Gastrointestinal dysfunction during enteral nutrition delivery in intensive care unit (ICU) patients: Risk factors, natural history, and clinical implications. A post-hoc analysis of The Augmented versus Routine approach to Giving Energy Trial (TARGET)

Tejaswini Arunachala Murthy,[1,2] Lee-anne S Chapple,[1,2,3] Kylie Lange,[1,3] Chinmay S Marathe,[1,3,4] Michael Horowitz,[1,3,4] Sandra L Peake,[1,5,6] and Marianne J Chapman,[1,2,3,6] On behalf of the TARGET Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group

[1]Adelaide Medicine School, University of Adelaide, Adelaide, Australia; [2]Intensive Care Unit, Royal Adelaide Hospital, Adelaide, Australia; [3]Centre for Research Excellence in Nutritional Physiology, Adelaide, Australia; [4]The Endocrine and Metabolic Unit, Royal Adelaide Hospital, Adelaide, Australia; [5]The Department of Intensive Care Medicine, The Queen Elizabeth Hospital, Adelaide, Australia; and [6]School of Epidemiology and Preventive Medicine, Monash University, Victoria, Australia

ABSTRACT

Background: Slow gastric emptying occurs frequently during critical illness and is roughly quantified at bedside by large gastric residual volumes (GRVs). A previously published trial (The Augmented versus Routine approach to Giving Energy Trial; TARGET) reported larger GRVs with energy-dense (1.5 kcal/mL) compared with standard (1.0 kcal/mL) enteral nutrition (EN), warranting further exploration.

Objective: To assess the incidence, risk factors, duration, and timing of large GRVs (≥250 mL) and its relation to clinical outcomes in mechanically ventilated adults.

Methods: A post-hoc analysis of TARGET data in patients with ≥1 GRV recorded. Data are *n* (%) or median [IQR].

Results: Of 3876 included patients, 1777 (46%) had ≥1 GRV ≥250 mL, which was more common in males (50 compared with 39%; $P < 0.001$) and in patients receiving energy-dense compared with standard EN (52 compared with 40%; RR = 1.27 (95% CI: 1.19, 1.36); $P < 0.001$) in whom it also lasted longer (1 [0–2] compared with 0 [0–1] d; $P < 0.001$), with no difference in time of onset after EN initiation (day 1 [0–2] compared with 1 [0–2]; $P = 0.970$). Patients with GRV ≥250 mL were more likely to have the following: vasopressor administration (88 compared with 76%; RR = 1.15 [1.12, 1.19]; $P < 0.001$), positive blood cultures (16 compared with 8%; RR = 1.92 [1.60, 2.31]; $P < 0.001$), intravenous antimicrobials (88 compared with 81%; RR = 1.09 [1.06, 1.12]; $P < 0.001$), and prolonged intensive care unit (ICU) stay (ICU-free days to day 28; 12.9 [0.0–21.0] compared with 20.0 [3.9–24.0]; $P < 0.001$), hospital stay (hospital-free days to day 28: 0.0 [0.0–12.0] compared with 7.0 [0.0–17.6] d; $P < 0.001$), ventilatory support (ventilator-free days to day 28: 16.0 [0.0–23.0] compared with 22.0 [8.0–25.0]; $P < 0.001$), and a higher 90-d mortality (29 compared with 23%; adjusted: RR = 1.17 [1.05, 1.30]; $P = 0.003$).

Conclusion: Large GRVs were more common in males and those receiving energy-dense formulae, occurred early and were short-lived, and were associated with a number of negative clinical sequelae, including increased mortality, even when adjusted for illness severity. This trial was registered at clinicaltrials.gov as NCT02306746. *Am J Clin Nutr* 2022;116:589–598.

Keywords: critical illness, gastric emptying, gastric residual volume, enteral nutrition, gastrointestinal dysfunction

Introduction

Gastrointestinal dysfunction is a frequent accompaniment to critical illness, complicating the delivery of enteral nutrition (EN). Broadly classified as acute functional impairment of the gastrointestinal tract, gastrointestinal dysfunction may include

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Supplemental Tables 1 and 2 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

Address correspondence to TAM (e-mail: tejaswini.arunachalamurthy@adelaide.edu.au).

Abbreviations used: APACHE score, Acute Physiology And Chronic Health Evaluation score; EN, enteral nutrition; GE, gastric emptying; GRV, gastric residual volume; ICU, intensive care unit; LOS, length of stay; PN, parenteral nutrition; RCT, randomized control trial; TARGET, The Augmented versus Routine approach to Giving Energy Trial.

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the development or increased severity of symptoms such as regurgitation, vomiting, abdominal distension, diarrhea, and constipation. In particular, delayed gastric emptying (GE) is common (30–60%) and frequently identified clinically by large gastric residual volumes (GRVs) (1, 2). Gastrointestinal dysfunction is associated with worse clinical outcomes, including prolonged duration of mechanical ventilation (3, 4), intensive care unit (ICU) length of stay (LOS) (5, 6), and mortality (3, 5, 7, 8).

In health, GE of liquid nutrient from the stomach occurs at an overall linear rate of 1–4 kcal/min, irrespective of the intragastric volume (9), primarily as a result of inhibitory feedback generated by the interaction of nutrients within the small intestine (10). The rate is influenced by the macronutrient composition of ingested nutrient: nutrients with a high lipid content empty slowly (11), and formulae with a greater energy density delay GE in both healthy people (12) and critically ill patients (13–15).

The Augmented versus Routine approach to Giving Energy Trial (TARGET) randomly assigned mechanically ventilated adults to receive an energy-dense (1.5 kcal/mL) or standard (1.0 kcal/mL) enteral formula delivered at the same rate for ≤28 d (16). Although 90-d mortality (primary outcome) was similar between the 2 groups, patients receiving the energy-dense EN had a higher incidence of upper gastrointestinal dysfunction with a higher median largest GRV in 24 h, greater incidence of regurgitation and vomiting, and greater administration of promotility agents. Given these initial findings, the relation between energy-dense EN and gastrointestinal dysfunction warrants further exploration.

The aims of this post-hoc analysis of TARGET data were to explore: *1*) gastrointestinal dysfunction, including incidence, timing, duration, and risk factors; *2*) relations between formula composition and the severity, timing, and duration of large GRVs (defined as GRV ≥250 mL); and *3*) implications of large GRVs including management, calorie delivery, and clinical outcomes.

Methods

Study design

This is a post-hoc analysis of data from patients included in TARGET, a multi-center, double-blind, randomized control trial (RCT) conducted in 46 ICUs in Australia and New Zealand between June 2016 and November 2017 that aimed to determine the effect of delivering more calories using an energy-dense compared with a standard enteral formula on 90-d survival. The contribution to the difference in calorie content between the energy-dense and standard EN was shared between fat (58 g per liter in the energy-dense EN compared with 27 g per liter in the standard EN) and carbohydrates (180 compared with 125 g per liter); the protein content of the 2 formulations was similar (56 compared with 55 g per liter) (16). The protocol (17), statistical plan (18), and primary results of this trial have been published (16). The trial was approved by all relevant local Institutional Review Boards. Data access for this post-hoc analysis was approved by the TARGET Investigators.

Patient population

In brief, TARGET recruited mechanically ventilated adult patients that were receiving, or suitable to receive, EN. Overall, 3957 patients were randomly assigned and included in the modified intention-to-treat analysis: 1971 in the energy-dense EN group and 1986 in the standard EN group. All patients enrolled in TARGET who had ≥1 GRV reported during the study period were included in this post-hoc analysis.

Data variables

Patient baseline characteristics.

Data were extracted on patient demographics (age, sex, body weight, BMI), history of diabetes, admission diagnosis using Acute Physiology and Chronic Health Evaluation (APACHE) III diagnostic criteria, illness severity using admission APACHE II scores, and baseline blood lactate and serum albumin concentrations.

Nutrition and gastrointestinal dysfunction variables.

Large GRVs were defined as any GRV ≥250 mL (19) and very large GRVs as GRV ≥500 mL (20). Data relating to nutrition delivered (volume of EN, calories from EN), incidence of GRV ≥250 mL during trial nutrition delivery, and gastrointestinal dysfunction during trial nutrition delivery for days 1–7 were extracted. Measures of gastrointestinal dysfunction included documentation of any of the following: large GRVs (using the above criteria), regurgitation or vomiting, diarrhea (≥4 bowel movements per chart day), or constipation (bowels not opened for ≥3 chart days). Data were also extracted on the duration, timing (time of onset after study enrollment), and management of gastrointestinal dysfunction, including: the incidence, timing of initiation, and duration of prokinetic administration (days 1–7); the incidence of postpyloric feeding (during trial nutrition delivery), and the incidence of parenteral nutrition (PN) (on all days to cessation of trial EN, i.e. day 28, death, ICU discharge, oral nutrition commencement).

Clinical outcomes.

Data on clinical outcomes including: daily vasopressor usage to day 28; ICU-, hospital-, and ventilator-free days to day 28; and 90-d mortality were also extracted.

Statistical analyses

All analyses have been conducted on the subset of the modified intention-to-treat population of the original TARGET data with patients who had ≥1 GRV reported during the study period. Continuous variables are presented as mean ± SD or median [IQR]. Categorical variables are presented as the number of observations (*n*) and percentages (%).

Patients were categorized into groups according to GRV: *1*) GRV <250 mL (normal) and *2*) any GRV ≥250 mL (large GRV). The primary outcome compared patients with a GRV ≥250 mL versus patients with a GRV <250 mL. Additional categorization compared any GRV ≥500 mL: (very large GRV) with GRV <500 mL. Between-group differences (by GRV or by treatment group) in energy delivery from the trial EN, the management and timing of management of gastrointestinal dysfunction, and clinical outcomes were analyzed using linear maximum-likelihood mixed

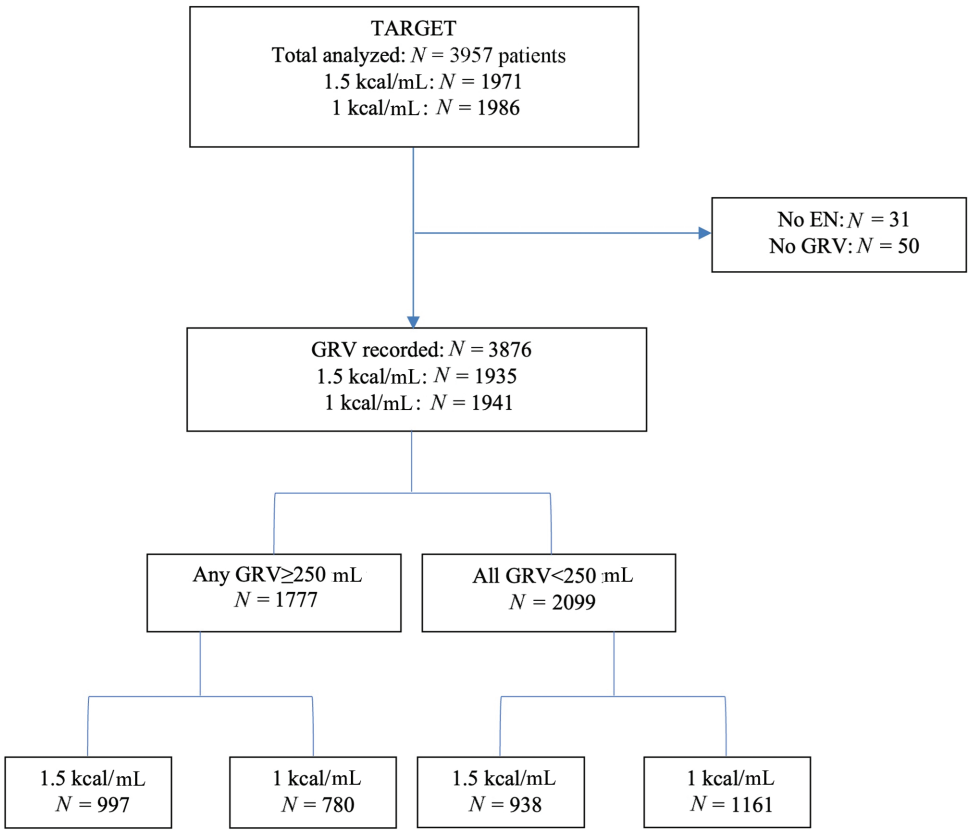

FIGURE 1 CONSORT diagram showing the distribution of participants receiving 1.5 kcal/mL (energy-dense formula) and 1 kcal/mL (standard formula) included in the analysis. EN, enteral nutrition; GRV, gastric residual volume; TARGET, The Augmented versus Routine approach to Giving Energy Trial.

effects models for continuous outcomes, with adjustment for site by inclusion of a site random effect. RRs and 95% CIs for binary outcomes were estimated from log-binomial regressions adjusted for site via a random effect. In analyses of binary outcomes, continuous baseline variables were entered as restricted cubic splines with 7 knots (except for lactate that used 5 knots) to allow for nonlinear relations, and the likelihood ratio test was reported for the overall association. Median differences and 95% CIs were calculated using the Hodges–Lehmann method. ICU-, hospital-, and ventilation-free days were rank transformed for analysis.

The effect of large GRVs on mortality adjusted for APACHE II score was estimated using a modified Poisson regression with robust SEs, due to numerical estimation problems with the log-binomial model. This followed the approach used in the primary TARGET Statistical Analysis Plan (18) and primary publication (16). A differential effect between the treatment groups of prokinetics on mortality was tested by the inclusion of an interaction term in the mixed effects model.

Analyses were performed using SPSS software (version 26, IBM Corp, 2018) and R 4.0.2 (R Core Team, 2020). Effects were considered statistically significant at $P \leq 0.05$. No adjustments for multiple comparisons were conducted.

Results

Baseline data

Of the 3957 patients whose data were analyzed in the original TARGET study, a total of 3876 met the inclusion criteria for this analysis. A total of 1777 (46%) patients had GRV ≥250 mL (Consolidated Standards of Reporting Trials (CONSORT) diagram; **Figure 1**). Baseline characteristics of the groups with and without large GRVs are shown in **Table 1**.

Risk factors for large GRVs

GRV ≥250 mL was more common in males (50 compared with 39%; $P < 0.001$). Although both illness severity and younger age were statistically related to large GRVs, the differences in the 2 groups were not clinically relevant (APACHE II scores 22 [17–29] compared with 21 [16–27]; $P = 0.001$, age 56.0 ± 16.8 compared with 58.5 ± 16.1 y; $P < 0.001$). One-fifth of patients had a past medical history of diabetes mellitus and they were less likely to have GRV ≥250 mL compared to those without (41 compared with 47%; $P = 0.038$).

Effect of energy density of EN on gastrointestinal dysfunction

The administration of energy-dense EN was associated with a higher incidence and a prolonged duration of large GRVs (GRV ≥250 mL; incidence 52 compared with 40%; RR = 1.27 [1.19, 1.36]; $P < 0.001$, duration 1 [0–2] compared with 0 [0–1] d; $P < 0.001$), without a difference in its time of onset from EN initiation (day 1 [0–2] compared with 1 [0–2]; $P = 0.970$; **Table 2**). A higher incidence of very large GRVs was also observed with energy-dense EN (GRV ≥500 mL: 19 compared

TABLE 1 Baseline characteristics of patients with any GRV ≥250 mL and all GRVs <250mL[1]

		Total (N = 3876)		Any GRV ≥250 mL (N = 1777)		All GRVs <250 mL (N = 2099)			
Characteristic		N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	RR (95% CI)	*P*[6]
Age at randomization, y		3876[2]	57.3 ± 16.5	1777	56.0 ± 16.8	2099	58.5 ± 16.1		<0.001[8]
Sex	Female[7]	1430		553 (39%)		877 (61%)		1.28 (1.18, 1.37)	<0.001
	Male	2446		1224 (50%)		1222 (50%)			
APACHE II score[3]		3876	21 [16–28]	1777	22 [17–29]	2099	21 [16–27]		0.001[8]
APACHE III diagnostic code	Cardiovascular	1005		540 (54%)		465 (46%)		1.24 (1.15, 1.33)	<0.001
	Respiratory	958		402 (42%)		556 (58%)		0.91 (0.83, 0.99)	0.022
	Gastrointestinal	138		78 (57%)		60 (43%)		1.19 (1.02, 1.38)	0.025
	Neurological	718		271 (38%)		447 (62%)		0.78 (0.70, 0.86)	<0.001
	Sepsis	356		170 (48%)		186 (52%)		1.10 (0.98, 1.23)	0.109
	Trauma	399		205 (51%)		194 (49%)		1.17 (1.06, 1.30)	0.002
	Other	302		111 (37%)		191 (63%)		0.79 (0.68, 0.92)	0.002
Admission type	Nonoperative[7]	2828		1270 (45%)		1558 (55%)			0.104
	Operative elective	388		200 (52%)		188 (48%)		1.13 (1.01, 1.26)	
	Operative emergency	660		307 (47%)		353 (53%)		1.02 (0.93, 1.12)	
Ideal body weight, kg		3876	64.6 ± 11.0	1777	66.0 ± 10.5	2099	63.4 ± 11.2		<0.001[8]
BMI,[4] kg/m^2		3876	29.3 ± 7.8	1777	28.9 ± 7.5	2099	29.6 ± 8.0		0.158[8]
Diabetes mellitus	No[7]	3096		1455 (47%)		1641 (53%)		0.91 (0.83, 0.99)	0.038
	Yes	780		322 (41%)		458 (59%)			
Insulin dependent DM	No[7]	3601		1649 (46%)		1952 (54%)		1.04 (0.91, 1.18)	0.566
	Yes	275		128 (47%)		147 (53%)			
Lactate,[5] mmol/L		1816	2.0 ± 1.8	826	2.2 ± 1.9	990	1.8 ± 1.6		<0.001[8]
Albumin, g/L		3776	28.5 ± 6.4	1726	28.1 ± 6.5	2050	28.8 ± 6.2		<0.001[8]

[1]Defined as ≥1 GRV ≥250 mL on any study day. APACHE II, Acute Physiology and Chronic Health Evaluation; DM, diabetes mellitus; GRV, gastric residual volume; TARGET, The Augmented versus Routine approach to Giving Energy Trial.

[2]TARGET cohort in whom GRVs were recorded.

[3]APACHE II scores range from 0 to 71, with higher scores indicating more severe disease and a higher risk of death. In the TARGET study this score was calculated with the values recorded for each variable that would result in the highest score during the 24 h immediately prior to randomization.

[4]BMI is the weight in kilograms divided by the square of the height in meters.

[5]Data available for 1816 patients only.

[6]Analyses via log binomial regressions with GRV group as the outcome and a random effect for site. *P* values are given for the RRs for categorical characteristics and the goodness of fit of a restricted cubic spline for continuous variables.

[7]Reference for calculation of RR.

[8]X (6)^2 values: Age = 24.6, APACHE II score = 22.5, ideal body weight = 61.4, BMI = 9.3, lactate = 34.6, albumin = 29.1.

TABLE 2 Gastrointestinal dysfunction and treatment in patients receiving energy-dense compared with standard enteral formula

		1.5 kcal/mL		1.0 kcal/mL		Group difference (95% CI)[11]	P[12]
	N	N	Median [IQR]	N	Median [IQR]		
Volume study EN delivered,[1] mL/d	3876[2]	1935	1262 [1040–1472]	1941	1268 [1073–1487]	–19 (–39, 1)	0.057
Volume study EN (delivered minus discarded),[1] mL/d	3876	1935	1188 [947–1420]	1941	1224 [995–1451]	–35 (–57, –13)	0.002
GRV[1]							
Total daily aspirate volume, mL/d	3876	1935	197 [78–403]	1941	132 [52–302]	42 (31, 53)	<0.001
Any GRV ≥250 mL	1777/3876 (46%)	997/1935 (52%)		780/1941 (40%)		1.27 (1.19, 1.36)	<0.001
Any GRV ≥500 mL	674/3876 (17%)	375/1935 (19%)		299/1941 (15%)		1.24 (1.09, 1.42)	0.002
Number of study days GRV ≥250 mL[3]	3876	1935	1.0 [0.0–2.0]	1941	0.0 [0.0–1.0]	0.0 (0.0, 0.0)	<0.001
Time (study days) from initiation of study EN to first GRV ≥250 mL	1777	997	1.0 [0.0–2.0]	780	1.0 [0.0–2.0]	0.0 (0.0, 0.0)	0.970
Regurgitation or vomiting[4]	674/3875 (17%)	367/1935 (19%)		307/1940 (16%)		1.20 (1.05, 1.37)	0.009
Constipation/diarrhea							
Constipation[5,6]	1624/3120 (52%)	827/1552 (53%)		797/1568 (51%)		1.04 (0.97, 1.11)	0.267
Diarrhea[4,7]	1124/3875 (29%)	559/1935 (29%)		565/1940 (29%)		0.99 (0.90, 1.09)	0.886
Time from initiation of study EN to first bowel action, d[3,8]	2580	1256	2.0 [1.0–3.0]	1324	2.0 [1.0–3.0]	0.0 (0.0, 0.0)	0.266
Management[9]							
Prokinetic use[4,10]	1699/3875 (44%)	926/1935 (48%)		773/1940 (40%)		1.18 (1.10, 1.26)	<0.001
Postpyloric feeding	130/3876 (3%)	73/1935 (4%)		57/1941 (3%)		1.26 (0.90, 1.75)	0.174
PN use	188/3876 (5%)	107/1935 (6%)		81/1941 (4%)		1.32 (1.00, 1.75)	0.051
Treatment administered after any GRV ≥250 mL							
Prokinetics	1210/1777 (68%)	681/997 (68%)		529/780 (68%)		1.02 (0.97, 1.07)	0.564
Postpyloric feeding	92/1777 (5%)	62/997 (6%)		30/780 (4%)		1.54 (1.02, 2.32)	0.041
PN	157/1777 (9%)	91/997 (9%)		66/780 (9%)		1.03 (0.76, 1.38)	0.865

[1]Values are for the total time during which trial nutrition was delivered.
[2]TARGET cohort in whom GRVs were recorded.
[3]Durations were calculated in days from the time of commencement of the trial nutrition until cessation of the last episode of trial nutrition per patient.
[4]Data not available for 1 patient in the 1.0 kcal/mL group.
[5]Constipation: No bowel actions for 3 days after EN initiation.
[6]Excludes 756 patients with missing data on bowel function (thus unable to exclude constipation) during this time period.
[7]Diarrhea: ≥4 bowel actions on any day during the study period.
[8]Excludes 1296 patients who did not have a bowel action or first bowel action was before initiation of study EN.
[9]Number of patients who received this treatment during the study period.
[10]Evaluated to day 7, while patient receiving trial nutrition.
[11]Differences between the groups are presented as differences in means, differences in medians (Hodges–Lehman estimate), or (for percentages) RR.
[12]Analyses via log binomial regressions with a random site effect for the categorical outcomes, and via mixed effects models with a random site effect for the rank-transformed continuous outcomes.
EN, enteral nutrition; GRV, gastric residual volume; PN, parenteral nutrition; TARGET, The Augmented versus Routine approach to Giving Energy Trial.

with 15%; RR = 1.24 [1.09, 1.42]; $P = 0.002$). There was also a higher incidence of regurgitation or vomiting (16) in the energy-dense group (19 compared with 16%; RR = 1.20 [1.05, 1.37]; $P = 0.009$). In contrast, there were no differences in bowel function between the 2 groups when reported as constipation (53 compared with 51%; RR = 1.04 [0.97, 1.11]; $P = 0.267$), or diarrhea (29 compared with 29%; RR = 0.99 [0.90, 1.09]; $P = 0.886$).

Gastrointestinal dysfunction, nutrition delivery, and management

There was no difference in enteral calorie delivery between those with delayed versus normal GE in either the energy-dense (GRV ≥250 compared with GRV <250 mL: 1854 ± 466 compared with 1881 ± 488 kcal/d; RR = –27 [–70, 15]; $P = 0.067$) or the standard (1262 ± 316 compared with 1267 ± 309 kcal/d; RR = –4 [–33, 24]; $P = 0.254$) EN groups (**Table 3**). Similarly, the presence of ≥1 GRV ≥500 mL did not affect enteral calorie delivery (1594 ± 517 compared with 1559 ± 499 kcal/d; RR = 35 [–7, 77]; $P = 0.448$; **Supplemental Table 1**).

Patients with ≥1 GRV ≥250 mL were more likely to receive prokinetics (70 compared with 21%; RR = 3.3 [3.0, 3.6]; $P < 0.001$), postpyloric feeding (5.3 compared with 1.7%; RR = 2.4 [1.6, 3.5]; $P < 0.001$), and PN (8.9 compared with 1.4%; RR = 6.4 [4.4, 9.4]; $P < 0.001$; Table 3). Similar relations were evident in patients with very large GRVs (GRV ≥500 mL) (Supplemental Table 1).

Clinical outcomes

Large GRVs were also associated with lower gastrointestinal dysfunction (GRV ≥250 mL compared with <250 mL: constipation 55 compared with 50%; RR = 1.09 [1.02, 1.17]; $P = 0.010$ and diarrhea 32 compared with 27%; RR = 1.19 [1.07, 1.31]; $P < 0.001$). More patients with large and very large GRVs received vasopressors at some point during the study period (GRV ≥250 mL compared with <250 mL: 88 compared with 76%; RR = 1.15 [1.12, 1.19]; $P < 0.001$; GRV ≥500 mL compared with <500 mL; 90 compared with 80%; RR = 1.13 [1.09, 1.16]; $P < 0.001$: **Table 4** and **Supplemental Table 2**). Both the incidence of positive blood cultures and the administration of intravenous antimicrobials were higher in those with large GRVs (GRV ≥250 mL compared with <250 mL: blood cultures 16 compared with 8%; RR = 1.92 [1.60, 2.31]; $P < 0.001$; antimicrobials 88 compared with 81%; RR = 1.09 [1.06, 1.12]; $P < 0.001$). Patients with ≥1 GRV ≥250 mL had a higher 90-d mortality (29 compared with 23%, RR = 1.17 [1.05, 1.30]; $P = 0.003$; Table 4), even when adjusted for illness severity, prolonged ICU stay (ICU-free days: 12.9 [0.0–21.0] compared with 20.0 [3.9–24.0] d; $P < 0.001$), hospital stay (hospital-free days: 0.0 [0.0–12.0] compared with 7.0 [0.0–17.6] d; $P < 0.001$), and ventilatory support (ventilator-free days: 16.0 [0.0–23.0] compared with 22.0 [8.0–25.0] d; $P < 0.001$). Similar associations were evident in patients with GRV ≥500 mL compared with GRV <500 mL (Supplemental Table 2). There was no association between lower gastrointestinal dysfunction and 90-d mortality (**Table 5**).

Of the 1777 patients with GRV ≥250 mL, 1762 patients had data collected on prokinetic administration, of whom 1241 (70%)

TABLE 3 Nutritional outcomes and management in patients with any GRV ≥250 mL

	Total	Any GRV ≥250 mL		All GRVs <250 mL		Group difference (95% CI)	P[4]
	N	N	Mean ± SD	N	Mean ± SD		
Volume study EN delivered, mL/d	3876	1777	1247 ± 313	2099	1261 ± 316	−14 (−33, 6)	0.019
1.5 kcal/mL	1935	997	1236 ± 311	938	1254 ± 325	−18 (−46, 10)	0.067
1.0 kcal/mL	1941	780	1262 ± 318	1161	1267 ± 309	−4 (−33, 24)	0.249
Actual volume study EN received (delivered minus discarded), mL/d	3876	1777	1079 ± 422	2099	1237 ± 335	−158 (−181, -134)	<0.001
Calories from study EN,[1] kcal/d	3876	1777	1594 ± 502	2099	1541 ± 502	53 (21, 85)	0.007
1.5 kcal/mL	1935	997	1854 ± 466	938	1881 ± 488	−27 (−70, 15)	0.067
1.0 kcal/mL	1941	780	1262 ± 316	1161	1267 ± 309	−4 (−33, 24)	0.254
Calories from study EN,[1] kcal/kg IBW/d	3876	1777	24.3 ± 7.0	2099	24.5 ± 7.1	−0.2 (−0.6, 0.3)	0.350
Actual calories received (delivered minus discarded), kcal/d	3876	1777	1379 ± 601	2099	1511 ± 517	−132 (−167, -96)	<0.001
Management[2,3]							
Prokinetics[3,4]	1699 (44%)	1252 (70%)		447 (21%)		3.3 (3.0, 3.6)	<0.001
Postpyloric feeding	130 (3.4%)	94 (5.3%)		36 (1.7%)		2.4 (1.6, 3.5)	<0.001
PN	188 (4.9%)	158 (8.9%)		30 (1.4%)		6.4 (4.4, 9.4)	<0.001

[1] Values are for the total time during which trial nutrition was delivered.
[2] Number of patients who received this treatment during the study period.
[3] Evaluated to day 7 while the patient was receiving the trial nutrition. Data not available for 1 patient in the 1.0 kcal/mL group.
[4] Analyses via log binomial regressions with a random site effect for the categorical outcomes, and via mixed effects models with a random site effect for the continuous outcomes.
EN, enteral nutrition; GRV, gastric residual volume; IBW, ideal body weight; PN, parenteral nutrition.

TABLE 4 Clinical outcomes in patients with any GRV ≥250 mL compared with patients with all GRVs <250 mL

	Total (N = 3876) N (%)	Any GRV ≥250 mL (N = 1777) N (%)	All GRVs <250 mL (N = 2099) N (%)	Group difference (95% CI)	*P*
Bowel motions:					
Constipation[1]	1624/3120 (52%)	846/1551 (55%)	778/1569 (50%)	1.09 (1.02, 1.17)	0.010
Diarrhea[2]	1124/3875 (29%)	564/1777 (32%)	560/2098 (27%)	1.19 (1.07, 1.31)	0.001
Vasopressors[3]					
1.5 kcal/mL	1576/1935 (81%)	874/997 (88%)	702/938 (75%)	1.17 (1.12, 1.22)	<0.001
1 kcal/mL	1582/1941 (82%)	685/780 (88%)	897/1161 (77%)	1.14 (1.09, 1.18)	<0.001
Total	3158/3876 (81%)	1559/1777 (88%)	1599/2099 (76%)	1.15 (1.12, 1.19)	<0.001
Positive blood cultures	440/3876 (11%)	276/1777 (16%)	164/2099 (8%)	1.92 (1.60, 2.31)	<0.001
Intravenous antimicrobial administration	3262/3876 (84%)	1565/1777 (88%)	1697/2099 (81%)	1.09 (1.06, 1.12)	<0.001
Mortality day 90 (*n* [%])[4]					
Unadjusted	1001/3835 (26%)	517/1762 (29%)	484/2073 (23%)	1.25 (1.12, 1.39)	<0.001
Adjusted for APACHE-II score				1.17 (1.05, 1.30)	0.003
	Median [IQR] (N = 3857)	Median [IQR] (N = 1769)	Median [IQR] (N = 2088)	Group difference (95% CI)	*P*
ICU-free days[5,6]	17.1 [0.0-23.0]	12.9 [0.0-21.0]	20.0 [3.9-24.0]	–2.9 (–3.6, –2.3)	<0.001
Hospital-free days[5,6]	2.9 [0.0-15.4]	0.0 [0.0-12.0]	7.0 [0.0-17.6]	0.0 (–0.2, 0.0)	<0.001
Ventilator-free days[6,7]	20.0 [0.0–25.0]	16.0 [0.0–23.0]	22.0 [8.0–25.0]	–3.0 (–3.0, –2.0)	<0.001

[1]Excludes 756 patients with missing data on bowel actions (thus unable to exclude constipation) in the 3 d following start of EN.

[2]Data unavailable for 1 patient.

[3]The number patients who received any vasopressor support at any time up to day 28.

[4]Excludes 23 patients lost to follow-up (9 in 1.0 kcal/mL group, 14 in 1.5 kcal/mL group) and 18 who withdrew consent/opted out (10 in 1.0 kcal/mL group, 8 in 1.5 kcal/mL group).

[5]ICU-free and hospital-free days were calculated from the time of randomization to day 28. Patients who died before day 28 were assigned 0.

[6]Excludes 8 patients lost to follow-up (3 in 1.0 kcal/mL group, 5 in 1.5 kcal/mL group) and 11 who withdrew consent/opted out (6 in 1.0 kcal/mL group, 5 in 1.5 kcal/mL group).

[7]The number of ventilator-free days was calculated from the number of whole calendar days without receiving invasive ventilation, after the final episode of organ support up to day 28.

APACHE II, Acute Physiology and Chronic Health Evaluation; EN, enteral nutrition; GRV, gastric residual volume; ICU, intensive care unit.

received prokinetics during the study period. In the patients with GRV ≥250 mL, mortality was lower in those who received prokinetics compared with those who did not (28 compared with 34%; RR = 0.82 [0.70, 0.95]; $P = 0.010$; Table 5). In contrast, prokinetic administration was not associated with mortality in patients who had a GRV <250 mL (25 compared with 23%; RR = 1.08 [0.89, 1.30]; $P = 0.451$; Table 5).

Discussion

TARGET provided a unique opportunity to conduct an in-depth investigation of risk factors and implications of gastrointestinal dysfunction in a large, prospectively collected data set of mechanically ventilated patients. This analysis confirmed that upper gastrointestinal dysfunction, particularly GRV ≥250 mL (19): occurred frequently and early in the ICU stay but was not sustained; occurred more commonly in men and with the use of energy-dense formulae; and was strongly associated with mortality and other negative outcomes, even when adjusted for illness severity. The energy-dense formula was not associated with lower gastrointestinal dysmotility (2).

Factors that affect GE in the general population include female sex, older age, medications, and diabetes (21, 22). In our cohort, GRV ≥250 mL occurred more frequently in males with no clinically significant relation to age. Although delayed GE occurs in 30–40% of ambulant persons with poorly controlled diabetes (23, 24), diabetes in our analysis was not associated with GRV ≥250 mL, consistent with previous data (25). The differences in risk factors in our analysis suggest that factors unique to critical illness, such as medications and gut neuroendocrine responses, may have a more profound influence on GE than usual determinants. In addition, our study showed diagnoses associated with GRV ≥250 mL included gastrointestinal and cardiovascular diseases, and trauma, which differ slightly from previous reports possibly due to variations in the populations studied, e.g. the exclusion of patients with burns in TARGET and the diagnostic criteria used (3, 26).

Illness severity did not appear to be a strong risk factor for large GRVs in our analysis as, although patients with GRV ≥250 mL had a statistically higher APACHE II score, the difference was marginal (22 compared with 21). The number of patients receiving vasopressors at any time was also higher in patients with GRV ≥250 mL (7); however, catecholamines have a direct sympathomimetic effect on gastrointestinal motility (27) so this may be indicative of an underlying cause of GRV ≥250 mL rather than a relation with illness severity. Weak associations between gastrointestinal dysfunction and illness severity have been reported by others; however, differing definitions of gastrointestinal failure render comparisons between these analyses and ours specious (3, 7).

Our analysis confirmed that the incidence of large GRVs was greater in patients receiving more calories (28–30). Several nutritional factors are known to affect the rate of GE, including energy density, volume, and macronutrient composition (13).

TABLE 5 Relations between gastrointestinal dysfunction, prokinetic administration, and 90-d mortality

	Total[1] N (%)	Dead N (%)	Group difference (95% CI)	P[4]	Interaction P
Presence of constipation for 3 d after EN initiation[2]	1611/3092 (52%)	419/1611 (26%)	0.97 (0.87, 1.10)	0.673	
No constipation	1481/3092 (48%)	392/1481 (26%)			
Presence of diarrhea on any day[3]	1115/3834 (29%)	282/1115 (25%)	0.96 (0.85, 1.08)	0.496	
No diarrhea[3]	2719/3834 (71%)	719/2719 (26%)			
In subgroup with:					
Any GRV ≥250 mL:					
Any prokinetics[3]	1241	342/1241 (28%)	0.82 (0.70, 0.95)	0.010	0.028
No prokinetics	521	175/521 (34%)			
All GRVs <250 mL:					
Any prokinetics[3]	442	109/442 (25%)	1.08 (0.89, 1.30)	0.451	
No prokinetics	1630	375/1630 (23%)			
Any GRV ≥250 mL:					
1.5 kcal/mL	986	280/986 (28%)	0.93 (0.80, 1.08)	0.326	0.103
1.0 kcal/mL	776	237/776 (31%)			
All GRVs <250 mL:					
1.5 kcal/mL	927	229/927 (25%)	1.11 (0.95, 1.30)	0.189	
1.0 kcal/mL	1146	255/1146 (22%)			

[1]Excludes 23 patients lost to follow-up and 18 who withdrew consent/opted out.
[2]Excludes 743 patients with incomplete data on bowel actions within the 3 d following start of EN.
[3]Data unavailable for 1 patient.
[4]Analyses via log binomial regressions with mortality as the outcome and random effect for site.
EN, enteral nutrition; GRV, gastric residual volume.

TARGET differs from previous trials in that the additional calorie delivery was achieved using energy-dense EN, with an increased lipid content rather than a higher volume of formula; lipids are known to slow GE in health (31) and diabetes (11, 32). These data suggest that energy-dense, high lipid formulae have the potential to further slow GE, a factor that should be considered prior to their prescription.

In contrast to previous studies, large GRVs were not associated with a reduction in the delivery of EN volume or calories (20, 33). In a multi-center prospective cohort study of 400 mechanically ventilated, enterally fed patients, Montejo et al. reported that gastrointestinal complications were associated with reduced caloric adequacy (20), potentially reflecting the withdrawal of EN in response to these complications. Similarly, a prospective observational study in 193 critically ill adult patients reported large GRVs to be the most common cause of reduced EN delivery (33). In TARGET, the clinical response to a large GRV may have been to use alternative strategies known to improve nutrition rather than to reduce the rate of EN delivery (2, 34), as demonstrated by the greater use of prokinetics, postpyloric feeding, and PN in those with a large GRV.

Several studies have previously reported a relation between gastrointestinal dysfunction and poor outcomes in critically ill patients, including LOS, infectious complications, and mortality (3, 35, 36), which has been confirmed in this analysis. It remains uncertain whether upper gastrointestinal dysfunction contributes directly to poor outcomes or is simply a marker of illness severity; yet the latter appears unlikely from our analysis. Furthermore, the demonstrated relation meets several of the Bradford Hill criteria for causality (37): the strength of the relation; consistency across multiple cohorts and populations; biological gradient; and a plausible mechanism, justifying further exploration. The increased mortality is unlikely to be attributable to underfeeding, given that patients with large GRVs did not receive less calories in this cohort and the accumulating evidence that calorie delivery has not impacted survival when provided early in critical illness (16, 38). Other plausible mechanisms are that large GRVs may be associated with microaspiration and pneumonia, or an increased risk of infectious complications from another source (such as gut translocation, due to loss of intestinal barrier function, altered bowel flora, and/or visceral hypoperfusion) (39). This is supported by our observation that large GRVs are associated with increased bloodstream infections and antimicrobial use.

We observed that patients with GRV ≥250 mL who were administered prokinetics (compared with those who were not) had a lower 90-d mortality. This requires careful interpretation. Firstly, the administration of prokinetics in TARGET was a clinical decision rather than determined by randomization. Secondly, our finding is inconsistent with results from a meta-analysis of 6 randomized control trials (RCTs) involving 691 critically ill patients which showed that although nonprotocolized prokinetic administration reduced the length of ICU and hospital stay there was no discernable effect on all-cause mortality (RR = 0.96, [95% CI: 0.81, 1.14]; P = 0.64; I2 = 0%) (40); although, our patient population was ~3 times the size of this cohort (16). Although prokinetics improve nutrition delivery (41) and accelerate GE (41–43) they have not been shown to reduce the incidence of nosocomial pneumonia (44–46), nor have an independent effect on reducing mortality in patients with delayed GE. Nevertheless, our observations should be considered hypothesis generating and an adequately powered RCT to examine the effect of prokinetic administration on clinical outcomes in patients with GRV ≥250 mL is justified.

This post-hoc analysis represents one of the largest data sets to explore gastrointestinal dysfunction in the critically ill and hence is highly generalizable. The data were collected prospectively as

part of a large multi-center RCT and hence should be considered robust. Findings are based on posteriori associations; thus, relations should be considered hypothesis generating rather than causal. Data were limited to that collected as part of TARGET and the nonprotocolized management of gastrointestinal dysfunction across participating sites should also be recognized as a potential limitation. It is also important to emphasize that the relations between energy-dense formulae and clinical outcomes in the presence of large GRVs remain complex and uncertain. These observational data support other published data (47, 48) showing that large GRVs are associated with poor outcomes; however, no such association has been shown between enteral feeding and poor outcomes and importantly there was no increased mortality observed in the energy-dense EN group in the TARGET trial (16).

In conclusion, risk factors for delayed GE in critical illness appear to differ substantially from those in health. Furthermore, a GRV $\geq$250 mL is associated with a number of negative sequalae including bloodstream infections, antibiotic administration and mortality; a causal relation cannot be discounted. Avoiding reversible risk factors such as the use of energy-dense or high lipid content enteral formulae, or the administration of catecholamines may assist but require further investigation.

The authors' responsibilities were as follows—TAM, LSC, and MJC: conceptualized and designed the research; TAM, LSC, and MJC: conducted the research; KL: performed the statistical analysis; TAM, LSC, and MJC: wrote the manuscript; CSM, MH, and SLP: reviewed the manuscript and had intellectual input; TAM: had primary responsibility for the final content; and all authors: read and approved the final manuscript. The authors report no conflicts of interest.

Data Availability

Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval.

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