**Impact of Refeeding Syndrome on Short- and Medium-Term All-Cause Mortality: A Systematic Review and Meta-Analysis**

# Impact of refeeding syndrome on short- and medium-term all-cause mortality: a systematic review and meta-analysis

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**Short title:** Refeeding syndrome and mortality: a meta-analysis.

## Abstract

Background. The refeeding syndrome has been described as a potentially life-threatening complication of re-nutrition. However, moving from single reports to larger population studies, the real impact of refeeding syndrome on all-cause mortality is still unknown.

Methods. PubMed/Medline, EMBASE, Cochrane library and CINAHL databases were systematically searched until September 2020 for studies reporting mortality rates in patients who developed the syndrome at re-nutrition, compared to those who did not develop it. Effect sizes were pooled through a random-effect model.

Results. Thirteen studies were finally considered in the meta-analysis, for a total of 3846 patients (mean age 64.5 years; 58% males). Pooled data showed a non-significant trend toward an increased short-term (≤ 1 month) mortality in patients developing the refeeding syndrome (OR 1.27, 95% CI 0.93-1.72), mostly driven by studies in which re-nutrition was not prescribed and supervised by a nutritional support team (p=0.01 at subgroup analysis) and by studies published in earlier years (p=0.04 at meta-regression). When examining medium-term (≤ 6 month) mortality, an overall statistical significance towards higher risk was observed (OR 1.54, 95% CI 1.04-2.28).

Conclusion. This was the first meta-analysis that specifically assessed the impact of refeeding syndrome on mortality. Our results suggested a non-significant trend towards increased mortality in the short-term, but a significantly increased mortality in the medium-term. The supervision/management of the refeeding process by a nutrition specialist might be a key factor for the limitation of this mortality excess.

## Introduction

The refeeding syndrome (RFS) has been described as a spectrum of biochemical and/or clinical alterations occurring as a consequence of the reintroduction of calories after a period of decreased caloric intake[1,2]. During prolonged periods of caloric deprivation, energy stores, vitamins and intracellular electrolytes (especially potassium, phosphates, and magnesium) are depleted[1–3]. After caloric replenishment, the supply of nutrients, in particular carbohydrates, determines a rise in insulin secretion. This, in the presence of a pre-existent total-body deficit of potassium, phosphorus or magnesium, may lead to a further drop in their serum concentrations. In fact, insulin drives these electrolytes inside cells both by direct effects and by increased intracellular demand[1,4–7].

The possible clinical consequences of these metabolic alterations may be various[1,2]. The most important ones affect cardiovascular system (decreased cardiac contractility, arrhythmias, water retention with volume overload)[8,9], nervous system (paraesthesia, altered mental status, seizures)[10,11], hematopoietic system (reduced oxygen release to tissues due to decreased production of 2,3-diphosphoglycerate)[12] and skeletal muscles (muscle weakness, muscle spasms, rhabdomyolysis)[8,13,14].

Despite being known for more than 70 years[15,16], the RFS has long been underdiagnosed and remains still frequently unrecognised[1,2,17,18]. This picture is further complicated by the lack of a homogeneous and commonly accepted RFS definition[1,2]. In April 2020, the American Society for Parenteral and Enteral Nutrition (ASPEN) published a consensus paper, where the RFS has been defined as a >10% decrease in the serum levels of at least one among phosphate, potassium and magnesium, associated or not with organ dysfunction resulting from a decrease in any of these or due to thiamine deficiency, occurring within 5 days of reinitiating energy provision[1]. However, most of available studies rely on different and non-standardized criteria, thus leading to heterogeneous data. This makes it difficult to draw clear conclusions about RFS incidence, risk factors, time of occurrence and clinical outcomes[2,17].

In particular, the impact of RFS on all-cause mortality is unclear[1,2,6,19]. When moving from single cases to patient cohorts, published studies did not unanimously show excess mortality in patients who developed the RFS compared to those who did not develop it[20–32]. In the last few years, some systematic reviews[2,17] addressed this issue as a secondary outcome and from a qualitative point of view, with neither definite conclusions, nor quantitative assessment of the mortality risk. The present study is therefore the first meta-analysis that specifically and quantitatively assess the impact of RFS on patient all-cause mortality.

## Methods

### Search strategy and study selection

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[33]. The process of literature search and study selection was made by two independent reviewers (I.C., M.P.); all disparities were resolved through consensus.

The following electronic databases were queried until the September 3rd 2020: PubMed/Medline (National Library of Medicine), EMBASE, Cochrane library and Cumulative Index to Nursing and Allied Health Literature (CINAHL). The search strategy was performed using a combination of relevant database-specific search terms to identify pertinent studies about RFS and mortality. Both medical subject headings (MeSH) and free text search terms were employed. The terms “refeeding” or “refeeding syndrome” were combined with other key words such as incidence, mortality, anorexia nervosa, critically ill patients, cancer patients, elderly or aged people, inpatients or hospitalized patients, artificial nutrition, malnutrition, phosphorus, potassium, magnesium, alcoholism, surgery and fasting. The full search strategy is presented in Appendix 1. The search was limited to data from

adult subjects, whereas no filters were applied for study design, language, and publication date. To expand the search, references of the retrieved articles were also screened for additional studies.

Outcomes

The primary outcome of interest was to examine differences in the risk of dying among patients who developed as compared with those who did not develop the RFS during re-nutrition. Subgroup analyses and meta-regressions were performed by taking in considerations all categorical and continuous factors listed in "Data extraction".

Data extraction

Three authors (F.B., I.C., V.P.) independently examined and extracted data from papers which met the inclusion criteria using pre-specified data extraction templates. For each eligible study, the following information were collected: 1) first author and publication year; 2) study country; 3) study design and aims; 4) patients' characteristics in terms of baseline diseases and conditions, according to inclusion and exclusion criteria; 5) number of subjects; 6) age, gender, and body mass index (BMI) of participants; 7) criteria used for RFS definition; 8) observed incidence rate of RFS; 9) mortality of patients developing RFS; 10) mortality of patients not developing RFS; 11) time point at which mortality was evaluated; 12) type of the feeding support adopted; 13) prescription and supervision of re-nutrition by a nutrition specialist and/or according to a specified international guideline, as reported by authors.

Risk of bias assessment

The risk of bias was independently assessed for each included study by two authors (F.B., S.B.) using the seven domains of ROBINS-I (Risk Of Bias In Non-randomized Studies of Intervention scale) tool[34]. This tool evaluates seven domains, that address (a) bias due to confounding, (b) bias in selection of participants into the study, (c) bias in measurement classification of interventions, (d) bias due to deviations from intended interventions, (e) bias due to missing data, (f) bias in measurement of outcomes, (g) bias in selection of the reported result. An additional evaluation of overall risk of bias is also provided as a summary measure; the options for a domain-level risk-of-bias judgement are 'Low', 'Moderate', 'Serious' or 'Critical', with an additional option of 'Unknown' if sufficient information for judgement is lacking.

Statistical analysis

A random-effect model was adopted for statistical pooling of all-cause mortality data, expressed as odds-ratios between patients who developed as compared with those who did not develop the RFS during re-nutrition. Higgins $I^2$ statistics and Cochran Q test were used to assess heterogeneity between studies. Subgroup analyses and meta-regressions were performed to test for interactions with other possible covariates. Publication bias was quantitatively assessed by Begg's test. Statistical analysis was performed using STATA 16 (StataCorp, College Station, Texas, USA).

## Results

Search results

A total of 4679 records were identified in the initial literature search. Removal of duplicates and non-original articles led to an overall pool of 975 studies. An accurate title and/or abstract revision was

142 sufficient to exclude 868 articles as not pertinent or not fulfilling our pre-specified inclusion/exclusion
143 criteria. The remaining 107 studies were assessed in full-text for eligibility and 13 of them finally met
144 all criteria for being included in the final analysis, encompassing 3846 patients[20–32] (Figure 1).

145

146 Characteristics of the included studies

147 Table 1 summarizes the basic study characteristics. All studies had an observational design, with five
148 prospective cohort[25,26,28,29,32] and eight retrospective cohort[20–24,27,30,31] studies. Two studies were
149 performed in patients with eating disorders and/or malnutrition[22,26], six studies were performed in
150 patients starting enteral or parenteral nutrition in general hospital wards[20,24,25,28,30,32] and five studies
151 were performed in patients starting enteral or parenteral nutrition in an Intensive Care Unit
152 (ICU)[21,23,27,29,31]. In two studies the refeeding process was handled and supervised by a dedicated
153 nutritional support team (NST)[27,30]. In three studies no explicit reference to a NST was present, but
154 re-nutrition was still managed according to specified and declared international guidelines[23,25,31]. In
155 six studies no explicit reference to the presence of a NST nor to the adherence to specific guidelines
156 was provided by the Authors[21,22,24,28,29,32]. The remaining two studies were characterized by the
157 presence of an intervention group in which the refeeding process was managed by a NST and a control
158 group in which it wasn't[20,26].

159 RFS was defined by biochemical criteria in eleven studies[20,21,23–31] and by clinical criteria in the
160 remaining two[22,32]. Among the eleven studies in which a biochemical definition of RFS was adopted,
161 all evaluated mortality in the short-term (one at 7 days[24], four at 1 month[20,23,25,26], six during hospital
162 stay[21,27–31]), while only three evaluated mortality in the medium-term (all at 6 months)[23,26,31]; no study
163 evaluated mortality at a time later than 6 months. Among the two studies in which a clinical definition
164 of RFS was adopted, both evaluated mortality in the short-term only (during hospital stay)[22,32]. Table
165 2 summarizes the available mortality data for each of the included studies. Of note, no study reported
166 any loss at follow-up.

When focusing on the two studies that examined mortality outcomes of clinically-defined RFS, in one of them[32], encompassing 243 patients, in-hospital death occurred in 0 out of 3 patients who developed clinical RFS and in 68 out of 240 patients who did not; in the other one[22], encompassing 68 patients, in-hospital death occurred in 5 out of 7 patients who developed clinical RFS and in 2 out of 61 patients who did not. The low number of studies made it unreasonable to provide a quantitative estimate of a pooled effect size; these studies were thus excluded from subsequent quantitative analyses.

Mortality of biochemically-defined RFS in the short-term

Eleven studies examined the mortality outcomes of biochemical RFS in the short-term. The time point for mortality evaluation was at 7 days in one study[24], at 1 month in four studies[20,23,25,26] and during hospital stay in the remaining six studies[21,27–31]. The application of a random-effect model on the available data showed a non-significant trend towards an increased short-term mortality in patients developing biochemical RFS after re-nutrition with respect to the control group (OR 1.27, 95% CI 0.93-1.72) (Figure 2).

Subgroup analyses were conducted in order to analyse if the outcome of interest was significantly associated with the categorical variables that were retrieved at a study-level, specified in the section describing data extraction. These analyses revealed the presence of a statistically significant difference (p=0.01) between studies in which re-nutrition was prescribed and supervised by a NST (OR 0.75, 95% CI 0.46-1.21), studies in which it was managed according to specified international guidelines (OR 1.77, 95% CI 0.88-3.58) and studies in which no explicit reference to the presence of a nutrition team nor to the adherence to specific guidelines was provided (OR 2.08, 95% CI 1.24-3.49) (Figure 3). As it can be noted, this difference was mostly driven by an apparent neutrality of RFS on mortality risk in the first subgroup; conversely, excess mortality seemed to be noticeable in the other two subgroups, namely as a trend in the second one and as a significant excess in the third.

192 The two studies that were conducted with mixed refeeding management protocols were excluded
193 from this analysis, as no sufficient information was provided for a separate estimation of the impact
194 of RFS on mortality according to the refeeding protocol used. No significant differences were found
195 when stratifying the studies according to the study country (Europe/USA, or other countries; p=0.37),
196 study design (retrospective or prospective; p=0.98), category of patients (malnourished, hospitalized
197 in general wards, hospitalized in ICU; p=0.66), type of re-nutrition (by mouth, enteral, parenteral, or
198 mixed; p=0.11), or overall risk of bias (low, moderate, or high; p=0.49).

199 Meta-regressions were conducted in order to verify if the outcome of interest was significantly
200 associated with the categorical variables that were retrieved at a study-level, specified in the section
201 describing data extraction. There was a statistically significant negative association between
202 publication year and RFS-related excess mortality (p=0.04) (Figure 4). No significant associations
203 were found between the outcome of interest and age (p=0.18), percentage of males (p=0.60), BMI
204 (p=0.96), number of patients in the study (p=0.20), percentage of patients developing RFS (p=0.49),
205 or cut-off used for the definition of refeeding hypophosphatemia (p=0.77).

206

207 Mortality of biochemically-defined RFS in the medium-term

208 Only three studies examined mortality outcomes of biochemical RFS in the medium-term. The time
209 point for mortality evaluation was at 6 months for all studies[23,26,31]. The application of a random-
210 effect model on the available data showed that the medium-term mortality risk in patients developing
211 biochemically-defined RFS was significantly higher than in the control group (OR 1.54, 95% CI 1.04-
212 2.28) (Figure 5). The limited number of studies available for this analysis did not allow to further
213 stratify results by subgroup analyses or meta-regressions.

214

215

Quality assessment and publication bias

The quality of the studies was assessed, in terms of risk of bias, using the ROBINS-I tool[34]. The major concerns were mostly related to the first two domains, i.e. bias due to confounding and bias in selection of participants into the study (Table 3). No significant publication bias was found at Begg's test, neither for short-term (p=0.35) nor for medium-term (p=1.00) mortality data.

## Discussion

The results of this systematic review and meta-analysis showed a non-significant trend towards a higher short-term mortality in patients who developed the RFS compared to those who did not develop it. This difference became statistically significant in the medium-term, namely at 6 months. Therefore, pooled estimates suggested that an impact of RFS on mortality might be present, and that the mortality gap between the two groups widened over time.

In a previous systematic review, Friedli et al.[2] provided a qualitative summary of the available evidence about the relationship between RFS and mortality, without finding a clear association. However, as acknowledged by the Authors, their conclusions were limited by the high eterogeneity of available studies. In fact, among the 11 studies considered by the authors, only 4 fullfilled the narrower inclusion criteria of our analysis; in the remaining 7, either mortality data were only reported for the RFS group (thus with lack of information in the comparison group), or hypophosphatemia was not clearly associated with the beginning of a refeeding process. More recently, Matthews-Rensch et al.[17] systematically revised the available evidence about the association between energy initiation rates and RFS outcomes. However, their review mostly focused on biochemical and organ-related outcomes; mortality rates were only reported descriptively, mostly as a whole-study measure and without a clear stratification between patients that developed the RFS and those who did not.

The short-term mortality rates observed for RFS patients were associated to the management and supervision modalities of the refeeding process; in particular, no excess mortality was apparently observed in studies in which a dedicated NST was explicitly in charge of re-nutrition, while a higher mortality risk was noticeable in studies were no explicit reference to a NST was made. These findings added another piece of evidence to the increasing body of literature supporting the importance of NSTs in hospital care[35].

Malnutrition and risk of malnutrition affect up to 50% of inpatients[36]; however, it is not a unitary phenomenon, showing complex interactions with inflammation and infecons, which both play a relevant role in its development and prognosis[36-39]. Multifaceted clinical knowledge is required to ensure optimal individual nutritional support. A NST ensures the quality and safety of nutritional interventions, thus helping in the prevention and adequate treatment of potential metabolic or systemic nutrition-related complications[35]. The involvement of a NST has been shown to increase appropriate nutritional indications[35,40,41], decrease complication rates[20,35,42,43], decrease all-cause mortality[35,42,44], and reduce healthcare-related costs[35,45]. However, robust data on the specific impact of a NST on RFS-related mortality are still lacking. Accordingly, our results suggested that the benefits deriving from NSTs are not only limited to the prevention of nutrition-related complications (as a likely result of appropriate nutrition indication/initiation), but they also extended to the amelioration of complication-related outcomes (as a likely result of appropriate nutrition monitoring/supervision and prompt complication management).

We found a significant association between mortality rates of RFS patients and the publication years of the studies. These findings suggested a likely increasing attention to the occurrence and the adverse outcomes of the syndrome among health professionals, as witnessed by the continuously growing number of inherent published studies. Using “refeeding syndrome” as a string search on PubMed, yearly results rose from 25 studies in 2010 to 70 studies in 2020 (date of search: January 10$^{th}$ 2021).

This greater awareness might have led, in the last decade, to a better recognition and to an earlier and more adequate management of the syndrome.

This was the first systematic review and meta-analysis that quantitatively assess the impact of RFS on patient mortality. Other strengths of our analysis were represented by the stratification of results by RFS definition and time-point for mortality evaluation, enhancing the homogeneity among pooled data, and the careful evaluation of relevant categorical or continuous parameters as potential predictors of the outcome measure.

Nevertheless, there were limitations, that are worth to be discussed. First of all, the quality was limited by the quality of the included studies, but the absence of a statistically significant association between the outcome measure and overall risk of bias reassured about the likely small impact of this issue on our final results. A second possible concern was represented by the heterogeneity among studies. The different RFS definitions represent a long-lasting unresolved issue; in addition, several other differences among studies in terms of population characteristics, inclusion criteria, and study design were present. The observed heterogeneity was however low-to-moderate in all our analyses, without reaching a statistical significance; thus, its influence could be reasonably considered as limited. Third, the available studies were mostly focused on hospitalized patients in developed countries; this limits the generalizability of our results to different geographic and sociopolitical contexts, such as conflict zones or non-industrialized countries, in which the impact of the RFS on mortality could be different. For example, the presence of a dedicated NST might also be considered as a proxy for the geopolitical context; if so, it is not unreasonable to think that the impact of RFS on mortality could be higher in the resource-poor setting of third-world countries. Finally, all reported effect sizes were based on crude odds-ratios, as derived by univariate analyses. Thus, the retrieved relationships between RFS and mortality may be either the consequence of a direct impact of RFS on mortality, or the consequence of the common association of both RFS and mortality with other clinically-relevant conditions, such as a greater number of comorbidities or a lower performance status.

In view of these limitations, definite conclusions about the mortality risk related to the development of RFS after re-nutrition cannot be drawn. To this scope, *ad-hoc* prospective observational studies specifically designed for the evaluation of mortality outcomes are needed, with larger population samples and longer follow-up times.

## Conclusions

The RFS was associated with a non-significant trend towards increased mortality in the short-term, and with a significantly increased mortality in the medium-term. The supervision/management of the refeeding process by a nutrition specialist might be a key factor for the limitation of this mortality excess.

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413

414 **Appendix 1.** Electronic search strategy

415

| **PubMed**<br>**No filters** |
|---|
| #1 Refeeding |
| #2 Refeeding OR refeeding syndrome |
| #3 #2 AND anorexia nervosa |
| #4 #2 AND incidence |
| #5 #2 AND critically ill patients |
| #6 #2 AND cancer patients |
| #7 #2 AND elderly or aged |
| #8 #2 AND inpatients |
| #9 #2 AND artificial nutrition |
| #10 #2 AND mortality |
| #11 #2 AND malnutrition |
| #12#2 AND outcome |
| #13 #2 AND phosphorus |
| #14 #2 AND potassium |
| #15 #2 AND magnesium |
| #16 #2 AND alcoholism |
| #17 #2 AND surgery |
| #18 #2 AND fasting |

416

| **Embase**<br>**No filters** |
| --- |
| #1 Refeeding |
| #2 Refeeding OR refeeding syndrome |
| #3 #2 AND anorexia nervosa |
| #4 #2 AND incidence |
| #5 #2 AND critically ill patients |
| #6 #2 AND malignant neoplasm |
| #7 #2 AND aged |
| #8 #2 AND hospital patients |
| #9 #2 AND artificial feeding |
| #10 #2 AND mortality |
| #11 #2 AND malnutrition |
| #12#2 AND outcome assessment |
| #13 #2 AND phosphorus |
| #14 #2 AND potassium |
| #15 #2 AND magnesium |
| #16 #2 AND alcoholism |
| #17 #2 AND surgery |
| #18 #2 AND fasting |

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| **CINAHL**<br>**No filters** |
| --- |
| #1 Refeeding |
| #2 Refeeding OR refeeding syndrome |
| #3 #2 AND anorexia nervosa |
| #4 #2 AND incidence |
| #5 #2 AND critically ill patients |
| #6 #2 AND cancer patients |
| #7 #2 AND elderly or aged or older or geriatric |
| #8 #2 AND inpatients or hospitalization or ‘hospitalized patients’ |
| #9 #2 AND artificial nutrition |
| #10 #2 AND mortality |
| #11 #2 AND malnutrition |
| #12#2 AND outcomes |
| #13 #2 AND phosphorus |
| #14 #2 AND potassium |
| #15 #2 AND magnesium |
| #16 #2 AND alcoholism |
| #17 #2 AND surgery |
| #18 #2 AND fasting |

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| **Cochrane library**<br>**No filters** |
| --- |
| #1 Refeeding OR refeeding syndrome |
| #2 #1 AND anorexia nervosa |
| #3 #1 AND incidence |
| #4 #1 AND critically ill |
| #5 #1 AND oncologic patient |
| #6 #1 AND elderly |
| #7 #1 AND inpatient |
| #8 #1 AND artificial feeding |
| #9 #1 AND mortality |
| #10 #1 AND malnutrition |
| #11 #1 AND outcomes |
| #12 #1 AND phosphorus |
| #13 #1 AND potassium |
| #14 #1 AND magnesium |
| #15 #1 AND alcoholism |
| #16 #1 AND surgery |
| #17 #1 AND fasting |

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