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Citation for published version:

Merriweather, JL, Griffith, D & Walsh, T 2018, 'Appetite during the recovery phase of critical illness: a cohort study', *European Journal of Clinical Nutrition*. <https://doi.org/10.1038/s41430-018-0181-3>

Digital Object Identifier (DOI):

[10.1038/s41430-018-0181-3](https://doi.org/10.1038/s41430-018-0181-3)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

European Journal of Clinical Nutrition

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1 **Appetite during the recovery phase of critical illness: a cohort study**

2

3 **Running title**

4 Appetite in ICU survivors

5

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19

20 **Sources of Support**

21 The authors declare that they have no conflicts of interest. The RECOVER trial on which this

22 analysis is based is registered as ISRCTN09412438. The RECOVER trial work was supported by

23 the Chief Scientists Office, Scotland

24 **Abstract**

25 **Background/Objectives:** Reduced appetite is a recognised physiological symptom in survivors of
26 critical illness. Whilst reduced appetite has been reported by patients after ICU, quantification
27 using visual analogue scales has not been previously performed, and follow-up duration has been
28 limited. We aimed to describe appetite scores in ICU survivors during the first three months post
29 ICU discharge and explore association with systemic inflammation.

30 **Subjects/Methods:** Secondary analysis of data collected in a complex rehabilitation intervention
31 trial (RECOVER). A subgroup of 193 patients provided specific consent for inclusion in the blood
32 sampling sub-study during consent for the main study. We studied appetite using a visual analogue
33 scale (VAS); serum C-reactive protein (CRP); interleukin 1 β and 6 (IL-1 β and IL-6); and hand-grip
34 strength (HGS).

35 **Results:** Median (IQR) score on 0-10 appetite visual analogue scale was 4.3 (2.0-6.5) 1 week after
36 ICU discharge, improving to 7.1 (4.6-8.9) by 3 months (mean difference 1.7 (0.9-2.4) $p < 0.01$).
37 Number of days spent in an acute hospital following an intensive care stay was associated with
38 poorer appetite scores ($p = 0.03$). CRP concentration and appetite were significantly associated at 1
39 week after ICU discharge ($p = 0.01$), but not at 3 months after ICU discharge ($p = 0.67$).

40 **Conclusions:** ICU survivors experience reduced appetite during the acute recovery phase of
41 critical illness that could impact on nutritional recovery and this was associated with CRP
42 concentration 1 week after ICU discharge.

43

44 **Introduction**

45 Survivors of critical illness suffer physical weakness caused by acquired neuromuscular deficits
46 often superimposed on pre-existing frailty⁽¹⁾. Skeletal muscle loss is part of this deficit and
47 occurs early during critical illness^(2,3). Efforts to improve physical outcomes have so far been
48 unsuccessful⁽⁴⁻¹⁰⁾. Optimising nutritional state during the recovery phase of critical illness is an

49 integral part of physical rehabilitation and reduced appetite at this time may impact on nutritional
50 intake.

51 Malnutrition is observed frequently in ICU patients with many (43%) being clinically malnourished
52 on admission ⁽¹¹⁾. Nutritional status declines during critical illness, and on the post-ICU ward
53 ^(11,12). Malnutrition is associated with muscle loss and functional decline ⁽¹³⁻¹⁶⁾. Optimal nutritional
54 support for ICU survivors is therefore crucial to post-ICU recovery ⁽¹⁷⁾.

55

56 During the early recovery period (during the first 7 days after tracheal extubation), patients do not
57 achieve their calorific targets, and consume fewer than 50% of their estimated protein requirements
58 ⁽¹⁸⁾. ICU survivors also fail to meet their nutritional targets up to three months after ICU discharge
59 ⁽¹⁹⁾. Poor appetite during this period has been shown to be an important barrier to eating ⁽¹⁸⁾.

60

61 The mechanisms underlying appetite suppression in survivors of critical illness remain unclear.
62 Ghrelin, a 28 amino-acid peptide released from the stomach is an important regulatory hormone
63 controlling appetite and metabolism in humans ⁽²⁰⁾. There is conflicting evidence regarding serum
64 ghrelin concentrations in critically ill patients with some studies reporting decreased circulating
65 levels of ghrelin and others higher ghrelin concentrations compared with healthy controls ^(21,12).
66 Pro-inflammatory cytokines, have a central depressive effect on both food intake ⁽²²⁾ and appetite
67 ⁽²³⁾. A recent inflammatory biomarker study showed that there was a high prevalence of systemic
68 inflammation after ICU (70% at ICU discharge and 30% at 3 months) suggesting a prolonged
69 inflammatory response ⁽²⁴⁾. We hypothesise that inflammation during recovery from critical illness
70 suppresses appetite, and could have an important impact on physical outcome.

71

72 In this analysis we aimed to study the longitudinal course of appetite scores after ICU discharge. A
73 secondary aim was to explore the relationship between appetite and biochemical markers of
74 systemic inflammation.

75

76

77 **Materials/Subjects and Methods**

78 **Ethics**

79 This study was approved by the Scotland ‘A’ research ethics committee and conducted in
80 accordance with the Helsinki Declaration of 1975 as revised in 1983.

81

82 **Patients**

83 The RECOVER study was a randomised trial of increased hospital-based physical rehabilitation
84 versus standard ward care for survivors of critical illness. The trial protocol and main results have
85 been previously published (^{4,25}).

86

87 Briefly, patients were eligible for RECOVER if they were adult survivors of critical illness, were
88 ventilated for greater than 48 hours and were deemed fit for ICU discharge by the treating
89 physician. Exclusion criteria included a primary neurological diagnosis, receipt of palliative care,
90 receipt of home ventilation or under 18 years of age.

91

92 At recruitment into the study patients were randomised into either the control or intervention group.
93 Both groups received existing ward-based physiotherapy, dietetics, occupational and
94 speech/language therapy until hospital discharge. The intervention patients received enhanced
95 hospital-based physical rehabilitation that increased the frequency and intensity of rehabilitation
96 during their ward stay. This was delivered by a generic rehabilitation assistant (GRA) with
97 nutritional interventions including support and encouragement to eat and greater attention to
98 monitoring of nutritional intake.

99

100 The between-group comparison of outcomes in the trial found no clinically or statistically
101 significant differences in measures of physical function, health-related quality of life (HRQoL),
102 psychological morbidity or self-reported symptoms (²⁵), and therefore the patients were treated as a
103 single group for the purpose of this analysis.

104

105 A subgroup of 193 patients provided specific consent for inclusion in the blood sampling sub-study
106 during consent for the main study.

107

108 **Measurements**

109 Appetite was assessed in study participants 1 week after study entry (equating to 1 week after ICU
110 discharge), weekly until hospital discharge, and again at a follow up appointment 3 months after
111 study entry. In those patients discharged from hospital during the follow up period i.e. those that
112 did not die in hospital (death in hospital = 4 patients) or were not still in hospital 3 months after
113 enrolment (inpatient at 3 months = 12 patients), appetite scores were reported at hospital discharge.

114

115 Appetite assessment was conducted using a 10 centimetre visual analogue scale (VAS). At each
116 end of the line words described the minimum and maximum extremes of the characteristic being
117 measured with the low end to the left on a horizontal scale (²⁶). Individuals were asked to mark on
118 the line at the point they felt indicated how they were currently feeling. The score was determined
119 by measuring the distance from the left hand end on a horizontal scale to the point marked by the
120 individual (²⁷). VAS are a reliable and reproducible tool for assessing appetite (²⁸), however it has
121 not been validated in the post ICU patient population.

122

123 To explore the medium-term nutritional consequences of appetite suppression on nutritional status,
124 we measured hand-grip strength 3 months after study enrolment (²⁹).

125

126 We measured the serum concentration of C-reactive protein (CRP), interleukin 6 (IL-6) and
127 interleukin 1 β (IL-1 β) by ELISA (R and D systems) to detect the presence of on-going
128 inflammation during the recovery phase of critical illness. For this study, blood was analysed at
129 two time points corresponding to the first appetite assessment and the 3 month follow up
130 assessment.

131

132 **Statistical Analysis**

133 VAS appetite scores had a non-parametric distribution and are presented as medians with
134 interquartile ranges for each time point. Paired differences between baseline and follow up samples
135 were normal in distribution and a t-test was applied to compare this difference to zero.

136

137 To explore the association between inflammation and appetite, we calculated Kendall's tau
138 correlation co-efficient for the VAS appetite score and inflammatory biomarkers at the time of the
139 first appetite assessment (1 week after study entry), and follow up (3 months after study entry).

140

141 To explore the medium-term functional consequences of appetite suppression we tested the
142 association between appetite score at hospital discharge, and hand grip strength at the 3 month
143 follow up stage using the Spearman's rho correlation co-efficient. In addition, the sample was
144 divided into 2 groups above and below the median appetite VAS score. The mean hand grip
145 strength in each of these groups was compared using an independent samples t-test. To take into
146 account the effects of age and gender on hand grip strength, percentage predicted hand-grip strength
147 was calculated using population norms derived from a previous study (³⁰) and the above analysis
148 repeated.

149

150 The correlation coefficients used in the analysis were selected on the basis of distributions and can
151 be justified (data not shown).

152

153 **Results**

154 **Patients and completeness of data**

155 240 patients were recruited to the RECOVER study between December 2010 and January 2013.

156 228 (95%) were followed up to 3 months. The baseline characteristics of the cohort are described

157 in Table 1. At the time of first assessment (1 week after study entry), 152 patients had appetite

158 VAS score measured. At final assessment, 188 patients had appetite VAS score measured.

159

160 193 patients (80%) gave consent for inclusion in the blood sampling sub-study. At the first

161 assessment (1 week after study entry), 109 patients had CRP, IL-1 β , and IL-6 measured. At the

162 final assessment, 123 patients had CRP measured, 120 patients had IL-6 and 120 patients had IL-1 β

163 measured.

164

165 **Appetite**

166 Appetite scores at each time point are presented in Figure 1. Median VAS appetite score was low

167 (below 5cm) at each time point until after ICU discharge. There was an improvement in appetite

168 from a median (IQR) of 4.3 (2.0-6.5) to 7.1 (4.6-8.9) during the first 3 months. The mean (95% CI)

169 for this difference was 1.7 (0.9 – 2.4) (p=0.000).

170

171 To illustrate change in appetite over time, patients available for assessment at both baseline and 3

172 months (n=130) were divided into 4 groups according to their appetite scores. The percentage of

173 patients within each group at each time point are illustrated in Figure 2.

174

175 **Post-hoc analysis**

176 For patients staying in hospital for many weeks after ICU discharge appetite scores appeared to be

177 particularly low (Figure 1). To explore this further, mean appetite scores were calculated for each

178 patient during their post-ICU hospital stay and the correlation between the number of days in
179 hospital after enrolment in RECOVER, and mean appetite score during hospitalisation was
180 calculated. Spearman's rho was -0.231 ($p=0.030$) for this correlation suggesting that patients who
181 spent longer periods in the acute hospital post ICU discharge was associated with poor appetite. To
182 illustrate this point, Figure 3 shows the appetite scores in the weeks following ICU discharge for
183 patients who spent ≤ 5 weeks in hospital ($n=130$) versus those spending >5 weeks in hospital
184 ($n=30$). Note those patients discharged home prior to 1 week after enrolment had no appetite score
185 measured in hospital and were not considered.

186

187 In the patients that were discharged from hospital alive ($n=141$), the median (IQR) appetite VAS
188 was 5.0 (3.0-8.0) at hospital discharge.

189

190 **Appetite and functional outcome**

191 There was no significant association between appetite at hospital discharge and predicted handgrip
192 strength at the 3-month follow up point (Pearson Correlation 0.032; $p=0.756$).

193

194 **Appetite and inflammation**

195 A summary of the analysis is given in Table 2. There was a significant correlation between CRP
196 concentration and appetite VAS at the first assessment point (Kendall's tau B -0.159 ($p=0.018$)). At
197 the 3-month assessment, the correlation was not significant (Kendall's tau B -0.026; $p=0.67$). There
198 was no significant association between IL-6 at first or follow up assessment. IL1- β was
199 undetectable in the majority of patients throughout the study and therefore formal tests of
200 correlation were not conducted for this molecule.

201

202 **Discussion**

203 **Appetite suppression**

204 In this paper we confirm the findings of previous studies that identified appetite suppression to be a
205 significant symptom in the early days of post-ICU recovery. In addition, we have shown that loss
206 of appetite is sustained during the period of post-ICU hospitalisation.

207

208 In contrast to previous studies, we have also identified appetite suppression at the point of hospital
209 discharge, a crucial transition in the nutritional care of ICU survivors. Although hospital discharge
210 defines the point where patients are physically able to cope with some activities of daily living, it is
211 also the point when the acute care rehabilitation, including dietetic input ceases (³¹) and a time when
212 even modest dietetic input can lead to nutritional and functional gains (³²).

213

214 Nutritional care is a key component of physical recovery after critical illness (¹⁷). Traditional
215 approaches to nutritional rehabilitation focus on supplementing hospital food to achieve nutritional
216 targets, approaches that fail when appetite is suppressed and patients have little inclination or
217 motivation to eat (¹²). With the knowledge that ICU patients suffer sustained appetite suppression,
218 efforts to improve post-ICU nutritional status must now focus on efforts to improve or circumvent
219 appetite suppression. In addition, greater efforts must be made to equip patients with information
220 and advice to help them recognise and overcome this common and limiting symptomatology after
221 hospital discharge.

222

223 Pharmacological modification of appetite in these patients may be possible in the future. Recent
224 animal studies have suggested the potential role of ghrelin as a future potential therapeutic utility to
225 stimulate feeding and growth hormone secretion by promoting gastric peristalsis and generating
226 hunger sensations (^{33,34}) In healthy humans, higher levels of ghrelin are seen during periods of
227 fasting and vice versa after meal, which are associated with elevated insulin and low glucose levels
228 (^{20,33,36}). There is a paucity of data with regard to the relationship between appetite and calorie
229 intake with ghrelin levels after ICU discharge.

230

231 More practical measures to promote nutritional intake in patients with poor appetite include offering
232 small frequent meals and the provision of energy dense foods ⁽³⁷⁾. Previous work has shown that
233 providing three meals a day is seen as a deterrent to post ICU patients with small appetites who find
234 larger meals off-putting ⁽³¹⁾.

235

236 The social nature of eating is an important contributor to increased food intake with energy intakes
237 increased by 36% in patients using a dining room compared to those who ate beside their bed ⁽³⁸⁾.
238 However, the application of this solution may require some creativity in a post-ICU cohort, many of
239 whom may be nursed in isolation for infection control reasons or experience reduced mobility due
240 to critical illness related muscle weakness.

241

242 The effect of exercise on appetite has been widely studied with a body of evidence suggesting that
243 an acute bout of exercise does not result in an increase in appetite and food intake ⁽³⁹⁻⁴¹⁾. It is now
244 widely reported that vigorous exercise can transiently suppress appetite ⁽⁴²⁾ however this response
245 is short lived and is not observed in low or moderate intensity exercise ⁽⁴³⁾. In the RECOVER
246 study ⁽²⁵⁾ there was no difference in appetite at 3 months between the intervention and control
247 groups, but we were unable to assess the impact of exercise frequency or intensity on appetite.

248

249 Critical illness is characterised by systemic inflammation, a defensive response carefully regulated
250 by circulating inflammatory cytokines. In many patients inflammation is sustained beyond ICU
251 discharge ⁽²⁴⁾. Previous studies have shown a possible role for inflammation in appetite
252 suppression in non-critically ill populations. Patients undergoing haemodialysis have appetite
253 suppression in association with higher concentrations of pro-inflammatory cytokines ⁽⁴⁴⁾. Poor
254 appetite was also linked to increased mortality, higher rates of hospitalisation and reduced quality of

255 life. Similar findings have been shown in patients with advanced cancer where increased levels of
256 inflammation were associated with a number of symptoms including pain, fatigue and anorexia⁽⁴⁵⁾.

257

258 One of the best-described pro-inflammatory cytokines is interleukin 1 β , which is known to exert a
259 profound depression of appetite mechanisms⁽²³⁾. Unfortunately, in our study IL1- β was
260 undetectable in the majority of patients, therefore we were unable to include this molecule in our
261 analysis. Tumor-necrosis factor- α (TNF- α) and interleukin-6 are the other pro-inflammatory
262 cytokines known to induce anorexia⁽⁴⁶⁾. The mechanisms by which these cytokines affect the
263 central nervous system controls of food intake are not fully understood⁽²²⁾. Through signalling in
264 the hypothalamus, the pro-inflammatory cytokines activate neuro-pathways that repress the desire
265 for food. These cytokines also activate signalling from the autonomic nervous system modulating
266 gastric motility and emptying. Additionally the cytokines stimulate the release of hormones that
267 suppress food intake such as leptin and insulin⁽⁴⁷⁾.

268

269 In our study, we found that patients with higher C-reactive protein concentrations soon after ICU
270 discharge had poorer appetite scores suggesting a potential role for systemic inflammation in post
271 intensive care appetite suppression, but found no association between CRP and appetite at 3 months
272 or IL-6 and appetite at either 1 week or 3 months.

273

274 In previous work, we explored risk factors for appetite at 3, 6, and 12 month time points after ICU
275 and found illness severity to be insignificant when compared to pre-ICU factors⁽⁴⁸⁾. Whether this
276 is the case for earlier time points remains unknown, but certainly the association with pro-
277 inflammatory mediators suggests that ongoing pathology may play a role.

278

279 There are several weaknesses of the study. First, this is a post-hoc analysis and the original
280 RECOVER trial was not powered to detect the correlations explored. Second, our measure of

281 appetite has not been used in this cohort previously and we have no control group to compare our
282 patients to. It is therefore difficult to determine whether the appetite scores noted in our results
283 could be considered normal, poor, or good. Third, we did not measure oral intake or calorific
284 consumption in this study so could not assess the impact of appetite suppression on eating
285 behaviour. Fourth, the cohort is representative of a ventilated mixed medical/surgical cohort, but it
286 is worth noting that a significant proportion had a GI diagnosis, potentially resulting in more severe
287 appetite suppression, depending on the comparator population.

288

289 **Conclusions**

290 ICU survivors experience a suppressed appetite during the acute recovery phase of critical illness.
291 Inflammation was found to be associated with appetite at time points close to ICU discharge
292 suggesting possible modifying effect of systemic inflammation on appetite in the early post-ICU
293 period, a crucial time for nutritional intervention. Nutritional management of ICU survivors should
294 include ways to maximise intake in order to help circumvent the suppression of appetite
295 encountered by this patient group, and modification of the inflammatory response may be a future
296 avenue for investigation.

297

298 **Conflict of Interest**

299 The authors declare that they have no conflicts of interest. The RECOVER trial on which this
300 analysis is based is registered as ISRCTN09412438. The RECOVER trial work was supported by
301 the Chief Scientists Office, Scotland

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429 Table 1: Participant characteristics at randomization.

430 Table 2: Kendall's tau correlation coefficients of inflammatory biomarkers with appetite visual
431 analogue scores.

432

433 Figure 1: Appetite scores by week after ICU discharge. Grey shading indicates the number of
434 patients assessed at each time. Only patients remaining in hospital had appetite VAS recorded
435 which explains the decline in n number but we aimed to assess all patients surviving to 3 months.

436

437 Figure 2: For patients with complete data, change in appetite score category between baseline and 3
438 months (n=130 patients).

439

440 Figure 3: Appetite scores after ICU discharge (median (IQR)). Square markers denote patients
441 staying in hospital up to 5 weeks after ICU discharge (n=130). Round markers denote patients
442 staying in hospital greater than 5 weeks after ICU discharge (n=30).

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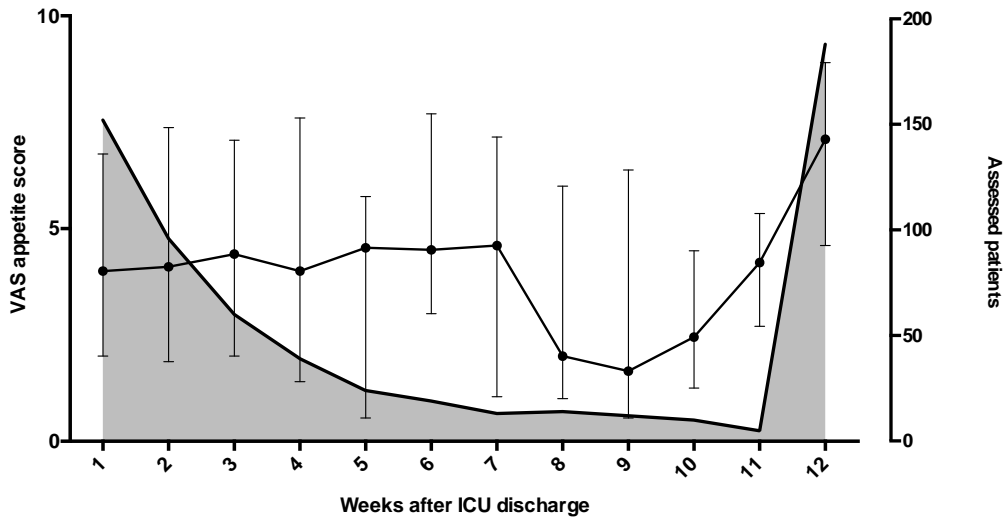
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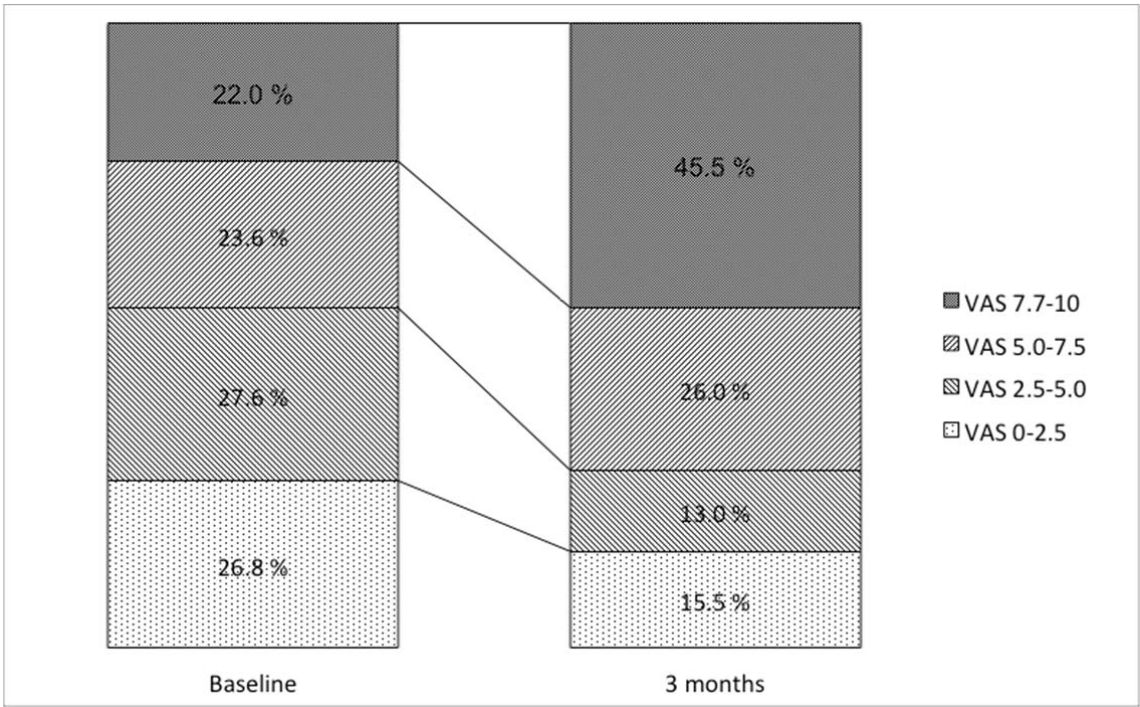
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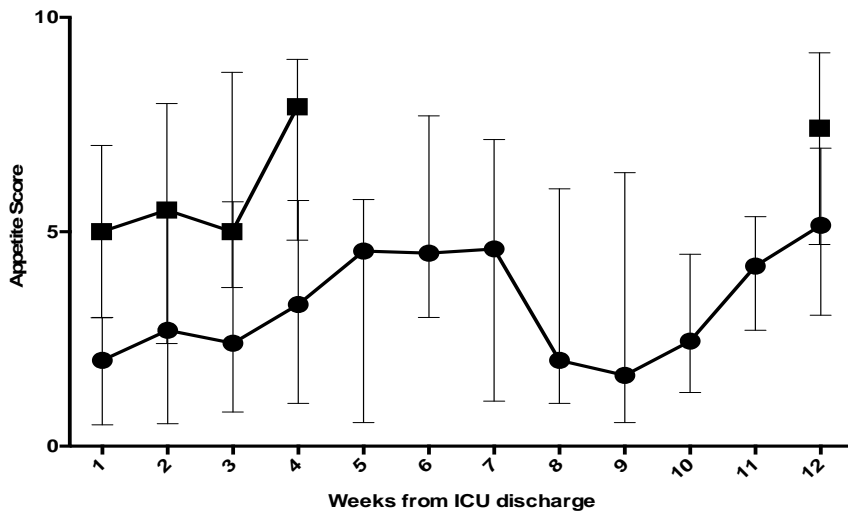
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Appetite VAS scores after ICU discharge







	RECOVER cohort (n=240)
Male N (%)	137 (57)
Age (median (1 st ;3 rd quartiles))	62 (52, 70)
Days of ventilation in ICU (median (1st ;3rd quartiles))	8 (5,15)
APACHE II score (median (1st ;3rd quartiles))	20 (16,25)
ICU admission diagnosis category N (%)	
<i>Respiratory</i>	84 (35)
<i>Cardiovascular</i>	70 (29)
<i>Gastrointestinal</i>	59 (25)
<i>Neurological</i>	12 (5)
<i>Trauma</i>	8 (3)
<i>Renal diagnosis</i>	4 (2)
<i>Miscellaneous diagnoses</i>	3 (1)
Well-nourished N (%)	107 (45)
Moderately malnourished N (%)	105 (43)
Severely malnourished N (%)	28 (12)
Ward destination N (%):	
Medical	135 (56)
Surgical	105 (44)

		Kendall's tau	p
CRP	1 week	-0.159	0.018
	3 months	-0.026	0.676
IL-6	1 week	-0.122	0.271
	3 months	0.008	0.897