-scores + number of GI symptoms, and survival				
Day 1	*P* value	OR	Lower CI 95 %	Upper CI 95 %
SOFA cardiovascular	0.757	1.030	0.854	1.242
SOFA respiratory	0.133	1.158	0.956	1.403
SOFA haematologic	0.075	1.261	0.977	1.628
SOFA hepatic	0.774	0.958	0.718	1.280
SOFA renal	<0.001	1.441	1.193	1.740
SOFA neurological	<0.001	1.469	1.262	1.710
Number of GI symptoms	0.089	1.264	0.965	1.656
Day 2				
SOFA cardiovascular	0.799	1.025	0.847	1.240
SOFA respiratory	0.261	1.119	0.919	1.363
SOFA haematologic	0.286	1.151	0.889	1.491
SOFA hepatic	0.738	0.940	0.653	1.353
SOFA renal	0.007	1.309	1.077	1.592
SOFA neurological	<0.001	1.331	1.146	1.546
Number of GI symptoms	0.002	1.606	1.184	2.179
Day 4				
SOFA cardiovascular	0.961	1.006	0.801	1.263
SOFA respiratory	0.447	1.105	0.854	1.432
SOFA haematologic	0.364	1.156	0.846	1.579
SOFA hepatic	0.771	1.061	0.713	1.577
SOFA renal	0.009	1.381	1.083	1.762
SOFA neurological	0.001	1.348	1.122	1.620
Number of GI symptoms	0.054	1.505	0.993	2.282
Day 7				
SOFA cardiovascular	0.133	1.227	0.940	1.603
SOFA respiratory	0.656	1.075	0.782	1.478
SOFA haematologic	0.045	1.502	1.008	2.237
SOFA hepatic	0.371	0.806	0.503	1.292
SOFA renal	0.588	1.082	0.814	1.438
SOFA neurological	0.045	1.238	1.005	1.525
Number of GI symptoms	0.010	1.882	1.164	3.042
Cumulative maximum				
SOFA cardiovascular	0.454	1.080	0.883	1.320
SOFA respiratory	0.390	1.101	0.884	1.371
SOFA haematologic	0.561	1.072	0.847	1.357
SOFA hepatic	0.888	1.020	0.777	1.338
SOFA renal	<0.001	1.475	1.246	1.747
SOFA neurological	<0.001	1.452	1.254	1.681
Number of GI symptoms	0.082	1.267	0.971	1.655

GI gastrointestinal, *SOFA* sequential organ failure assessment

Despite being the largest prospective multicentre international study to assess the GI dysfunction in MV patients, the current study has several limitations. First, most of the GI dysfunction definitions are subjective, an issue currently limiting the research in this area. Second, missing data was a considerable problem in our study, mainly because the FI could not be identified in many cases. Third, even though the inclusion of a wide variety of ICUs have made the results more generalizable, it might as well be considered as a limitation due to associated variations in treatment practice. Fourth, the aimed number of patients was not reached in our study. A greater number of patients is needed to create a reliable score in future studies. Fifth, the exclusion of patients with an expected short ventilation period makes our results apply to a population of more severely ill ICU population.

Conclusions

The current prospective worldwide multicentre study shows that a severely ill subgroup of mechanically ventilated ICU patients frequently has GI symptoms and IAH. Absent bowel sounds, GI bleeding, and an increasing number of coincident GI symptoms were associated with 28-day mortality. Based on the data of this study it was however not possible to develop a valid GI dysfunction score that improved the accuracy of the SOFA score.

Table 6 ROC analyses for SOFA score alone and SOFA combined with the score based on the number of GI symptoms

SOFA	AUC	SE	95 %CI
Day 1	0.703	0.03	0.643–0.762
Day 2	0.682	0.03	0.616–0.748
Day 4	0.696	0.04	0.620–0.772
Day 7	0.691	0.05	0.602–0.780
Cumulative maximum	0.732	0.03	0.676–0.789
Number of GI symptoms			
Day 1	0.571	0.03	0.508–0.635
Day 2	0.607	0.03	0.541–0.673
Day 4	0.591	0.02	0.512–0.670
Day 7	0.624	0.05	0.533–0.714
Cumulative maximum	0.581	0.01	0.517–0.644
SOFA + number of GI symptoms			
Day 1	0.706	0.03	0.647–0.766
Day 2	0.687	0.03	0.622–0.752
Day 4	0.698	0.04	0.623–0.772
Day 7	0.700	0.04	0.614–0.785
Cumulative maximum	0.734	0.03	0.678–0.790

GI gastrointestinal, *SOFA* sequential organ failure assessment, *Cumulative maximum* maximal daily score during the study

This may either be due to data set limitations, definition problems, or may indicate that GI dysfunction is often secondary to and not the primary cause of other organ failure. A larger study is needed to unravel this possible interaction.

Acknowledgments We cordially thank all the study nurses, doctors, students and other personnel who participated in screening and enrolment of patients, data collection and correspondence in all participating hospitals. Current study was supported by World Society of Abdominal Compartment Syndrome, Estonian Science Foundation (Grant no. 6950 and 8717), target financing from Ministry of Education and Science of Estonia (SF0180004s12) and European Society of Intensive Care Medicine.

Appendix

Gastro-Intestinal Failure Trial Group

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