Percentage from Target Weight (PFTW) Predicts Re-hospitalization in Adolescent Anorexia Nervosa

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ABSTRACT

Background: The aim of the current study was to investigate whether the percentage of the discharge weight relative to recommended target weight (PFTW) during inpatient treatment predicts re-hospitalization in adolescent anorexia nervosa (AN).

Method: 51 hospitalized adolescents with AN were weighed and completed self-reports on admission and discharge. We examined reports regarding re-hospitalization within the first year after discharge.

Results: 19 patients (37.25%) required re-hospitalization. The proportion of the actual discharge weight relative to target weight (PFTW), previous re-hospitalizations and parental marital status were found to be significant predictors of re-hospitalization.

Conclusions: The study highlights the importance of discharge weight relative to target weight (PFTW) for long-term outcome. Failure to obtain discharge target weight is a significant predictor of re-hospitalization in adolescent AN.

INTRODUCTION

Among psychiatric illnesses, eating disorders are unique as patients have both physical and psychological disturbances (1). The restoration of healthy body weight is one of the key goals in the treatment of anorexia nervosa (AN) (1, 2). The role of inpatient hospitalization in the treatment of AN among adolescents has been a focus of debate (3-6). However, nutritional rehabilitation remained an essential component of inpatient treatment of adolescent AN (2). The goals of refeeding and weight restoration are often time consuming. Managed care companies frequently fail to provide approval for the ample length of stays required to provide proper care (7, 8).

On the one hand, recent studies support the use of a more rigid approach to nutritional rehabilitation in order to decrease hospital stays and improve social reintegration and post-hospitalization functioning (9-11). On the other hand, shorter hospitalizations do not appear to be effective for adolescent AN patients (8). There are higher rates of readmissions as the length of stays decreases (8). In addition, discharge at lower weights has been associated with increased relapse rates and poorer prognosis (12).

Alternative approaches to weight restoration are based on findings indicating that adolescent patients suffering from AN may also achieve target weight in less restrictive, less expensive settings (5, 13). For example, a recent study demonstrated that for adolescent patients with non-chronic AN, day-patient treatment (DP) (after short inpatient care) is not less effective than inpatient treatment (IP) – both for weight restoration and weight maintenance during the first year after admission. Thus, DP might be a safe and less costly alternative to IP (13).

However, common practice highlights weight restoration to be the gold standard of good clinical practice in adolescent AN. This is supported by findings indicating that weight gain during inpatient treatment as well as weight maintenance afterward are important prognostic factors (13). Studies have found that inpatients with AN who left treatment while still underweight had a poorer outcome.
and a higher risk for relapse than those who completed treatment and obtained target weight (12, 14-16).

A study by Kaplan et al. (17) conducted with a mixed sample of adolescents and young adults with AN indicated that body mass index (BMI) at discharge from an inpatient unit and the rate of weight loss within the following 28 days were the strongest predictors of BMI maintenance during the first 6 to 12 months following discharge. The authors defined discharge weight as BMI (kg/m²)>19.0. They concluded that weight maintenance after discharge may be improved by helping patients achieve a higher BMI during the weight-restoration phase of treatment.

Similarly, in a long-term multisite retrospective follow-up of 8.3 years, Steinhausen et al. (18) found that 44.8% of adolescent patients with AN required at least one re-hospitalization after inpatient treatment. The authors found that “insufficient weight gain” during first admission and the resulting lower BMI at discharge were risk factors for re-hospitalization. However, they provided no information regarding the definition of target weight at first admission. The retrospective design of the study and the lack of standardized treatment or discharge criteria are significant limitations of this study.

On the other hand, in a one-year follow-up Castro et al. (19) found that even after total weight restoration during first admission to inpatient treatment, 25 out of 101 (24.8%) adolescent patients with AN still required re-hospitalization. In this study, BMI at discharge did not emerge as a significant outcome predictor. In addition, there was no target weight definition (19). In another study investigating outcome within one year after inpatient treatment of adolescent AN, Salbach-Andrae et al. (20) found only BMI at admission and psychiatric comorbidity to be significant outcome predictors. BMI at discharge was not included as a predictor for future admissions. Moreover, no clear target weight criteria were included in the program description.

In this new era guided by principles of cost-effectiveness and featuring less coercive, less restrictive day-treatments for adolescent AN, there is a renewed interest to evaluate whether obtaining target weight within inpatient treatment is important. The current study had two main goals. The first was to investigate the impact of achieving target weight at discharge on re-hospitalization within the first year. For that purpose we used the variable PFTW (percent from target weight), which enabled us to examine the discharge weight percentage from the recommended target weight. The second aim was to identify demographic and psychological predictors of re-hospitalization. These questions were explored within the unique setting of a medical psychiatric unit, based on an open, voluntary, motivation-oriented intervention with high parental involvement and early community exposure (21).

METHOD

PARTICIPANTS

The sample consisted of 51 adolescent patients (males=5, females=46) between the ages of 11.8 to 18.8 years (Mean=14.98, SD=1.81). All were hospitalized between the years 2009-2013 in a child and adolescent medical psychiatric unit specializing in eating disorders. All were diagnosed with AN - restrictive (AN-R, n=44, 86.27%) or binge/purging (AN-B/P, n=7, 13.73%) subtypes (1).

Due to the patients’ young age, some of the diagnostic criteria for AN were not always relevant for diagnosis (especially the menstrual criterion). Thus, although evaluated using the DSM-IV, the patients’ diagnoses are also congruent with the new criteria of DSM-5 (1). Patients arrived at the unit upon referrals from physicians or community psychiatrists. In other cases, they transferred from other pediatric units within the medical center (5).

Two patients were excluded from the original sample (N=53) after they were discharged because they required more restrictive psychiatric care due to serious psychological comorbidity and insufficient weight gain. Two of the participants included in the sample were admitted while they were minors but became adults during the follow up. Thirteen out of the 51 patients (25.5% of total sample) had not reached target weight upon discharge. Baseline characteristics of these patients were not significantly different from those who obtained target weight.

PROCEDURE

The protocol of the research project has been approved by the Ethics Committee of the Medical Center’s Institutional Review Board (IRB). It conforms to the provisions of the Declaration of Helsinki. The patients and their parents received explanations regarding the aims and procedures of the study. A written consent was obtained from patients and parents and anonymity was guaranteed.

The unit’s director (SF) assessed the patients for clinical diagnoses. Patients were diagnosed based on information from clinical interviews, observation, parents’ reports and medical evaluations (5). In addition, the adolescents filled in self-report questionnaires at the beginning (first two weeks) and at the end (last two weeks) of their inpatient treatment. The questionnaires were an integral part of clinical assessment.
and provided information about eating disorder symptoms, depression, anxiety and suicidal ideation. Re-hospitalization was defined as patient admission to a psychiatric or specialized eating disorder unit due to acute AN symptoms including weight loss within a year of discharge from the unit. Since patients could be hospitalized in any other hospital in Israel, re-hospitalization information was based on a combination of sources: The OFEK system (an official national computerized registry), family physicians’ reports, reports from the admitting unit as well as parents’ reports.

**TREATMENT PROGRAM**

The Child and Adolescent Medical Psychiatric Unit is an open, voluntary inpatient facility that specializes in the treatment of body-mind pathologies and eating disorders (22). Patients are mostly adolescents, with ages ranging from 6 to 18 years at admission. The treatment program has two phases: an intensive inpatient phase and a shorter phase of a half-day outpatient program. This two-phase structure exemplifies the community-based orientation of the program allowing patients reintegration into the community. A few weeks after admission a target weight is established. Target weight determination includes processing genetic, developmental and medical information. Parents and patients are informed about the final decision and from then on the exact individual “target weight” becomes the final weight goal that allows the discharge from the program (after two weeks of target weight maintenance). The target weight is defined as a range of 2 kg from a minimal recommended weight.

The unit clinical dietician sets the patients’ target weight, taking into consideration different psychological and physical variables such as age, current weight and growth potential. Patients’ goal is to gain a minimum of 500 grams per week. According to Golden et al. (11), setting target weight for adolescent patients must be an individualized process, taking into account pubertal stage, prior growth percentiles, growth potential, height and age. Treatment target weight is the weight at which the patient is well functioning medically. For girls, it is when menstruation and ovulation are restored. When patients attain target weight, they transfer into a half-day outpatient treatment format.

Treatment is voluntary and patients refusing hospitalization are referred to other psychiatric facilities with more restrictive programs, or discharged back into community settings according to their medical condition (fewer than 5%) (5). Patients requesting discharge prior to achieving the target weight are discharged against medical recommendation and are put under a social worker legal supervision.

The two-phase program integrates behavioral/motivational elements and focuses on weight restoration through structured group-supervised meals. The adolescents are under dietary supervision and are weighed twice a week (5). Individual therapy integrates Cognitive Behavioral Therapy (CBT) and dynamic principles and consists of twice-a-week sessions. The program includes weekly parental guidance and family-oriented therapy, as well as a variety of group therapies (e.g., psychodrama, nutrition, dynamic group therapy).

Weight restoration is the primary goal during the inpatient phase and secondary goals include active participation in the treatment program, and improvement of eating habits and communication skills. Patients who achieve their weekly goals move up in seven successive “functioning/therapeutic levels” that define the level of responsibility patients are prepared to assume, their privileges on the unit, and the degree of home and community exposure they can handle. The program includes no use of coercive measures (5).

During the second phase of the half-day outpatient program, the adolescents attend the unit twice a week for two weeks, with the same therapeutic components offered. The major aim of this phase is maintenance of target weight over time until final discharge (5).

**INSTRUMENTS**

**Diagnostic information:** We diagnosed patients based on clinical interviews, patients’ observation, parental information and medical evaluations. The head of the unit (SF) performed all evaluations. We measured the patients’ weight twice per week and height three times during hospitalization. BMI was calculated and we recorded BMI percentiles as well.

**Demographic questionnaire:** This self-report questionnaire includes personal details such as gender, age, education, place of birth, nationality, religion, family status (i.e., intact family/ not intact family). In addition, the questionnaire includes items related to clinical features of the patient’s eating disorder including weight, height, nutrition, minimal and maximal weight, previous hospitalizations, and onset and duration of eating problems.

**Eating Disorders Examination Questionnaire (EDE-Q) (23):** This self-report questionnaire assesses attitudes and behaviors related to eating disorders. It consists of 28 items that compose four subscales: weight concern, shape concern, eating concern and dietary restraint. Each item is rated on a scale of 0 (none) to 6 (every day). Higher scores reflect greater severity or higher frequency of symptoms during the previous 28 days. The sum of the subscales...
In order to evaluate the relative predictive power of each variable, we entered a selection of predictors for each block of variables that significantly differed between the groups. The model and the specific variables were all significant. Taken together, these variables correctly predicted 36% of patients who were re-hospitalized.

Nine out of the 51 patients did not complete the discharge assessment questionnaire (missing data). For the statistical analysis, we considered these patients as the intent-to-treat group. We used t-test for independent samples to analyze differences between those nine patients (intent-to-treat group) and the remainder of the sample. We found no significant differences between those groups in baseline characteristics, and therefore we report the full sample (N=51). In the intent-to-treat analysis, the admission scores of the nine patients who did not have the discharge assessment data were carried forward.

RESULTS

Of the 51 adolescents in the sample, 19 adolescents (37.25%) (males=1; females=18) were re-hospitalized during the first year after discharge. The average time between discharge and re-hospitalization was 5.4 months (SD= 3.8).

The percent from the target weight (PFTW) measure was found to significantly differ between the groups (t=2.47, P <0.05). In the re-hospitalization group, the PFTW was significantly lower (M=98.18%, SD=0.04%) in comparison to the non-re-hospitalization group (M=101.15%, SD=0.03%). Patients who had been hospitalized before the current hospitalization showed a higher rate of re-hospitalization relative to patients for whom the current hospitalization was their first one (χ² = 5.78, p < 0.05).

In addition, patients whose parents were not married showed a higher rate of re-hospitalization (χ² = 4.401, p < 0.05) relative to those whose parents were married. However, we found no significant differences between the re-hospitalization group and the non-re-hospitalization group in other demographic characteristics such as gender, age, education, weight, height, BMI at admission, onset and duration of the eating disorder (Table 1). Moreover, we found no significant differences in eating disorder symptomatology, depressive symptomology and suicidal ideation between these two groups (Table 2).

LOGISTIC REGRESSION PREDICTING RE-HOSPITALIZATION:

In a Logistic Regression, we examined the predictive power of the all variables that we found in the previous analysis to significantly differ between the groups. The block of variables included demographic characteristics such as PFTW, number of previous re-hospitalizations and parental marital status. The model and the specific variables were all significant. Taken together, these variables correctly predicted 36% of patients who were...
Percentage from target weight predicts re-hospitalization

Discussion

The aim of the current study was to examine whether the percentage of actual weight at discharge from the recommended target weight during inpatient intensive weight restoration predicts re-hospitalization among adolescent diagnosed with AN. The main finding of this study is that PFTW at discharge was significantly lower among patients who were later re-hospitalized (the re-hospitalization group) relative to patients who were not. Patients in the re-hospitalization group reached discharge in a weight that was lower than their recommended target weight.

Table 1. Differences between Patients Who Were Re-hospitalized (N=19 (37.25%) and Patients Who Were Not (N=32 (62.74%)

<table>
<thead>
<tr>
<th>Re-hospitalization</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
<th>df</th>
<th>t</th>
<th>x²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male-1 (5.2%)</td>
<td>Female-18 (94.8%)</td>
<td>Male-4 (12.5%)</td>
<td>Female-28 (87.5%)</td>
<td>Male-5 (9.8%)</td>
<td>Female-46 (90.2%)</td>
</tr>
<tr>
<td>Age</td>
<td>14.60 (1.53)</td>
<td>Range 12-17</td>
<td>15.21 (1.94)</td>
<td>Range 11.8-18.8</td>
<td>14.98 (1.81)</td>
<td>Range 11.8-18.8</td>
</tr>
<tr>
<td>Type AN</td>
<td>Purging -4 (21.05%)</td>
<td>Restrictive -15 (78.94%)</td>
<td>Purging -3 (9.37%)</td>
<td>Restrictive -29 (90.62%)</td>
<td>Purging -7 (13.72%)</td>
<td>Restrictive -44 (86.27%)</td>
</tr>
<tr>
<td>Social Economic Status</td>
<td>High-0 (6%)</td>
<td>Mid-11 (57.89%)</td>
<td>Low-0 (0%)</td>
<td>Unknown-8 (42.10%)</td>
<td>High-2 (6.25%)</td>
<td>Mid-25 (78.12%)</td>
</tr>
<tr>
<td>Place of birth</td>
<td>Israel-17 (89.4%)</td>
<td>Other-2 (10.52%)</td>
<td>Israel-30 (93.75%)</td>
<td>Other-2 (6.25%)</td>
<td>Israel-47 (92.15%)</td>
<td>Other-4 (7.84%)</td>
</tr>
<tr>
<td>Family status of parents</td>
<td>Married-11 (57.89%)</td>
<td>Not married-8 (42.10%)</td>
<td>Married-27 (84.37%)</td>
<td>Not married-5 (15.62%)</td>
<td>Married-38 (74.50%)</td>
<td>Not married-13 (25.49%)</td>
</tr>
<tr>
<td>Duration of illness (in years)</td>
<td>2.11 (0.99)</td>
<td>Range 0-13.5</td>
<td>2.25 (3.3)</td>
<td>Range 0-13.5</td>
<td>2.2 (3.19)</td>
<td>Range 0-13.5</td>
</tr>
<tr>
<td>Duration of Hospitalization (in days)</td>
<td>112 (69.58)</td>
<td>Range 12-274</td>
<td>113.81 (34.83)</td>
<td>Range 53-181</td>
<td>113.13 (49.96)</td>
<td>Range 12-262</td>
</tr>
<tr>
<td>Previous hospitalization</td>
<td>Yes-6 (31.57%)</td>
<td>No-13 (68.42%)</td>
<td>Yes-2 (6.25%)</td>
<td>No-30 (93.75%)</td>
<td>Yes-8 (15.68%)</td>
<td>No-43 (84.31%)</td>
</tr>
<tr>
<td>PFTW-percent from target weight</td>
<td>98.18% (0.37%)</td>
<td>Range 86-104%</td>
<td>101.15% (0.03%)</td>
<td>Range 99-109%</td>
<td>100% (0.04%)</td>
<td>Range 86-109%</td>
</tr>
<tr>
<td>BMI admission</td>
<td>16.44 (1.80)</td>
<td>Range 12-19.6</td>
<td>16.39 (2.01)</td>
<td>Range 13-11.22.7</td>
<td>16.41 (1.91)</td>
<td>Range 12-22.7</td>
</tr>
<tr>
<td>BMI discharge</td>
<td>19.56 (1.05)</td>
<td>Range 16.9-21.2</td>
<td>19.89 (1.19)</td>
<td>Range 17.5-23.41</td>
<td>19.77 (1.14)</td>
<td>Range 16.9-23.41</td>
</tr>
<tr>
<td>Weight loss (in kg)</td>
<td>10.55 (4.35)</td>
<td>Range 3.5-22</td>
<td>15 (16.4)</td>
<td>Range 3.5-89</td>
<td>13.34 (13.34)</td>
<td>Range 3.5-89</td>
</tr>
</tbody>
</table>

* = p<0.05, ** = p<0.01

Table 2. Differences in Characteristics at Admission and Discharge between Patients with (N=19) and without (N=32) Re-hospitalization

<table>
<thead>
<tr>
<th>Re-hospitalization</th>
<th>T1 - Admission</th>
<th>T2 - Discharge</th>
<th>F</th>
<th>T1 - Admission</th>
<th>T2 - Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDE total</td>
<td>3.66 (1.39)</td>
<td>3.11 (1.79)</td>
<td>1.11</td>
<td>3.13 (1.80)</td>
<td>2.58 (1.77)</td>
</tr>
<tr>
<td>EDE Subscales</td>
<td>3.85 (1.74)</td>
<td>3.31 (2.30)</td>
<td>0.66</td>
<td>3.22 (2.14)</td>
<td>2.42 (2.10)</td>
</tr>
<tr>
<td>EDE-eating concern</td>
<td>2.89 (1.59)</td>
<td>2.58 (1.69)</td>
<td>0.36</td>
<td>2.31 (1.96)</td>
<td>1.84 (1.89)</td>
</tr>
<tr>
<td>EDE-weight concern</td>
<td>4.44 (1.77)</td>
<td>3.75 (2.21)</td>
<td>1.10</td>
<td>3.81 (2.52)</td>
<td>2.00 (1.90)</td>
</tr>
<tr>
<td>EDE-shape concern</td>
<td>4.83 (1.56)</td>
<td>3.99 (2.21)</td>
<td>1.76</td>
<td>4.37 (2.18)</td>
<td>3.97 (2.31)</td>
</tr>
<tr>
<td>BDI</td>
<td>21.00 (14.8)</td>
<td>19.62 (10.23)</td>
<td>0.17</td>
<td>16.46 (13.75)</td>
<td>13.46 (12.58)</td>
</tr>
<tr>
<td>SIQ</td>
<td>35.44 (23.43)</td>
<td>26.95 (17.41)</td>
<td>1.93</td>
<td>37.92 (19.36)</td>
<td>31.75 (21.22)</td>
</tr>
</tbody>
</table>

* = p<0.05, ** = p<0.01

Re-hospitalized (χ²=15.84, p<0.01). Table 3 presents the Logistic Regression for prediction of re-hospitalization.
Despite these limitations, our study highlights the importance of achieving full target weight during inpatient stays (15-17). A study on adults with AN found that patients who achieved 90% or less of their target weight at the time of transfer to a day hospital program were more likely to be re-hospitalized (16). The current study further demonstrates that reaching the target weight in full is also highly important among adolescents. It seems that even little less than 100% of target weight means a higher risk for re-hospitalization. This finding is in line with the recommendation by Howard et al. (16), who recommend a restoration of 100% of the target weight before transferring a patient to a less intensive level of care. They further claim that reaching less than normal body weight at discharge from inpatient settings is one of the most important predictors of short-term anorexic relapse.

Traditionally, the field of AN has focused on the significance of objectively low body weight, often measured by body mass index (BMI) (29). In contrast, we did not find BMI at admission and discharge to be variables with significant predictive power. This finding is consistent with a previous study (19) and partially consistent with Salbach-Andrae et al. (20), who found BMI at admission, but not at discharge, to be an important factor for outcome prediction. Based only on height and weight, without accounting for unique phenomena such as short stature or stunted linear growth due to malnutrition, BMI may be less sensitive of a measure (29), particularly with adolescents. It is also possible that a relative weight measure such as PFTW is more effective than BMI in measuring clinical outcomes such as re-hospitalization.

Our study also indicates that 37.25% of adolescent patients with AN were re-hospitalized during the first year following their discharge from inpatient treatment. This rate is higher than the rate found in the study by Castro et al. (19), which similarly examined re-hospitalization among adolescent patients within one-year follow-up. The higher re-hospitalization rate in our study may be explained by differences between our sample to the one used by Castro and colleagues. Castro et al.’s sample included patients who had their first inpatient stay and reached discharge after achieving a complete weight recovery. By contrast, in our sample eight patients (15.68%) had previous hospitalizations and 13 (25.5%) did not obtain target weight at discharge.

An additional finding of our study indicates the significant correlation between family status and re-hospitalization. This finding is consistent with findings from previous studies (30, 31). Perhaps single or divorced parents have fewer resources to prevent relapse. Perhaps such parents fit less well to deal with the specific demands characterizing the recovery process of anorexic patients (e.g., supervised home meals). However, it seems difficult to form any firm conclusions about the association between family status and re-hospitalization without a better understanding of variables such as perceptions of family relations and attachment style.

Unlike other studies, no significant demographic differences were found between patients in the different groups. For example, age predicted re-hospitalization in the study by Castro et al. (19), but in our study, we found only a non-significant trend toward a higher re-hospitalization rate among younger patients. AN subtype was also not found to have a predictive value. In this regard, it is noteworthy that only 13.71% of the patients in our sample were purging, a lower rate in comparison to the study by Castro-Fornieles et al. (32), in which 25% of patients were with AN, purging subtype. Due to the small number of purging patients in our sample, it is difficult to draw conclusions regarding the role of AN subtype.

The current study has several limitations. First, it included a small sample size that may preclude conclusions regarding negative findings. However, we conducted a retrospective power analysis which indicated that the effect size between re-hospitalization and non-hospitalization groups in PFTW was large (Cohen’s d=5.99). Second, the study has a relatively short follow-up period. It is possible that a longer follow-up would yield different outcomes. Third, we measured psychological variables by using only self-report questionnaires, which are exposed to self-report biases. Fourth, we did not include measurement of perceptions of family relations and attachment style that could provide a better understanding regarding the role of the family in adolescent AN. Lastly, although we tried to obtain information on re-hospitalization from several sources, some of the information may remain confidential.

Despite these limitations, our study highlights the importance of achieving full target weight during inpa-

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**Table 3. Logistic Regression Predicting Re-hospitalization:**

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>Var. Sig.</th>
<th>Chi-square</th>
<th>Model Sig.</th>
<th>Nagelkerke R Square</th>
</tr>
</thead>
<tbody>
<tr>
<td>block1  - demographic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFTW</td>
<td>-19.53</td>
<td>0.041*</td>
<td>15.84**</td>
<td>0.00</td>
<td>0.36</td>
</tr>
<tr>
<td>Parents Marital Status</td>
<td>-1.58</td>
<td>0.038*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous Hospitalization</td>
<td>-1.97</td>
<td>0.038*</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* p<0.05, ** p<0.01
tient treatment of adolescent AN for prevention of relapse and re-hospitalization. Our results indicate that reaching even 98% of the target weight might not be sufficient. This missing 2% (which usually means a small difference of only 1kg or less) has a significant impact on the clinical outcome and can help in the prediction of re-hospitalization. Therefore, premature discharge, without reaching the target weight, may contribute to the probability of relapse and re-hospitalization. These results highlight how important it is for policy makers to aim for longer hospitalization, enabling patients to achieve target weight in full during hospitalization. Moreover, patients and their families should receive psycho-education about the importance of achieving full target weight.

Authors’ contributions

- IH, conception and design, analysis and interpretation of data.
- ABS, conception and design, interpretation of data, critical revision, final approval.
- GG, conception and design, critical revision, final approval.
- AH, conception and design, interpretation of data, critical revision, final approval.
- MH, conception and design, critical revision, final approval.
- SF, conception and design, interpretation of data, critical revision, final approval.

The authors declare that they have no competing interests.

References