



# Comparison of energy intake in critical illness survivors, general medical patients, and healthy volunteers: A descriptive cohort study

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## Funding information

This study was funded by a Royal Adelaide Hospital Clinical Research Grant (MYIP 10945, HREC CALHN ref: 12700). Abbott Nutrition provided the liquid test-meal in-kind. E.V.S. is funded by an Australian Government—Research Training Program (RTP) Scholarship and a Central Adelaide Local Health Network—Dawes Scholarship. I.W.K.K. is supported by a Dutch Research Council Rubicon Fellowship. L.S.C. is supported by a National Health and Medical Research Council (NHMRC) Early Career Fellowship

## Abstract

**Background:** Intensive care unit (ICU) survivors have reduced oral intake; it is unknown whether intake and associated barriers are unique to this group.

**Objective:** To quantify energy intake and potential barriers in ICU survivors compared with general medical (GM) patients and healthy volunteers.

**Design:** A descriptive cohort study in ICU survivors, GM patients, and healthy volunteers. Following an overnight fast, participants consumed a 200 ml test-meal (213 kcal) and 180 min later an ad libitum meal to measure energy intake (primary outcome). Secondary outcomes; taste recognition, nutrition-impacting symptoms, malnutrition, and quality of life (QoL). Data are mean  $\pm$  SD, median (interquartile range [IQR]) or number [percentage].

**Results:** Twelve ICU survivors ( $57 \pm 17$  years, BMI:  $30 \pm 6$ ), eight GM patients ( $69 \pm 19$  years, BMI:  $30 \pm 6$ ), and 25 healthy volunteers ( $58 \pm 27$  years, BMI:  $25 \pm 4$ ) were included. Recruitment ceased early because of slow recruitment and SARS-CoV-2. Energy intake was lower in both patient groups than in health (ICU: 289 [288, 809], GM: 426 [336, 592], health: 815 [654, 1165] kcal). Loss of appetite was most common (ICU: 78%, GM: 67%). For ICU survivors, GM patients and healthy volunteers, respectively, severe malnutrition prevalence; 40%, 14%, and 0%; taste identification; 8.5 [7.0, 11.0], 8.5 [7.0, 9.5], and 8.0 [6.0, 11.0]; and QoL; 60 [40–65], 50 [31–55], and 90 [81–95] out of 100.

**Conclusions:** Energy intake at a buffet meal is lower in hospital patients than in healthy volunteers but similar between ICU survivors and GM patients. Appetite loss potentially contributes to reduced energy intake.

## KEYWORDS

appetite, ICU survivors, malnutrition, nutrition-impacting symptoms, oral intake

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## CLINICAL RELEVANCY STATEMENT

Oral intake on the post intensive care unit (ICU) ward is frequently below estimated requirements. This study quantified oral intake and potential barriers to intake in ICU survivors on the post-ICU ward, compared with general medical (GM) patients. Energy intake at a weighed buffet appeared similar between ICU survivors and GM patients but was nearly half that of healthy volunteers. Barriers to intake were diverse and although some were shared between both groups, loss of appetite and severe malnutrition were particularly prevalent in ICU survivors.

## INTRODUCTION

Poor nutrition status is negatively associated with clinical outcomes in patients admitted to the intensive care unit (ICU), including an increased risk of infection, length of stay, mortality, and readmission to the ICU.<sup>1</sup> Poor nutrition status may be exacerbated further on the post-ICU ward, contributing to ongoing impaired recovery, including reduced functional capacity and weakness.<sup>2</sup>

Nutrition intake in patients throughout the hospital is typically below estimated requirements.<sup>3,4</sup> In the ICU, nutrition delivery achieves ~50%–60% of prescribed energy and protein targets, largely reflecting delays in initiation, fasting for procedures, and gastrointestinal (GI) intolerance.<sup>5–7</sup> On the post-ICU ward, oral intake is the most common route of nutrition and is associated with lower nutrition intake when compared with enteral nutrition alone (37% of energy and 48% of protein requirements vs 62% energy and 59% protein requirements, respectively).<sup>4</sup> Reasons for reduced nutrition intake during the post-ICU period have not been well quantified but are likely to be multifactorial, including patient-related, clinician-related, and system-related factors.<sup>8</sup>

Observational studies suggest that reduced nutrition intake in general hospitalized patients is associated with worse outcomes<sup>9</sup> and a randomized control trial (RCT) has shown that individualized nutrition support interventions improve outcomes in a general medical (GM) population<sup>10</sup>; hence, there is potential that improving intake in hospitalized patients after ICU discharge may lead to improved outcomes.<sup>10</sup> To determine whether physiological barriers known to affect nutrition delivery during the ICU stay extend to the post-ICU period, our group previously quantified gastric emptying, glucose absorption, and metabolic rate in 26 critically ill patients during ICU stay and in the post-ICU ward, compared with 10 healthy volunteers.<sup>11</sup> All three physiological factors were markedly impaired in ICU compared with healthy volunteers but returned to relatively normal levels on the post-ICU ward. The study by Whitehead et al therefore highlighted that other potential barriers to oral intake in ICU survivors should be examined and questioned whether these barriers are unique to this patient group when compared with other hospitalized populations. The primary aim of the current study was to compare oral intake in ICU survivors to GM patients. The secondary aims were to determine what factors may impact intake in ICU survivors and if these differed to barriers in GM patients, with healthy volunteers acting as a control group.

## METHODS

### Study design

This is a descriptive cohort study of ICU survivors, GM patients, and healthy volunteers. The Central Adelaide Local Health Network Human Research Ethics Committee approved the study (reference number:12700) and the protocol was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12620000845932). All participants were informed of the purpose of the study, the experimental procedures, and possible risks before written informed consent to participate was obtained. Procedures were conducted in accordance with the ethical standards outlined in the Helsinki Declaration of 1975 as revised in October 2013.

### Participants

Patients were screened and recruited in parallel from inpatient wards at the Royal Adelaide Hospital on weekdays between March 1 and December 23, 2021. Detailed inclusion and exclusion criteria are shown in Table S1. In brief, ICU survivors were identified as patients discharged from the ICU to the ward for active treatment and were studied on the ward within 7 days of ICU discharge. GM patients admitted directly to two GM wards for  $\geq 72$  h were studied within 7 days of their admission to the hospital. Key exclusion criteria for both hospitalized groups included patients unable to follow commands, unable to consume the individual buffet meal, had previously undergone GI surgery, or were taking medications that significantly impacted GI motility. Healthy volunteers were recruited from an existing pool of adults who had previously consented to being contacted regarding research and from advertisements at the University of South Australia and The University of Adelaide.

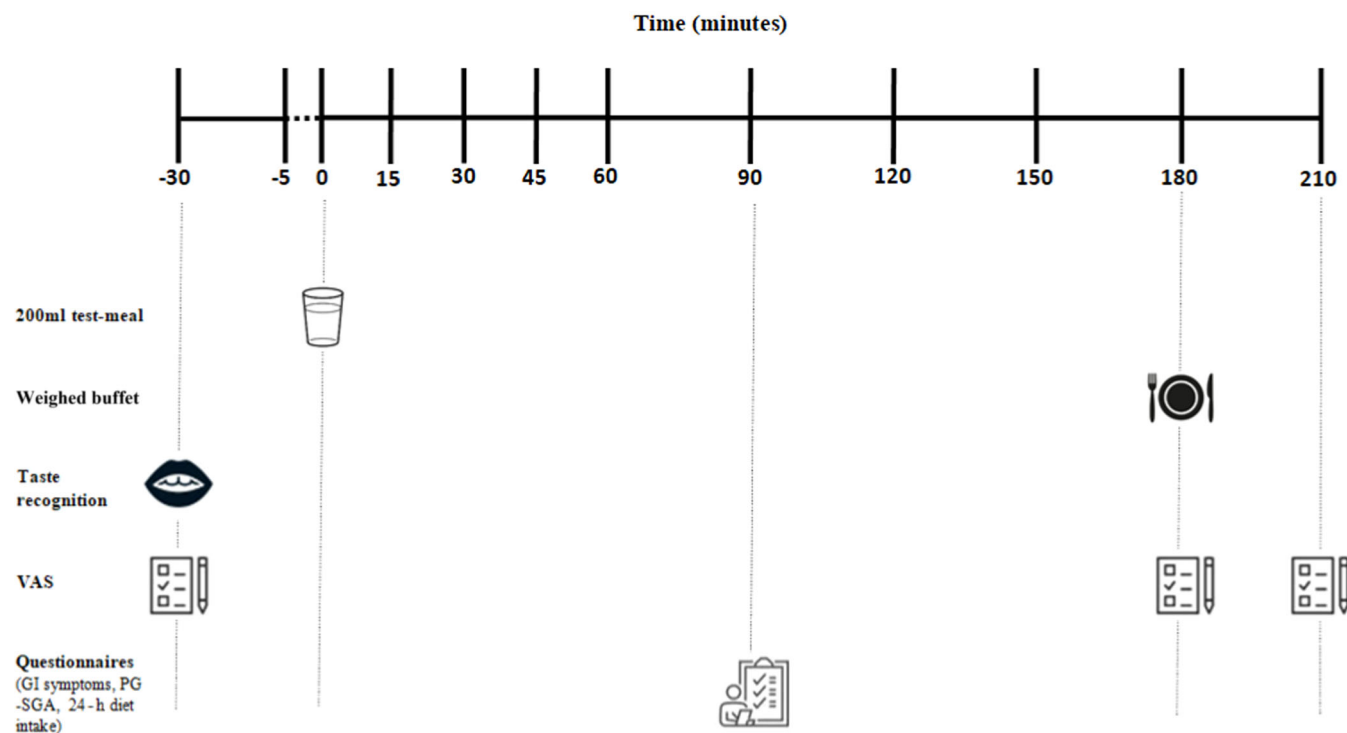
### Patient characteristics

Demographic data, including date of birth, sex, and ICU and hospital admission and discharge dates, were collected from the hospital's Electronic Medical Record (EMR) system. EMR was also used to determine if a dietetic consultation had occurred prior to the study day. For ICU patients, Acute Physiology And Chronic Health Evaluation II scores were extracted from the COMET (CORE Outcome Measurement and Evaluation Tool) database.

### Study procedures

Over a 4-h study period commencing at 8 a.m., energy intake at a weighed buffet meal and barriers to oral intake were quantified as shown in Figure 1.

Following a fast from midnight (excluding prescribed medications ingested with sips of water), all participants were asked to consume a



**FIGURE 1** Overview of the study protocol in which ICU survivors, GM patients, and healthy volunteers consumed a 200 ml test-meal ( $t = 0$  min) followed 180 min later by an ad libitum buffet meal. GI, gastrointestinal; GM, general medical; ICU, intensive care unit; PG-SGA, Patient-Generated Subjective Global Assessment; VAS, visual analogue scale.

200 ml mixed-macronutrient liquid “test-meal” (Ensure, Abbot; 213 kcal, 8 g protein, 34 g carbohydrate, 5 g fat) over a 5-min period, completion of which was considered  $t = 0$  min. Consumption of this test-meal allowed for following standardized nutrient intake at the beginning of the study to reduce the impact of meal composition on subsequent nutrition intake and barriers to be quantified. At  $t = 180$  min (approximately midday for each participant) participants were provided with a standard weighed buffet meal (totalling; 2303 kcal, 115 g protein, 79 g lipid, 266 g carbohydrate, individual items listed in Table S2)<sup>12</sup> presented as individual items on a single hospital tray at the bedside for patients to select items for consumption. Patients were instructed to consume the buffet until comfortably full over a 30-min period and were not informed that the primary purpose of the buffet meal was to assess energy intake. The composition of the buffet meal was consistent with the International Dysphagia Diet Standardization Initiative “easy to chew” and “thin fluids” requirements as per a registered speech pathologist. Individual meal items were weighed prior to consumption and at completion of the meal, and energy (primary outcome) and macronutrient intake were quantified using FoodWorks 8.0 dietary analysis software (Xyris Pty Ltd).

### Dietary recall

A 24-h dietary recall to capture dietary intake from the calendar day prior to the study was conducted by a trained dietitian. All food items

were entered into FoodWorks dietary analysis software to quantify energy and macronutrient consumption.

### Taste, appetite, and GI symptoms

At  $t = -30$  min, participants undertook a taste test to identify taste recognition, in which they were randomly assigned to one of two sequences of 16 blinded paper “paddles” infused with varying flavor strengths (sweet, salty, bitter, sour) and asked to identify the flavor present or “no taste.”<sup>13</sup> Participants were instructed to rinse their mouth with water between samples to minimize the potential for flavor cross-contamination.<sup>13</sup> One point was allocated for a correct score (maximum score 16), with a higher score indicating better taste recognition.

Qualitative assessment of appetite (hunger and satiety) using a validated visual analogue scale (VAS)<sup>14</sup> was conducted at three timepoints; in the fasted state ( $t = -30$  min) and before ( $t = 180$  min) and immediately after ( $t = 210$  min) consumption of the ad libitum weighed buffet meal. Each VAS consisted of a 100-mm horizontal line, in which 0 mm represented “sensation not felt at all” and 100 mm represented “sensation felt the greatest.” This provided information regarding the participants level of hunger and satiety. Self-reported GI symptoms were assessed ( $t = 90$  min) via a validated questionnaire—“GI symptoms questionnaire”<sup>15</sup>—using a Likert scale from “none” to “unbearable” (0–7 options), with the higher number representing greater symptom severity.

## Nutrition status

Nutrition status was quantified by a trained dietitian using the Patient-Generated Subjective Global Assessment (PG-SGA)<sup>16</sup> and categorized as A (well-nourished), B (moderate/suspected malnutrition), or C (severely malnourished). In the absence of a validated tool to determine nutrition-impacting symptoms, Box 3 of the PG-SGA has been used to score nutrition-impacting symptoms patients may have experienced that directly impact on their oral intake.

## Quality of life (QoL)

Self-reported QoL was determined using the EuroQol five-dimension five-level (EQ-5D-5L) score<sup>17</sup> at  $t = 90$  min. The EQ-5D-5L assesses capacity across five domains—mobility, self-care, usual activities, pain/discomfort, anxiety/depression—with a single number summarizing the five domains into one index value representing “good” (1) or “bad” (0) health compared with reference values.

## Statistical analysis

Based on a previous nutrition study in ICU survivors,<sup>12</sup> an a priori sample size of 25 participants per group was calculated using a two-sided independent samples  $t$  test ( $\alpha$  of 0.05, 80% power) to detect a difference in energy intake of 280 kcal with a SD of 346 kcal. Descriptive statistics were used for baseline demographics, including mean  $\pm$  standard deviation (SD) or median (interquartile range [IQR]) for continuous data and number (percentage) for categorical data. Because of SARS-CoV-2 and slow recruitment, early cessation of recruitment meant the desired sample size was not reached; therefore, the study was considered to be descriptive, and hypothesis-generating in nature only. Because of the study being descriptive and exploratory in nature, statistical analyses were not undertaken and primary and secondary outcomes are presented as descriptive results only. Data are presented as mean ( $\pm$ SD), median ([IQR]), or number (percentage) as appropriate. Statistical analysis was completed in IBM, SPSS Inc (2022).

## RESULTS

### Participants

Participant recruitment, enrollment, and inclusion flow are presented in Figure 2. Baseline characteristics of included participants are reported in Table 1. Overall, 12 ICU survivors ( $57 \pm 17$  years, BMI:  $30 \pm 6$ ), eight GM patients ( $69 \pm 19$  years, BMI:  $30 \pm 6$ ), and 25 healthy volunteers ( $58 \pm 27$  years, BMI:  $25 \pm 4$ ) completed the study. One participant withdrew during the study as he was discharged to a rehabilitation facility during the study day.

## Dietary intake

Dietary intake data are presented in Table 2. Energy intake from the weighed buffet meal appear similar between ICU survivors and GM patients (389 [288, 809] vs 426 [336, 592] kcal) but was lower in ICU survivors compared with healthy volunteers (815 [654, 1165] kcal).

The energy intake from the 24-h recall for ICU survivors, GM patients, and healthy volunteers was 1612 [1033, 2192], 1486 [431, 1620], and 1794 [1545, 2440] kcal, respectively. All nutrition intake in the 24-h recall was from oral intake alone as no patient was receiving artificial nutrition support in the 24-h prior to the study day.

## Taste, appetite, and GI symptoms

Taste identification (out of 16) for ICU survivors, GM patients, and healthy volunteers was 8.5 [7.0, 11.0], 8.5 [7.0, 9.5], and 8.0 [6.0, 11.0], respectively.

At  $t = 180$  min, hunger ratings were 53 [39, 72] in ICU survivors, 26 [0, 42] in GM patients, and 72 [65, 80] in healthy volunteers (Table S3). Reported feelings of drowsiness at three timepoints ( $t = -30$  min,  $t = 180$  min and  $t = 210$  min) were ICU survivors: 8 [2,21], 53 [18, 81], 52 [24, 73]; GM patients: 39 [24, 56], 50 [20, 83], 54 [34, 70]; and healthy volunteers: 9 [2, 25], 10 [1, 52], 2 [0, 15].

On the GI symptoms questionnaire, the most frequently reported GI symptoms in the ICU survivors were loss of appetite (78%), flatulence (78%), and belching (60%), whereas in the GM patients, the most common symptoms were flatulence, abdominal rumbling, and belching (all 100%) (Table S4). For those hospitalized patients who experienced loss of appetite, the severity for ICU survivors was scored as 2.4 out of 7 and 2.3 out of 7 for GM patients.

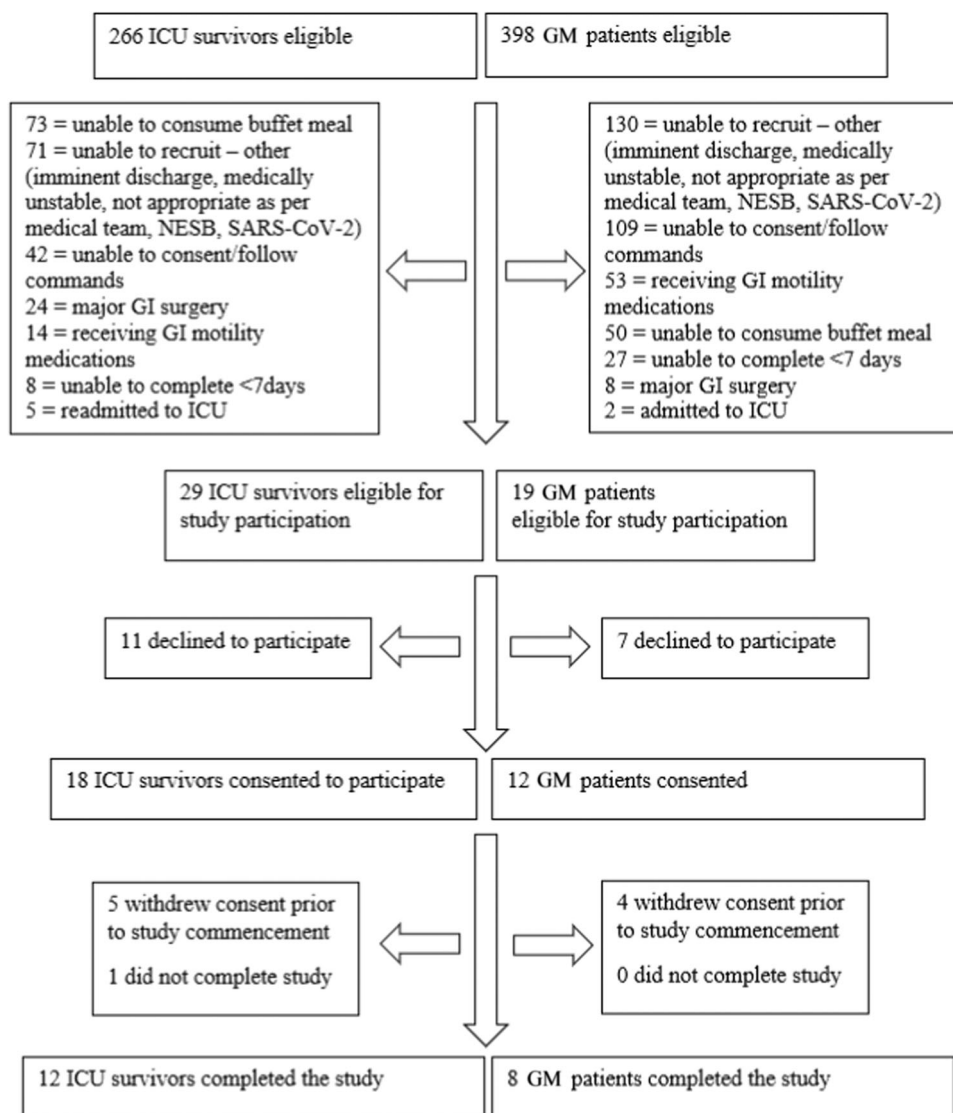
From the PG-SGA, the most frequently reported nutrition-impacting symptom for ICU survivors was “no appetite” (70%), followed by “feel full quickly” (60%) and “fatigue” (60%) (Table S5). GM patients reported “no appetite,” “feel full quickly,” and “fatigue” as the three most common symptoms (57%). Nutrition-impacting symptoms were reported infrequently by healthy volunteers (Table S5).

## Nutrition status

Nutrition status using the PG-SGA is presented in Table 1. Severe malnutrition was prevalent in 40% of ICU survivors, compared with 14% of GM patients, with no healthy volunteers being severely malnourished.

## QoL

Self-reported QoL scores for the ICU survivors, GM patients, and healthy volunteers were 60 [40–65], 50 [31–55], and 90 [81–95], respectively (Table S6). Problems with mobility, self-care, and completion of usual daily activities were the domains in which ICU



**FIGURE 2** CONSORT flow diagram of ICU survivor and GM patient recruitment. Patients meeting all inclusion criteria were considered “eligible.” GI, gastrointestinal; GM, general medical; ICU, intensive care unit; NESB, non-english speaking background.

survivors most frequently reported problems (all 89%). Pain/discomfort and completion of usual activities were the domains in which GM patients most frequently reported problems (both 86%). The converted EQ-5D-5L index scores, for ICU survivors, GM patients, and healthy volunteers, were 0.34, 0.19, and 0.93, respectively.

**DISCUSSION**

This is the first study to compare energy intake of ICU survivors on the post-ICU ward with other hospitalized patients by quantifying oral intake at a weighed buffet. It also contributes to the current literature by quantifying barriers to intake in ICU survivors on the post-ICU ward and comparing these to GM patients and healthy volunteers. Energy intake in patients from the weighed buffet meal was nearly half that consumed by the healthy volunteers but appear

similar between ICU survivors and GM patients. Multiple barriers that could potentially impact nutrition intake were reported.

In this study, energy intake from the weighed buffet meal appeared similar between ICU survivors and GM patients; albeit limited by the small cohorts. The concept known as “anorexia of the aging” (in which energy intake reduces with age)<sup>18</sup> may in part account for the lower intake in the GM patients given their average age was 10 years older than the healthy volunteers. The reduced intake in the ICU survivors may reflect acute illness as patients recover from critical illness, which we have previously demonstrated improves over time: at 3-month follow-up, energy intake at a buffet meal did not differ between  $n = 51$  ICU survivors and  $n = 25$  healthy volunteers (658 vs 736 kcal;  $P = 0.15$ ).<sup>11</sup> These data, combined with the results of the our current study, suggest that oral intake is likely impaired early after ICU discharge but improves over time and that “anorexia of critical illness” may be present in ICU survivors.

**TABLE 1** Participant characteristics of ICU survivors, GM patients, and healthy volunteers.

	ICU survivors n = 12	GM patients n = 8	Healthy volunteers n = 25
Age (years)	56.5 ± 16.9	68.6 ± 19.4	58.4 ± 26.8
Sex (male), n (%)	7 (58)	2 (25)	13 (52)
Weight (kg)	86.3 ± 23.2	84.6 ± 21.3	74.5 ± 18.2
BMI	29.9 ± 6.0	30.1 ± 5.7	25.4 ± 4.4
PG-SGA score, n (%)			
- Well-nourished	3 (30)	2 (29)	25 (100)
- Moderately malnourished	3 (30)	4 (57)	0 (0)
- Severely malnourished	4 (40)	1 (14)	0 (0)
- Not available	2	1	0
APACHE II at ICU admission	17.3 ± 6.1	N/A	N/A
Admission diagnosis			
- Cardiovascular	3 (25)	0 (0)	N/A
- Musculoskeletal/skin	2 (17)	2 (25)	
- Neurological	4 (33)	1 (13)	
- Respiratory	2 (17)	1 (13)	
- Sepsis	0 (0)	2 (25)	
- Trauma	1 (8)	2 (25)	
Day of ward admission studied (days)	4.3 ± 1.7 <sup>a</sup>	5.8 ± 1.0 <sup>b</sup>	N/A
Day of hospital admission studied (days)	16.5 [11.3, 32.3]	6.0 [5.0, 6.3]	N/A
Length of ICU admission (days)	10.2 [4.8, 16.6]	N/A	N/A
Length of hospital admission (days)	22.6 [18.0, 37.0]	10.8 [5.9, 12.6]	N/A
Hospital mortality	0 (0)	0 (0)	N/A
Dietetic consultation	6 (50%)	1 (13%)	N/A

Note: Data are presented as mean ± SD or median [IQR]. BMI is calculated as weight in kilograms divided by height in meters squared.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; GM, general medical; ICU, intensive care unit; PG-SGA, Patient-Generated Subjective Global Assessment.

<sup>a</sup>Number of days post-ICU discharge (ICU survivors).

<sup>b</sup>Number of days post-hospital admission (GM patients).

From the 24-h recall, ICU survivors consumed ~130 kcal more than GM patients (1612 [1033, 2192] vs 1486 [431, 1620] kcal) but ~180 kcal less than healthy volunteers (1794 [1545, 2440] kcal). The additional energy in the ICU survivors may be contributed to by oral nutrition supplements consumed by nearly 50% of these patients, which are known to contribute to energy intake.<sup>4</sup> In addition, more ICU survivors compared with GM patients (50% vs 13%) received a dietetic consultation, though this may be expected given their longer hospital stay 16.5 [11.3, 32.3] vs 6.0 [5.0, 6.3] days, respectively). Individualized nutrition support has been demonstrated to increase energy intake and improve outcomes in an RCT of GM patients<sup>10</sup> and may have had a similar impact for the ICU survivors seen by a dietitian in this study.

Less than 45% of participants in each group reported subjective problems with taste; yet the objective taste test demonstrated impaired taste across all groups when compared with previously published reference data.<sup>19,20</sup> A previous study reported lower taste identification in hospitalized patients compared with healthy volunteers ( $n = 174$  vs 65,  $8.7 \pm 2.6$  vs  $9.5 \pm 2.5$ ;  $P = 0.035$ ),<sup>20</sup> yet all our groups in our study scored values similar to the patient group in this study. Of note, our healthy cohort scored lower values and lower total score than reference values for age-matched groups (54% vs 69%).<sup>19</sup> Reasons for this are unclear and may relate to the specific taste identification methodology used, impeding the ability to detect differences between groups.

**TABLE 2** Nutrition intake data from the weighed buffet and 24-h diet recall in ICU survivors, GM patients, and healthy volunteers.

	ICU survivors	GM patients	Healthy volunteers
Weighed buffet meal	<i>n</i> = 12	<i>n</i> = 8	<i>n</i> = 25
Energy			
kcal	389 [288, 809]	426 [336, 592]	815 [654, 1165]
Protein			
g	19.4 [12.9, 39.8]	21.7 [14.6, 38.1]	46.4 [28.0, 64.1]
Carbohydrate			
g	40.8 [20.9, 83.9]	51.7 [36.4, 69.9]	111.7 [84.0, 130.3]
Fat intake			
g	18.1 [10.3, 27.4]	12.5 [5.4, 24.0]	22.8 [14.2, 38.6]
24-h recall	<i>n</i> = 10	<i>n</i> = 5	<i>n</i> = 25
Energy			
kcal	1612 [1033, 2192]	1486 [431, 1620]	1794 [1545, 2440]
Protein			
g	64.9 [51.0, 95.0]	54.8 [29.6, 61.7]	75.8 [64.5, 102.2]
Carbohydrate			
g	180.8 [116.9, 230.5]	231.1 [40.4, 247.3]	226.4 [197.6, 283.9]
Fat			
g	59.4 [41.6, 77.0]	33.1 [15.1, 37.2]	61.9 [46.0, 88.9]

Note: Data are presented as median [IQR].

Abbreviations: GM, general medical; ICU, intensive care unit.

Energy intake at the buffet was similar between patient cohorts despite self-reported hunger appearing higher in the ICU survivors, whereas post buffet, ICU survivors were less satisfied and reported a greater desire to eat. The inability for ICU survivors to eat to satisfaction is likely a result of other nutrition-impacting symptoms, such as fatigue, which was reported in 67% of ICU survivors in our study, with similar rates observed in other post-ICU cohorts.<sup>21</sup> These nutrition-impacting symptoms warrant further investigation.

A number of additional nutrition-impact symptoms were identified in our study, including survivors having reported a range of lower GI symptoms. Although data post-ICU is sparse, a systematic review of bowel motions in ICU reported rates of diarrhea at 3%–78% and constipation at 20%–83%,<sup>22</sup> with broad ranges likely the result of a lack of standardization in the definition and measurement of these GI symptoms.<sup>22–24</sup> Although limited quantification of appetite post-ICU exists, reduced appetite has been reported in 24%–38% of patients in the initial 7 days post liberation from mechanical ventilation,<sup>25,26</sup> and in non-ICU populations, loss of appetite has been associated with reduced oral intake.<sup>27</sup> These symptoms may be contributors to poor nutrition intake in ICU survivors, and strategies to mitigate these symptoms should be explored.

ICU survivors in our study experienced malnutrition (70%) and a reduced QoL. Malnutrition status was not assessed on admission to

ICU, therefore, it is unknown whether this was pre-existing or ICU-acquired, yet previous data show malnutrition prevalence increases over the hospital admission.<sup>28</sup> It is logical to investigate the role of nutrition in improving these outcomes.

A strength of this investigation is the prospective nature of the study with precise quantification of nutrients by weighed food intake and multiple factors that may affect it, using both subjective and objective measurement techniques. The key limitation is the small number of patients included, as such results of this study should be considered descriptive and hypothesis-generating only. Of those screened, only 11% of ICU survivors and 5% of GM patients were eligible to participate because of exclusion criteria that aimed to ensure this study was safe and feasible. Importantly, the patients able to participate may have been less unwell than those who were excluded or declined and, hence, may not be truly representative of the target patient groups, resulting in a potential overestimation of oral intake and underestimation of barriers. Similarly, as is common in ICU research, the heterogeneity within the cohorts is a limitation, particularly given the small sample size. There is incomplete data for some outcomes because of patients' fatigue or feeling unwell during data collection thus preventing data collection completion, further highlighting the challenges with research in this population group.

## CONCLUSION

Energy intake at a weighed buffet was observed to be reduced in hospital patients compared with healthy volunteers but similar between ICU survivors and GM patients. Hospital patients experience multiple nutrition-impacting symptoms, warranting exploration of strategies that aim to improve oral intake, such as dietetic intervention or oral nutrition supplements. Given the small cohorts included, these data should be considered hypothesis-generating, and the challenges of conducting physiological studies post-ICU should be carefully considered.

## AUTHORSHIP STATEMENT

Lee-anne S. Chapple, Matthew J. Summers, Karen L. Jones, and Michael Horowitz conceptualized and designed the research; Elizabeth Viner Smith, Lee-anne S. Chapple, Imre W. K. Kouw, Matthew J. Summers, and Rhea Louis conducted the research; Elizabeth Viner Smith performed the statistical analysis (with assistance from biostatistician Kylie Lange); Elizabeth Viner Smith and Lee-anne S. Chapple wrote the manuscript; Imre W. K. Kouw, Matthew J. Summers, Rhea Louis, Laurence Trahair, Stephanie N. O'Connor, Karen L. Jones, Michael Horowitz, and Marianne J. Chapman reviewed the manuscript and had intellectual input; and Elizabeth Viner Smith had primary responsibility for the final content. All authors read and approved the final manuscript.

## ACKNOWLEDGMENTS

The investigators would like to acknowledge: Anne Gatley (Registered Speech Pathologist, Royal Adelaide Hospital) for her assistance in ensuring the buffet meal met the appropriate International Dysphagia Diet Standardization Index criteria; ICU medical staff for their assistance in placing intravenous peripheral cannulas (Dr Eamon Raith, Dr Ewout Termote, A/Professor Mark Plummer, Dr Palash Kar, Dr Stanley Bart, and Dr Tejaswini Arunachala Murthy); and Ms Kylie Lange for her guidance of the statistical analysis. Open access publishing facilitated by The University of Adelaide, as part of the Wiley - The University of Adelaide agreement via the Council of Australian University Librarians.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Viner Smith E, Kouw IWK, Summers MJ, et al. Comparison of energy intake in critical illness survivors, general medical patients, and healthy volunteers: a descriptive cohort study. *J Parenter Enteral Nutr*. 2024;48:275-283. doi:10.1002/jpen.2612