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This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1794815> since 2021-07-23T11:11:34Z

Published version:

DOI:10.1016/j.amjmed.2021.03.010

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

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19 **Funding source:** This research did not receive any specific grant.

20 **Disclosure:** The authors report no conflicts of interest in this work.

21 **Contributions:** All authors participated in the preparation of the manuscript and approved its final
22 version.

23 **Type of manuscript:** Clinical Research Study.

24 **Keywords:** Refeeding syndrome; Mortality; Nutritional support team; Systematic review; Meta-
25 analysis.

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

27

28 **Abstract**

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

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

36 Results. Thirteen studies were finally considered in the meta-analysis, for a total of 3846 patients
37 (mean age 64.5 years; 58% males). Pooled data showed a non-significant trend toward an increased
38 short-term (≤ 1 month) mortality in patients developing the refeeding syndrome (OR 1.27, 95% CI
39 0.93-1.72), mostly driven by studies in which re-nutrition was not prescribed and supervised by a
40 nutritional support team ($p=0.01$ at subgroup analysis) and by studies published in earlier years
41 ($p=0.04$ at meta-regression). When examining medium-term (≤ 6 month) mortality, an overall
42 statistical significance towards higher risk was observed (OR 1.54, 95% CI 1.04-2.28).

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

48

49 **Introduction**

50 The refeeding syndrome (RFS) has been described as a spectrum of biochemical and/or clinical
51 alterations occurring as a consequence of the reintroduction of calories after a period of decreased
52 caloric intake^{1,2}. During prolonged periods of caloric deprivation, energy stores, vitamins and
53 intracellular electrolytes (especially potassium, phosphates, and magnesium) are depleted¹⁻³. After
54 caloric replenishment, the supply of nutrients, in particular carbohydrates, determines a rise in insulin
55 secretion. This, in the presence of a pre-existent total-body deficit of potassium, phosphorus or
56 magnesium, may lead to a further drop in their serum concentrations. In fact, insulin drives these
57 electrolytes inside cells both by direct effects and by increased intracellular demand^{1,4-7}.

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

64 Despite being known for more than 70 years^{15,16}, the RFS has long been underdiagnosed and remains
65 still frequently unrecognised^{1,2,17,18}. This picture is further complicated by the lack of a homogeneous
66 and commonly accepted RFS definition^{1,2}. In April 2020, the American Society for Parenteral and
67 Enteral Nutrition (ASPEN) published a consensus paper, where the RFS has been defined as a >10%
68 decrease in the serum levels of at least one among phosphate, potassium and magnesium, associated
69 or not with organ dysfunction resulting from a decrease in any of these or due to thiamine deficiency,
70 occurring within 5 days of reinitiating energy provision¹. However, most of available studies rely on
71 different and non-standardized criteria, thus leading to heterogeneous data. This makes it difficult to
72 draw clear conclusions about RFS incidence, risk factors, time of occurrence and clinical
73 outcomes^{2,17}.

74 In particular, the impact of RFS on all-cause mortality is unclear^{1,2,6,19}. When moving from single
75 cases to patient cohorts, published studies did not unanimously show excess mortality in patients who
76 developed the RFS compared to those who did not develop it²⁰⁻³². In the last few years, some
77 systematic reviews^{2,17} addressed this issue as a secondary outcome and from a qualitative point of
78 view, with neither definite conclusions, nor quantitative assessment of the mortality risk. The present
79 study is therefore the first meta-analysis that specifically and quantitatively assess the impact of RFS
80 on patient all-cause mortality.

81

82

83 **Methods**

84 Search strategy and study selection

85 This study was conducted according to the Preferred Reporting Items for Systematic Reviews and
86 Meta-Analysis (PRISMA) guidelines³³. The process of literature search and study selection was made
87 by two independent reviewers (I.C., M.P.); all disparities were resolved through consensus.

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

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

99

100 Outcomes

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

105

106 Data extraction

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

117

118 Risk of bias assessment

119 The risk of bias was independently assessed for each included study by two authors (F.B., S.B.) using
120 the seven domains of ROBINS-I (Risk Of Bias In Non-randomized Studies of Intervention scale)
121 tool³⁴. This tool evaluates seven domains, that address (a) bias due to confounding, (b) bias in
122 selection of participants into the study, (c) bias in measurement classification of interventions, (d)
123 bias due to deviations from intended interventions, (e) bias due to missing data, (f) bias in
124 measurement of outcomes, (g) bias in selection of the reported result. An additional evaluation of
125 overall risk of bias is also provided as a summary measure; the options for a domain-level risk-of-
126 bias judgement are ‘Low’, ‘Moderate’, ‘Serious’ or ‘Critical’, with an additional option of ‘Unknown’
127 if sufficient information for judgement is lacking.

128

129 Statistical analysis

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

136

137

138 **Results**

139 Search results

140 A total of 4679 records were identified in the initial literature search. Removal of duplicates and non-
141 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 patients²⁰⁻³² (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 days²⁴, 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.

167 When focusing on the two studies that examined mortality outcomes of clinically-defined RFS, in
168 one of them³², encompassing 243 patients, in-hospital death occurred in 0 out of 3 patients who
169 developed clinical RFS and in 68 out of 240 patients who did not; in the other one²², encompassing
170 68 patients, in-hospital death occurred in 5 out of 7 patients who developed clinical RFS and in 2 out
171 of 61 patients who did not. The low number of studies made it unreasonable to provide a quantitative
172 estimate of a pooled effect size; these studies were thus excluded from subsequent quantitative
173 analyses.

174

175 Mortality of biochemically-defined RFS in the short-term

176 Eleven studies examined the mortality outcomes of biochemical RFS in the short-term. The time point
177 for mortality evaluation was at 7 days in one study²⁴, at 1 month in four studies^{20,23,25,26} and during
178 hospital stay in the remaining six studies^{21,27-31}. The application of a random-effect model on the
179 available data showed a non-significant trend towards an increased short-term mortality in patients
180 developing biochemical RFS after re-nutrition with respect to the control group (OR 1.27, 95% CI
181 0.93-1.72) (Figure 2).

182 Subgroup analyses were conducted in order to analyse if the outcome of interest was significantly
183 associated with the categorical variables that were retrieved at a study-level, specified in the section
184 describing data extraction. These analyses revealed the presence of a statistically significant
185 difference ($p=0.01$) between studies in which re-nutrition was prescribed and supervised by a NST
186 (OR 0.75, 95% CI 0.46-1.21), studies in which it was managed according to specified international
187 guidelines (OR 1.77, 95% CI 0.88-3.58) and studies in which no explicit reference to the presence of
188 a nutrition team nor to the adherence to specific guidelines was provided (OR 2.08, 95% CI 1.24-
189 3.49) (Figure 3). As it can be noted, this difference was mostly driven by an apparent neutrality of
190 RFS on mortality risk in the first subgroup; conversely, excess mortality seemed to be noticeable in
191 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

216 Quality assessment and publication bias

217 The quality of the studies was assessed, in terms of risk of bias, using the ROBINS-I tool³⁴. The major
218 concerns were mostly related to the first two domains, i.e. bias due to confounding and bias in
219 selection of participants into the study (Table 3). No significant publication bias was found at Begg's
220 test, neither for short-term ($p=0.35$) nor for medium-term ($p=1.00$) mortality data.

221

222

223 **Discussion**

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

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

240 The short-term mortality rates observed for RFS patients were associated to the management and
241 supervision modalities of the refeeding process; in particular, no excess mortality was apparently
242 observed in studies in which a dedicated NST was explicitly in charge of re-nutrition, while a higher
243 mortality risk was noticeable in studies where no explicit reference to a NST was made. These findings
244 added another piece of evidence to the increasing body of literature supporting the importance of
245 NSTs in hospital care³⁵.

246 Malnutrition and risk of malnutrition affect up to 50% of inpatients³⁶; however, it is not a unitary
247 phenomenon, showing complex interactions with inflammation and infections, which both play a
248 relevant role in its development and prognosis³⁶⁻³⁹. Multifaceted clinical knowledge is required to
249 ensure optimal individual nutritional support. A NST ensures the quality and safety of nutritional
250 interventions, thus helping in the prevention and adequate treatment of potential metabolic or
251 systemic nutrition-related complications³⁵. The involvement of a NST has been shown to increase
252 appropriate nutritional indications^{35,40,41}, decrease complication rates^{20,35,42,43}, decrease all-cause
253 mortality^{35,42,44}, and reduce healthcare-related costs^{35,45}. However, robust data on the specific impact
254 of a NST on RFS-related mortality are still lacking. Accordingly, our results suggested that the
255 benefits deriving from NSTs are not only limited to the prevention of nutrition-related complications
256 (as a likely result of appropriate nutrition indication/initiation), but they also extended to the
257 amelioration of complication-related outcomes (as a likely result of appropriate nutrition
258 monitoring/supervision and prompt complication management).

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

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

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

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

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

293

294

295 **Conclusions**

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

300

301

302 **Acknowledgements**

303 None.

304

305

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414 **Appendix 1.** Electronic search strategy

415

PubMed

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
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

CINAHL**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

Cochrane library
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
