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PREVALENCE OF RISK FACTORS FOR THE REFEEDING SYNDROME IN OLDER HOSPITALIZED PATIENTS

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Abstract: *Objectives:* The incidence of refeeding syndrome (RFS) in older patients is not well-known. The aim of the study was to determine the prevalence of known risk factors for RFS in older individuals during hospitalization at geriatric hospital departments. *Design and setting:* 342 consecutive older participants (222 females) who admitted at acute geriatric hospital wards were included in a cross-sectional study. We applied the National Institute for Health and Clinical Excellence (NICE) criteria for determining patients at risk of RFS. In addition, Mini Nutritional Assessment Short Form (MNA®-SF) was used to identify patients at risk of malnutrition. Weight and height were assessed. The degree of weight loss was obtained by interview. Serum phosphate, magnesium, potassium, sodium, calcium, creatinine and urea were analyzed according to standard procedures. *Results:* Of 342 older participants included in the study (mean age 83.1 ± 6.8, BMI range of 14.7–43.6 kg/m2), 239 (69.9%) were considered to be at risk of RFS, in which 43.5% and 11.7% were at risk of malnutrition and malnourished, respectively, according to MNA-SF. Patients in the risk group had significantly higher weight loss, lower phosphate and magnesium levels. In a multivariate logistic regression analysis, low levels of phosphate and magnesium followed by weight loss were the major risk factors for fulfilling the NICE criteria. *Conclusion:* The incidence of risk factors for RFS was relatively high in older individuals acutely admitted in geriatric hospital units, suggesting that, RFS maybe more frequent among older persons than we are aware of. Patients with low serum levels of phosphate and magnesium and higher weight loss are at increased risk of RFS. The clinical characteristics of the older participants at risk of RFS indicate that these patients had a relatively poor nutritional status which can help us better understand the potential scale of RFS on admission or during the hospital stay.

Key words: Refeeding syndrome, older persons, malnutrition, hypophosphatemia.

Introduction

Refeeding syndrome (RFS) is a life-threatening complication which arises as a result of over-rapid or unbalanced nutritional support after a period of starvation or fasting (1, 2). This potentially lethal condition has been characterized as a clinical complex, which includes fatal shifts in fluid and electrolytes associated with metabolic abnormalities in malnourished patients or starved individuals undergoing refeeding whether orally, enterally or parenterally (1). The clinical symptoms of RFS cover a wide spectrum of conditions include fluid retention with peripheral oedema, congestive heart failure, cardiac arrhythmia, respiratory compromise, delirium, encephalopathy and other severe organ dysfunctions (3, 4). RFS usually arises within 2 to 5 days of starting to refeed (3, 5).

It is generally agreed that prevention, careful patient monitoring and management of RFS by the multidisciplinary nutrition team may help to mitigate RFS complications (5, 6). According to the guidelines of the National Institute for Health and Clinical Excellence (NICE) (7), for patients at high risk for RFS, nutrition repletion of energy should be started slowly, and then can be progressively increased to provide adequate nutrition demands over four to seven days (3-5). Using this strategy, a recent randomized clinical trial in 13 hospital intensive care units demonstrated a higher overall survival time and lower mortality in critically ill adults (8). In addition, correction of plasma electrolytes (i.e. phosphate, magnesium, potassium and sodium) and fluid imbalance along with refeeding as well as vitamin and trace-element deficiencies (i.e. thiamine) are recommended (3, 4).

Although, several risk factors for development of RFS have been identified, one of the predominant risk factor of the RFS is hypophosphatemia (2, 3). Prevalence of hypophosphatemia in patients at risk of RFS is high (9, 10). In a prospective cohort study of a heterogeneous group of intensive care unit (ICU) patients, Marik and Bedigian have shown that 34% of patients experienced refeeding hypophosphatemia soon after feeding was started (9). In another study of 106 cancer patients, the incidence of hypophosphatemia was 25% (10). Although this is important to emphasize, there are several causes of hypophosphatemia which are not necessarily associated to RFS (5). Other biochemical abnormalities of RFS are common comprising severely low serum electrolytes concentration of magnesium and potassium, disorders of sodium and fluid balance and thiamine deficiency (11, 12). In addition, acute and chronic malnutrition are the most important clinical risk factors

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for RFS. Hise et al (13) and Morley et al. (14) estimated that the prevalence of malnutrition in older hospitalized patients is between 30 to 50% and 35 to 65%, respectively.

Since there is no universally accepted definition of RFS, it is not surprising that the incidence of RFS is unknown and varies in different studies as wide as 0.4 – 34% (1, 4, 6). Hence, the guidelines of the NICE criteria are recognized as a useful tool for screening and identifying patients at high risk of developing RFS (7). In one recent study of 178 internal medicine patients, 97 patients (54%) were considered to be at risk of RFS and 14 patients actually developed RFS (11). However, the authors of that study applied NICE criteria for determining people at risk of RFS and they took hypophosphatasemia as the main indicator for the presence of this syndrome.

RFS has been confirmed in those with chronic alcoholism, individuals with anorexia nervosa, oncology patients receiving chemotherapy and depleted patients with acute illness (15-17). In addition, more specifically, the fast growing populations of hospitalized older subjects are known to be considered at high risk of RFS due to many underlying comorbidities and high prevalence of malnutrition as a consequence of dementia, dysphagia, depression and others (18-20). In one case-control study of hospitalized patients older than 65 years, Kagansky et al. reported that about 14.1% of 2307 older patients had hypophosphatemia compatible with the RFS on average on day 10 of hospitalization (21). In addition, other studies have found low serum phosphate and magnesium levels amongst older hospitalized patients (18, 22). RFS can be considered as a common reason of low serum phosphate and magnesium levels in older individuals due to significant overlap between risk factors for hypophosphatemia and hypomagnesemia and those for RFS (18) .

On the other hand, RFS is likely underdiagnosed in older hospitalized persons and those in long-term care facilities due to nonspecific initial symptoms among this population (18, 23). Although pathophysiology of RFS has evolved, the potential dangers of refeeding and understanding the circumstances under which RFS arises in fragile older adults are less well known (24). Older patients often suffer from multi-comorbidity that overlaps with the typical symptoms of RFS which impairs the early recognition of RFS (24, 25). Whenever patients with RFS are not properly treated, the consequences can be fatal. Accordingly, identifying patients prone to RFS is essential due to minimizing its occurrence and avoiding mortality and morbidity related with this phenomenon (26).

Therefore, the aims of this study were i) to determine the prevalence of risk factors for RFS according to NICE criteria in older hospitalized patients aged 60-100 years and ii) to demonstrate the major clinical risk factors of RFS among this population.

Subjects and Methods

Study design and subjects

The study population consisted of 342 older participants (222 women and 120 men), aged between 60 and 100 years with a body mass index (BMI) range of 14.7–43.6 kg/m2 who consecutively hospitalized between July 2015 and February 2016. This cross-sectional study was performed at six different geriatric hospital departments in Germany. Exclusion criteria were age < 60 years, missing or withdrawn consent of the patients, hypercalcemia and hyperparathyroidism. The study protocol had been approved by the ethical committee of Friedrich-Alexander-University, Erlangen-Nürnberg.

NICE criteria have been applied for determining persons at high risk of RFS in all patients acutely admitted (Table 1) and subjects were grouped into two categories according to the guideline. First, subjects with at least one or more of the major parameter of NICE criteria were considered as positive NICE I. Second, subjects with two or more of the minor parameter of NICE criteria were considered as positive NICE II. In addition, Mini Nutritional Assessment Short Form (MNA®-SF) was used to identify patients at risk of malnutrition (27). Further, weight was measured without shoes and with light clothing at an accuracy of 0.01 kg and height was assessed to the nearest 0.5 cm at time of hospital admission. The degree of weight loss (WL) was obtained by interview. The medication histories at time of hospital admission were obtained either through interview or from the medication lists of the general practitioner.

Laboratory methods

Blood tests were performed on the day of admission at each hospital clinical chemistry laboratory and serum phosphate, magnesium, potassium, sodium, calcium, creatinine and urea were analyzed according to standard procedures. Serum phosphate level < 0.8 mmol/l was defined as hypophosphatemia as well as serum magnesium and potassium levels < 0.70 mmol/l and 3.5 mmol/l were considered as hypomagnesemia and hypokalemia, respectively.

Statistical analysis

The statistical analysis was performed with SPSS statistical software (SPSS Statistics for Windows, IBM Corp, Version 23.0, Armonk, NY, USA). Continuous variables are expressed by their means and standard deviations (SDs). Categorical variables are expressed as n (%). Differences between females and males and between patients at refeeding risk and not at refeeding risk were analyzed by using an unpaired t test in normally distributed variables. Categorical variables were compared by the Chi square test or the Fisher's exact test, as appropriate. Multivariate logistic regression analyses were performed for identifying the clinical parameters that were independent risk factors for RFS (28). The independent variables included in the model were those variables that were

significantly associated with NICE-refeeding risk criteria as dependent variable in univariate analysis: initial body weight, BMI, WL during first to six months, serum phosphate, magnesium and potassium levels, diuretics, no significant nutrition intake, antiacids and insulin therapy. The Hosmer and Lemeshow test were calculated for the goodness-of-fit of the logistic regression model. All tests were 2-tailed, and P<0.05 was accepted as the limit of significance.

Results

Baseline characteristics and laboratory data of study participants stratified by sex are presented in Table 2. Of 342 old participants, 65% of subjects were women. The age range was between 60 and 100 years. Women were significantly younger than men. According to MNA-SF, in total study population, the prevalence of the patients at risk of malnutrition and malnourished subjects were 44.7% and 11.1%, respectively.

Table 1

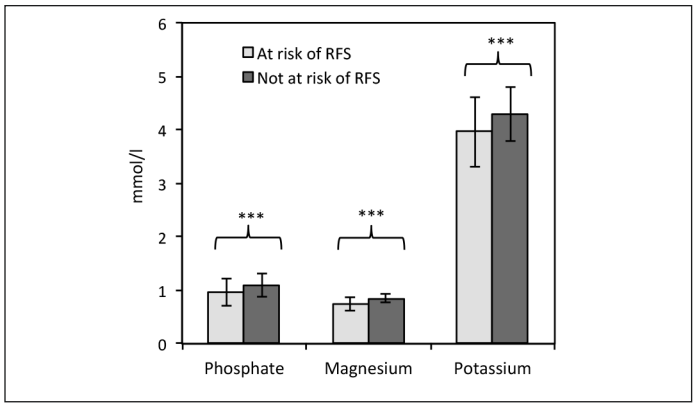
Criteria for identifying patients at high risk of refeeding syndrome according to the Guidelines of the National Institute for Health and Clinical Excellence (NICE)

NICE I (At least 1 or more of the following major criteria)
• Body mass index (kg/m2) < 16
• Unintentional weight loss > 15% in the previous 3 to 6 months
• Little or no food intake for > 10 days
• Low levels of potassium, phosphate, or magnesium before feeding is reintroduced
NICE II (Presence of 2 or more of the following minor criteria)
• Body mass index (kg/m2) <18.5
• Unintentional weight loss > 10% in the previous 3 to 6 months
• Little or no food intake for > 5 days
• History of alcoholism, insulin use, chemotherapy, diuretics, or antacids

The study population showed a wide BMI range with no sex differences (P=0.916). Compared with women, men had significantly higher actual body weight, height as well as WL during first, second, third and sixth months (WL ranged from 0 to 17.3% in females compared to range from 0 to 20.5% in males at sixth months; P<0.01). In addition, BMI less than 16 kg/m2 and 18.5 kg/m2 were observed in 1.2 % and 5.0% of the study population, respectively. There were no significant differences in all laboratory data between sexes, except for creatinine with lower values in females than males (P<0.01). In total population, 51 participants (14.9%) had hypophosphataemia of which 33 were females. Furthermore, prevalence of hypomagnesaemia and hypokalemia were 16.7% (57 subjects) and 10.8% (37 subjects), respectively (Table 2).

Diagnostic work-up for identifying patients at risk for RFS according to the guidelines of the NICE criteria in total study population are shown in Table 3. Using the criteria NICE I and NICE II (Table 1), diagnosis of risk factors for RFS was confirmed in 168 participants (49.1%) and 173 participants (50.6%), respectively. Based on NICE I, no significant nutritional intake for > 10d (21.3%) followed by hypomagnesaemia (16.7%) and hypophosphataemia (14.9%) were the most common risk factors of RFS. By contrast, diuretics (55.8%), no significant nutritional intake for > 5d (40.9%), and antiacids (39.5%) were the major determinants of risk factors for RFS according to NICE II. In addition, 32.2% of study participants (110 subjects) were at risk for RFS according to both criteria concurrently. With regards to this overlap, 69.9% of total study population (239 subjects) was considered to be at risk of RFS (Table 3).

Figure 1



***Statistically significant differences in phosphate, magnesium and potassium levels between patients with (n=168) and without (n=174) risk of refeeding syndrome according to NICE I at the day of admission (P = 0.000)

Descriptive characteristics and laboratory data of the study participants stratified by NICE criteria for determining people at high risk of RFS are given in Table 4. According to the NICE I and NICE II, patients at risk of RFS had significantly higher WL during the last 6 months (P < 0.01) than the patients not at risk of RFS, with no differences in age and BMI. In addition, based on MNA-SF, the prevalence of malnourished subjects was higher in refeeding risk groups compared to not at risk of RFS. Of 239 of older patients at risk of RFS, 43.5% and 11.7% were at risk of malnutrition and malnourished, respectively. Moreover, lower mean serum phosphate, magnesium and potassium levels were seen in patients at risk of RFS (Figure 1, P < 0.001), as expected considering the NICE I criteria.

A multivariate logistic regression analysis was performed for identifying the clinical parameters that were the important independent risk factors for RFS according to the NICE guideline (Table 5). Low levels of phosphate and magnesium followed by WL (in 3 months) were the major independent predictors for risk of RFS. In addition, low levels of potassium, diuretics and no significant nutrition intake were the other independents determinants for risk of RFS. Furthermore, age and gender do not impact the risk factors in NICE criteria (age, P=0.750; gender, P=0.840).

Table 2
Characteristics of the study population stratified by gender at baseline (Mean ± SD)

	All (n=342)	Females (n=222; 65 %)	Males (n=120; 35 %)
Age (y)	83.06 ± 6.77	83.93 ± 6.49	81.45 ± 7.04**
Height (m)	1.65 ± 0.08	1.61 ± 0.07	1.73 ± 0.06***
Actual body weight (kg)	72.27 ± 16.90	68.54 ± 16.50	79.09 ± 15.52***
BMI (kg/m^2)	26.30 ± 5.36	26.27 ± 5.68	26.33 ± 4.75
MNA®-SF (n; %)			
Normal nutritional status	151 (44.2 %)	100 (45.0 %)	50 (42.0 %)
At risk of malnutrition	153 (44.7 %)	95 (42.8 %)	58 (48.7 %)
Malnourished	38 (11.1 %)	27 (12.2 %)	12 (9.2 %)
WL in 1 months (kg)	0.85 ± 1.54	0.68 ± 1.15	1.17 ± 2.05*
WL in 2 months (kg)	1.02 ± 1.84	0.82 ± 1.52	1.40 ± 2.29*
WL in 3 months (kg)	1.17 ± 2.12	0.91 ± 1.66	1.67 ± 2.72**
WL in 6 months (kg)	1.47 ± 2.65	1.03 ± 1.86	2.29 ± 3.57***
BMI < 16 kg/m^2 (n, %)	(4, 1.2 %)	(3, 1.4 %)	(1, 0.8 %)
BMI < 18.5 kg/m^2 (n, %)	(17, 5.0 %)	(14, 6.3 %)	(3, 2.5 %)
Laboratory data			
Phosphate (mmol/l)	1.03 ± 0.25	1.05 ± 0.27	1.01 ± 0.21
Magnesium (mmol/l)	0.80 ± 0.11	0.72 ± 0.20	0.80 ± 0.12
Potassium (mmol/l)	4.15 ± 0.61	4.11 ± 0.63	4.23 ± 0.56
Sodium (mmol/l)	138.64 ± 8.64	138.15 ± 10.20	139.53 ± 4.42
Calcium (mmol/l)	2.26 ± 0.17	2.27 ± 0.18	2.25 ± 0.15
Creatinine (mmol/l)	1.18 ± 0.65	1.09 ± 0.58	1.35 ± 0.75**
Urea (mg/dl)	53.17 ± 32.85	50.67 ± 31.35	57.96 ± 35.20
Hypomagnesaemia (n, %)	(57, 16.7 %)	(36, 16.2 %)	(21, 17.6 %)
Hypophosphatasemia (n, %)	(51, 14.9 %)	(33, 14.9 %)	(17, 14.3 %)
Hypokalemia (n, %)	(37, 10.8 %)	(27, 12.2 %)	(10, 8.4 %)

BMI; body mass index measured as actual body weight (kg)/height (m)2, MNA®-SF; Mini Nutritional Assessment Short Form (normal nutritional status with 12-14 points; at risk of malnutrition with 8-11 points; malnourished with 0-7 points); WL; weight loss; *P < 0.05, **P < 0.001, ***P < 0.001 difference between gender (unpaired t test)

Discussion

The majority of older hospitalized patients are frail with several concomitant chronic conditions (29-32). Previous studies have shown the increased prevalence of multi-comorbidity with age (31, 32). RFS represents a potentially fatal condition which is considered to be a serious clinical problem, particularly, in the population of hospitalized older patients (1, 18). The actual prevalence of RFS is debatable possibility due to the absence of accepted diagnostic criteria, differences in definition used, study design and sample size (2, 9, 33). In addition, the incidence or risk of RFS is not well-known among geriatric patients because of significant overlap which exists between the symptoms of RFS and the symptoms of multi-comorbidity, resulting in poor recognition of RFS in older subjects. Accordingly, due to the lack of reliable RFS incidence data, preventing or minimizing its occurrence and identifying the high risk patients are crucial (4, 34).

To the best of our knowledge, there are very few studies exploring the incidence or risk of RFS in older patients acutely admitted to the geriatric hospital wards. As shown here and in previous studies (35, 36), many of older patients are malnourished or at risk of malnutrition, and therefore require nutrition therapy. When the risk of RFS is not properly identified or treated, this may lead to replacement of risk of malnutrition with risk of RFS. In this study, according to the NICE criteria, 69.9 % of the older patients were at risk of RFS suggesting that RFS maybe more frequent among geriatric patients than we are currently aware of. The high prevalence of risk factors found in the current study is in accordance with the recent study of internal medicine patients, in which 54% of participants were considered to be at risk of RFS (11). As reported by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) (37), 19% of those patients who meet the NICE risk criteria are expected to develop RFS. The recent study by Kraaijenbrink indicated that 14% of patients at risk of RFS actually developed the syndrome (11). Concurrently, Rio et al. found only a 1% prevalence of RFS among all hospital patients started on artificial nutrition (2). However, the incidence or risk of RFS depends on the degree of

malnutrition and the feeding strategy which can therefore not be compared between studies.

Table 3
Diagnostic work-up for identifying patients at risk for refeeding syndrome according to NICE criteria in total study population (n=342)

Action		RFS
NICE I	*(n, %)*	*RFS I (n, %)*
BMI < 16 (kg/m^2)	4; 1.2 %	168; 49.1 %
Unintentional WL>15% in last 3-6 months	6; 1.8 %	
No significant nutritional intake for>10d	73; 21.3 %	
Hypophosphatasemia	51; 14.9 %	
Hypomagnesaemia	57, 16.7 %	
Hypokalemia	37; 10.8 %	
NICE II		*RFS II (n, %)*
BMI < 18.5 (kg/m2)	17; 5.0 %	173; 50.6 %
Unintentional WL>10% in last 3-6 months	12; 3.5 %	
No significant nutritional intake for>5d	140; 40.9 %	
Insulin therapy	48; 14.0 %	
Diuretics	191; 55.8 %	
Antiacids	135; 39.5 %	
Alcohol abuse	12; 3.5%	
NICE I + NICE II		*RFS I + RFS II*
		110; 32.2 %
Prevalence of risk for RFS in total population		239; 69.9 %

NICE I; according to the Guidelines of the National Institute for Health and Clinical Excellence, one of the following features is required, NICE II; according to the NICE criteria, two of the following features are required, RFS I; Risk of refeeding syndrome according to NICE I, RFS II; Risk of refeeding syndrome according to NICE II, WL; weight loss

In addition, our study demonstrates that older individuals at risk of RFS had significantly higher WL followed by lower levels of serum phosphate and magnesium. These data indicate that the refeeding risk group was in a relatively poor nutritional state that might assist in understanding the potential scale of RFS. Nutritional problems are numerous in geriatric patients and sometimes misdiagnosed (34, 38). Previous studies of hospitalized older subjects reported that 20% - 65% of this population experience nutritional deficiencies (36, 38-40) and the incidence of malnutrition in long-term care facilities is considered to be 30% - 60% (41). In a hospital based study of 32,837 patients, Imoberdof et al. (35) found that approximately one in five patients were severely undernourished or to be at risk of undernutrition and the risk was directly associated with age (age<45 y: 8%; 45-64 y: 11%; 65-84 y: 22%; >85 y: 28%). In the current study, in total study population, prevalence of the patients at risk of malnutrition and malnourished subjects were 63.1% and 31.9%, respectively. Consequently, the multi-morbidity and the relatively high age of our study participants may explain the higher number of the patients at risk of RFS.

Furthermore, hypomagnesemia and hypophosphatemia were common findings in our study population. About 16.7 % and 14.9 % of the patients were found to have hypomagnesemia and hypophosphatemia, respectively. The incidence of hypophosphatemia in our study population was similar with the 14.1% rate reported in a case-control study of older hospitalized patients (21) and almost half the rate (29%) reported in a cohort study of older hospitalized women (22). When a multivariate model was performed in our study, low levels of phosphate and magnesium followed by WL were the major independent risk factors for fulfilling the NICE criteria. However, hypophosphatemia is the hallmark of RFS, but its presence in our older patients is not necessarily meant that RFS would develop, since there are other possible reasons for low phosphate levels (18, 21). Recently Kraaijenbrink et al. found that of all 97 older patients at risk of RFS, 14 patients developed hypophosphatemia and consequently RFS (11).

Some limitations to the present study should be discussed. We did not address the real occurrence of RFS and it is not clear how many of the older patients at risk of RFS actually developed the syndrome. In addition, development of electrolyte disturbances over time and any type of nutritional therapy have not been assessed in our study. Therefore, future research is needed to provide detailed information of this syndrome and its occurrence in older patients to ascertain the best preventative strategies.

Conclusion

RFS is underestimated and is probably often underdiagnosed in a large proportion of geriatric patients with multiple comorbidities those who suffer from malnutrition and nutritional difficulties for several consecutive days (11, 34, 42). This study found that prevalence of risk factors for RFS is relatively high in older patients acutely admitted in geriatric hospitals, suggesting that, RFS maybe more frequent among older adults than we are aware of.

In this study, the clinical characteristics of the patients at risk of RFS, especially the associations of RFS with WL, hypophosphatemia, hypomagnesemia and other risk factors suggest that many of these older patients maybe are at increased risk of developing RFS. These findings revealed that the older patients at risk of RFS had a relatively poor nutritional state which may help the early identification of high-risk older individuals on admission or during the hospital stay and allow us to develop novel strategies in order to minimize risk of RFS among these patients. Our results indicate the need for better recognition and monitoring of hospitalized older patients at risk for the development of RFS.

Table 4
Characteristics and laboratory data of the study population stratified by NICE criteria for determining people at high risk of refeeding syndrome (Mean ± SD)

	NICE I†		NICE II	
	Refeeding risk (n=168; F=106)	**No refeeding risk (n=174; F=116)**	**Refeeding risk (n=173; F=115)**	**No refeeding risk (n=169; F=107)**
Age (y)	83.01 ± 6.93	83.12 ± 6.63	82.88 ± 7.20	83.25 ± 6.31
Height (m)	1.65 ± 0.09	1.65 ± 0.08	1.65 ± 0.08	1.65 ± 0.09
Actual body weight (kg)	71.41 ± 17.10	73.10 ± 16.71	72.72 ± 18.65	71.81 ± 14.93
BMI (kg/m^2)	25.90 ± 5.51	26.70 ± 5.20	26.30 ± 5.94	26.27 ± 4.72
MNA®-SF (n; %)				
Normal nutritional status	69 (41.1 %)	82 (47.1 %)	79 (45.7 %)	72 (42.6 %)
At risk of malnutrition	77 (45.8 %)	76 (43.7 %)	70 (40.4 %)	83 (49.1 %)
Malnourished	22 (13.1 %)	16 (9.2 %)	24 (13.9 %)	14 (8.3 %)
WL in 1 months (kg)	1.19 ± 1.88	0.52 ± 1.02***	1.19 ± 1.88	0.50 ± 0.98***
WL in 2 months (kg)	1.49 ± 2.28	0.58 ± 1.13***	1.46 ± 2.27	0.58 ± 1.10***
WL in 3 months (kg)	1.69± 2.66	0.67 ± 1.22***	1.71 ± 2.64	0.61 ± 1.17***
WL in 6 months (kg)	2.14 ± 3.33	0.82 ± 1.52***	2.12 ± 3.26	0.80 ± 1.58***
Laboratory data				
Phosphate (mmol/l)	0.96 ± 0.26	1.10 ± 0.22***	1.04 ± 0.29	1.02 ± 0.21
Magnesium (mmol/l)	0.75 ± 0.13	0.84 ± 0.08***	0.79 ± 0.12	0.80 ± 0.10
Potassium (mmol/l)	3.96 ± 0.65	4.33 ± 0.51***	4.12 ± 0.60	4.18 ± 0.62
Sodium (mmol/l)	139.15 ± 5.88	138.14 ± 10.64	138.87 ± 5.88	138.40 ± 10.76
Calcium (mmol/l)	2.23 ± 0.20	2. 30 ± 0.14***	2.26 ± 0.20	2.27 ± 0.15
Creatinine (mmol/l)	1.23 ± 0.70	1.13 ± 0.60	1.27 ± 0.72	1.09 ± 0.56**
Urea (mg/dl)	54.51 ± 35.32	51.88 ± 30.32	58.89± 39.40	47.38 ± 23.22**

†According to the guidelines of the national institute for health and clinical excellence (NICE) criteria; BMI; body mass index measured as actual body weight (kg)/height (m)^2, MNA®-SF; Mini Nutritional Assessment Short Form (normal nutritional status with 12-14 points; at risk of malnutrition with 8-11 points; malnourished with 0-7 points), WL; weight loss; **P < 0.01; *** P <0.001 difference between refeeding risk and no refeeding risk groups (unpaired t test)

Table 5
Multivariate logistic regression analysis for identifying major risk factors for RFS according to the NICE criteria in total study population (n=342)

Action	**RFS**		
	OR	**95 % CI**	**P value**
Phosphate	3.44	2.07 – 8.31	0.000
Magnesium	2.61	1.09 - 6.13	0.000
WL in 3 months	2.37	1.41 – 3.99	0.000
WL in 6 months	2.01	1.20 – 5.30	0.003
Potassium	1.50	0.25 – 2.73	0.002
Diuretics	1.06	0.12 – 1.28	0.026
No significant nutrition intake	1.01	0.09 – 1.24	0.032
Antiacids	1.00	0.60 – 2.3	0.671
Insulin therapy	0.86	0.52 – 1.44	0.703

WL; weight loss, RFS; refeeding syndrome, OR; odds ratio, CI; confidence interval.

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Conflicts of interest: The authors declare no conflict of interest.

Financial disclosure: The study received no financial support.

Ethical standard: The authors declare that the study procedures comply with current ethical standards for research involving human participants in Germany. The study protocol had been approved by the ethical committee of Friedrich-Alexander-University, Erlangen-Nürnberg.

Author contributions: The study was designed by all authors. Data were obtained by RW, IC, IG, CM, MKM and HPW. Statistical analysis was performed by MP. MP, DV and RW prepared the manuscript. All authors read and approved the final manuscript.

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