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SPECIAL ARTICLE

Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials

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Abstract— Background & Aims: A system for screening of nutritional risk is described. It is based on the concept that nutritional support is indicated in patients who are severely ill with increased nutritional requirements, or who are severely undernourished, or who have certain degrees of severity of disease in combination with certain degrees of undernutrition. Degrees of severity of disease and undernutrition were defined as absent, mild, moderate or severe from data sets in a selected number of randomized controlled trials (RCTs) and converted to a numeric score. After completion, the screening system was validated against all published RCTs known to us of nutritional support vs spontaneous intake to investigate whether the screening system could distinguish between trials with a positive outcome and trials with no effect on outcome.

Methods: The total number of randomized trials identified was 128. In each trial, the group of patients was classified with respect to nutritional status and severity of disease, and it was determined whether the effect of nutritional intervention on clinical outcome was positive or absent.

Results: Among 75 studies of patients classified as being nutritionally at-risk, 43 showed a positive effect of nutritional support on clinical outcome. Among 53 studies of patients not considered to be nutritionally at-risk, 14 showed a positive effect (P=0.0006). This corresponded to a likelihood ratio (true positive/false positive) of 1.7 (95% CI: 2.3–1.2). For 71 studies of parenteral nutrition, the likelihood ratio was 1.4 (1.9–1.0), and for 56 studies of enteral or oral nutrition the likelihood ratio was 2.9 (5.9–1.4).

Conclusion: The screening system appears to be able to distinguish between trials with a positive effect vs no effect, and it can therefore probably also identify patients who are likely to benefit from nutritional support.

Key words: food; hospital; patients; nutrition; enteral; parenteral; clinical outcome; screening

Introduction

Undernutrition is common in hospitals and one study showed that among the 40% of the patients, who were undernourished at admission, about 75% lost further weight during hospitalization (1). The deterioration of nutritional status is probably linked to several factors concerning food supply, apart from the disease process itself (2, 3). However, the lack of a widely accepted screening system which will detect patients who might benefit clinically from nutritional support may be considered a major factor. A survey among doctors and nurses in Danish hospitals showed that the lack of a proper screening tool was seen as one of the major reasons for not initiating nutritional support (4).

Up to the present, the available screening systems, however, have not been validated with respect to clinical outcome, as also stated recently by the ASPEN board of directors (5). They also suggested that, in the absence of an outcomes validated approach, a combination of clinical and biochemical parameters should be used to assess the presence of malnutrition. They suggest to use the subjective global assessment, SGA (6), which classifies patients subjectively on the basis of data obtained from history and physical examination, since this system has been validated in several ways other than with respect to clinical outcome. On the other hand, a number of randomized controlled trials (RCTs) have been carried out to investigate the clinical effect of nutritional support, and some of these have shown a positive effect, while others have not. In most of these studies, some measure of nutritional status was used as a criterion for inclusion, stratification or description, but

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commonly used screening systems were seldom used as inclusion criteria (7, 8).

We therefore attempted to establish a screening system[2] using a retrospective analysis of controlled trials and the nutritional criteria or characteristics and clinical outcome in these studies. The system was developed on the assumption that the indications for nutritional support are the severity of undernutrition and the increase in nutritional requirements, resulting from the disease, i.e. that severe undernutrition or severe disease by themselves or in varying combinations may indicate the need for nutritional support. This will also include patients who are not undernourished at the time but are at risk of becoming so because of disease and/or its treatment, e.g. major trauma, surgery or chemotherapy, since both may cause impairment of food intake and increased stress-metabolism. The concept of relating nutritional status to severity of disease is well-recognized, as displayed for example in the decision box (2), which emphasizes the need for acting on possible further impairment of nutritional status during the clinical course of the disease. These concepts are illustrated both by the study of Bastow et al. (9) in elderly women with fractured neck of femur, which showed that nutritional support was effective only in those who were particularly undernourished, but not in those who were less undernourished, and the study by Müller et al. (10) which showed that the positive effect of preoperative nutritional support disappeared when the surgical technique was changed from a transthoracic procedure to a less invasive stapling procedure.

Our screening system which was designed to include measures of current potential undernutrition as well as disease severity was then validated against all controlled trials of nutritional support known to us, in order to evaluate whether it was capable of distinguishing those with a positive clinical outcome from those that showed no benefit from nutritional support. The analysis and the recommendations were reviewed and discussed with an ESPEN ad hoc working group under the auspices of the ESPEN Educational Committee.

Methods

Screening system

Table 1 shows the screening system, developed as explained in detail in the appendix. Patients are scored in each of the two components (1) undernutrition and (2) disease severity, according to whether they are absent, mild, moderate or severe, giving a total score 0–6. Patients with a total score of ≥ 3 are classified as nutritionally at-risk. Undernutrition was estimated using three variables used in most screening tools: BMI, percent recent weight loss and change in food intake, since these have a reasonable evidence base in the literature, correlating with changes in function and clinical outcome (see Appendix). In some studies, other anthropometric measures, e.g. mid-arm circumference (MAC), have been used to characterize patients and these have therefore been correlated with BMI (see Discussion). Estimation of disease severity is necessarily arbitrary to a certain extent, but the scores we have chosen relate to a careful assessment of the literature as explained in the appendix.

Validation study

After completion of the screening tool, published in the official recommendations for provison of food in Danish hospitals in 1999 (21), it was decided to carry out the validation study described here. A complete database of RCTs of the effect of nutritional support vs no support or spontaneous intake on clinical outcome was prepared by searching for studies published as full papers in Medline and available reviews (22–37). The search was completed in October 2001, after the publication of the 2 latest meta-analyses (36, 37), i.e. after presentation of preliminary results (38). The majority of studies were carried out in hospital but out-patient studies were also included. A total of 128 RCTs were included in the analysis (7–9, 11–16, 18–20, 39–151). Three studies (18, 19, 87) were included despite the fact that the control groups received EN. However, since the purpose of these studies was to compare adequate nutritional support with inadequate EN feeding in the control groups, these studies were included. Studies excluded from the analysis were (1) those considered to be duplicates or preliminary to later publications (152–168), (2) studies not written in English (169–174), (3) studies of clearly inadequate nutritional preparations, e.g. amino acids with or without isotonic glucose vs glucose alone (175–181), (4) studies included in the reviews mentioned above that did not describe clinical end-points (182–191), (5) studies dealing with the effect of branched-chain amino acids on hepatic encephalopathy and studies of modified compositions vs a standard preparation, e.g. protein hydrolysates or immunutritive preparations, (6) studies in neonates or children. In the meta-analysis by Koretz et al. (36) hypocaloric studies, i.e. mainly peripheral parenteral nutrition, and studies in which the control groups received high amounts of glucose were not included in the main analysis. In our analysis most of these studies were also excluded by (3) and (5).

Each of the four authors read all papers blind to the views of the others and classified the patient groups in the studies with respect to undernutrition and severity of disease. The objective was to define these as absent, mild, moderate or severe from all information given in a

[2] By our definitions, a screening system is a rapid identification of patients who require nutritional support, carried out by the admitting staff and organized by the ward staff. A nutritional assessment is performed by a nutrition expert in the few patients who may have particular metabolic or nutritional problems and may require special feeding techniques.

Table 1 Screening for nutritional risk

Impaired nutritional status		Severity of disease (≈stress metabolism)	
Absent Score 0	Normal nutritional status	Absent Score 0	Normal nutritional requirements
Mild Score 1	Wt loss > 5% in 3 months Or Food intake below 50–75% of normal requirement in preceding week	Mild Score 1	Hip fracture Chronic patients, in particular with acute complications: cirrhosis (11), COPD (12) *Chronic hemodialysis, diabetes, oncology*
Moderate Score 2	Wt loss > 5% in 2 months Or BMI 18.5 – 20.5 + impaired general condition Or Food intake 25–50% of normal requirement in preceding week	Moderate Score 2	Major abdominal surgery (13–15). Stroke (16) *Severe pneumonia, hematologic malignancy*
Severe Score 3	Wt loss > 5% in 1 month (≈ > 15% in 3 months (17)) Or BMI < 18.5 + impaired general condition (17) Or Food intake 0–25% of normal requirement in preceding week in preceding week.	Severe Score 3	Head injury (18, 19) Bone marrow transplantation (20) *Intensive care patients (APACHE 10*
Score:	+		
Total score:			

Calculate the total score:

1. Find score (0–3) for Impaired nutritional status (only one: choose the variable with highest score) and Severity of disease (≈stress metabolism, i.e. increase in nutritional requirements).
2. Add the two scores (→ total score)
3. If age ≥70 years: add 1 to the total score to correct for frailty of elderly
4. If age-corrected total ≥3: start nutritional support

Note: See text on p. 330: as a prototype, a patient with a score = 1 in severity of disease is admitted to hospital due to complications associated with a chronic disease. The patient is weak but out of bed regularly. Protein requirement is increased, but can be covered by oral diet or supplements in most cases. The prototype of score = 2 is a patient confined to bed due to illness, e.g. following major abdominal surgery or due to severe infection. Protein requirement is substantially increased but can be covered, although artificial feeding is required in many cases. The prototype of score = 3 is the intensive care patient with assisted ventilation, inotropic drugs, etc. Protein requirement is increased to the extent, that in most cases it cannot be covered by artificial feeding, but protein breakdown and N loss can be attenuated significantly.

particular study, using the studies cited in Table 1 as 'bench-marks'. Each author also independently decided whether the effect on clinical outcome should be considered 'positive' or 'no effect' and they were instructed not to count paraclinical variables such as improvements in blood tests. A positive effect on clinical outcome would be accelerated mobilization, reduced rate of infections or other complications, reduced length of stay (see Table 2), while improvements solely in nitrogen balance, liver function tests or similar physiological or biochemical tests would not be counted as positive. It was further noted whether parenteral nutrition (PN), enteral nutrition (EN, i.e. tube feeding) or oral nutrition (ON, i.e. supplements or food) had been used.

Twenty of the studies (39, 41, 44, 53, 55, 66, 70, 78, 84, 92, 97, 107, 110, 121, 124, 129, 132, 138, 141, 192) did not provide any concise information about nutritional status (height, weight, BMI, recent weight loss or anthropometric measures). In these studies, the category of nutritional status was judged according to the author's clinical experience with that group of patients. The analysis was not censored according to the quality of the studies. A double blinded design was used in a few studies only (15, 39, 52, 105, 116, 148). A large number of the studies did not provide information about the intake of the control groups, and therefore the actual efficacy of treatment was not documented. In most cases, the outcome variables were clearly defined, but in many cases it was not documented that outcome variables were evaluated blindly. Strict criteria of quality would therefore eliminate many studies and any other scoring of quality would become highly arbitrary in the present context. Six studies with a borderline statistically significant effect were categorized as positive (7, 16, 50, 96, 103, 146) showing P values of 0.05–0.08 with respect to effect on survival or occurrence of major complications. Studies that claimed a positive effect which could not be confirmed by their data (51) or by a proper statistical test (110) were categorized as showing no effect.

After the first evaluation, studies where the authors disagreed more than 1 score unit for undernutrition or severity of disease, were resubmitted for independent re-evaluation by all authors, i.e. without knowing the scores given by the other authors. The final number of papers with the disagreement mentioned (1 score unit) were 8 and 2 for undernutrition and severity of disease, respectively. For the final scores and calculation of results, the average of the four authors' scores was used.

Statistics

Statistical analysis was performed using Fisher's test for contingency tables, ANOVA, Mann–Whitney's test for group differences and logistic regression analysis, either by GraphPad Prism, GraphPad Software (San Diego, California, USA), or by Systat 10, SPSS (Chicago, Illinois, USA). Diagnostic tests can be evaluated in several ways related to sensitivity and specificity. The commonly used negative and positive predictive values are considered to be of limited usefulness since predictive values of a positive test for a disease depend more on its prevalence than the sensitivity and/or specificity of the test (193). Instead, a *receiver operating characteristic* curve (ROC analysis) gives information about the diagnostic performance of a particular test at various cut-off points for the test, while likelihood ratios give information about the likelihood for an individual to have a disease at various cut-off points, especially when combined with pre-test odds (194). Both approaches offer the advantage of including all data available in the analysis. The screening system described here is not simply a diagnostic test, but rather a test to predict clinical outcome after intervention based on the test result, and such a measure has in fact been described as an ideal way to evaluate a new diagnostic test (193). Analysis of ROC and calculation of confidence intervals of likelihood ratios were done according to (194, 195).

Results

A total of 128 studies containing a total of 8944 patients were analyzed. Table 2 shows the categorization of studies, outcome variables, patient categories and mode of feeding. Only one study was in category 0 with respect to severity of disease (126) and only one study was in category 3 with respect to undernutrition (134), and therefore these categories are not shown in the table. Some studies, using predominantly parenteral nutrition, showed a negative effect on outcome: more major complications (49), more infections (55, 126), more toxicity to cancer therapy (81, 143, 197), impaired tumor response (133), persistence of ascites (111), prolonged length of stay (129, 137) or increased mortality (114). It is apparent from Table 2 that the proportion of studies showing a positive effect rose with increasing scores for undernutrition as well as severity of disease. The analysis in Figure 1 shows that the proportion of studies with a positive outcome was significantly higher in the group with a total score ≥ 3, compared to the group of studies with a score < 3. Sensitivity and specificity were 75% and 55%, respectively. For the individual authors, the sensitivities and specificities were 86% and 37%, 88% and 41%, 86% and 21%, and 79% and 59%, respectively. The inter-author variation in specificity was caused by varied proportions of studies given a total score ≥ 3, ranging from 58% to 82%, but only 45% of the studies were agreed by all four authors to have a total score ≥ 3. Only with this agreement, the average score used in the analyses was ≥ 3 and this explains why the overall sensitivites and specificities are not simple means of the individual results. When analyzed without the 10 studies cited in the right column of Table 1, the analysis showed a P value of 0.002, and when analyzed without the borderline significant studies ($N = 6$), and

Table 2 Classification of controlled trials with respect to nutritional status, severity of disease and outcome

Nutritional Status	Severity of disease ≥1 & <2		≥ 2 & <3		=3	
	Outcome		Outcome		Outcome	
	Positive effect	No effect	Positive effect	No effect	Positive effect	No effect
<1	inf/GI surg/PN (88) tox/canc/ON (102) LOS/femur/ON (60) LOS/fem/ON (141) surv/fem/EN (196)	muscl/GI surg/PN (130) muscl/COPD/ON (128) compl/GI surg/PN (74) compl/canc/ON (42) compl/GI surg/EN (66) inf/GI surg/EN (51) inf/cirrh/EN (59) inf/GI surg/PN (101) inf/spine/ (192) tox/canc/ON (65) tox/canc/PN (81) surv/canc/PN (118)	inf/trauma/EN (108) inf/GI surg/PN (68) inf/GI surg/EN (15) LOS/GI surg/PN (43)	inf/GI surg/PN (53) inf/trauma/EN (131) inf/GI surgPN (62) compl/GI surg/PN (119) compl/GI surg/PN (71) compl/GI surg/PN (75)	inf/burns/EN (87) LOS/traum/EN (19) surv/traum/PN (18) surv/BMT/PN (20)	LOS/trauma/EN (54) surv/burns/PN (79)
≥1 & <2	ADL/geria/ON (149) QL/canc/EN (144) CI/cirrh/PN (61) inf/GI surg/EN (73) inf/ GI surg/PN (78) tox/canc/PN (86) tox/canc/PN (94) tox/canc/ON (112) enc/cirrh/EN (93) surv/GI surg/PN (109) surv/canc/PN (138) surv/geria/ON (142)	QL/canc/ON (115) QL/canc/ON (117) QL/HIV/ON (120) inf/canc/PN (55) inf/pancr/PN (129) inf/GI surg/PN (85) inf/GI surg/PN (89) inf/GI surg/PN (80) inf/spine/PN (84) inf/GI surg/PN (90) muscl/COPD/ON (99) muscl/COPD/ON (95) compl/ GI surg/PN (83) compl/cirrh/PN (110) compl/canc/PN (125) compl/canc/ON (72) compl/cirrh/PN (111) tox/canc/PN (91) tox/canc/PN (143) tox/canc/PN (58) rec/canc/PN (133) resp/canc/PN (98) resp/canc/PN (123) resp/ canc/EN (197) resp/canc/ON (67) tox/canc/ON (63) surv/canc/PN (114) surv/canc/PN (132) surv/canc/ON (107) surv/cirrh/PN (41) surv/cirrh/PN (105)	compl/GI surg/PN (56) compl/GI surg/PN (103) inf/GI surg/ON (13) inf/GI surg/PN/EN (146) inf/cirrh/EN (77) inf/GI surg/ON (14) inf/GI surg/EN (136) inf/GI surg/EN (45) ADL/geria/ON (145) LOS/GI surg/EN (124) compl/GI surg/PN (198) LOS/cirrh/PN (121) surv/ATIN/PN (39) surv/ATIN/PN (44) surv/canc/PN (92) surv/stroke/ON (16) surv/cirrh/ON (96)	inf/GI surg/PN (140) inf//GI surg/PN (113) inf/GI surg/PN (46) inf/BMT/PN (100) inf//GI surg/PN (151) inf//GI surg/PN (127) inf/GI surg/PN (49) compl/GI surg/PN (69) compl//GI surg/ (76) compl/GI surg/PN (150) compl/GI surg/PN (8) compl//GI surg/EN (147) compl/BMT/PN (52) LOS/GI surg/EN (137) surv/ATIN/PN (97) surv/ATIN/PN (70)	None	None
≥2 & <3	wound/GI surg/PN (106) inf/cirrh/ON (82) muscl/COPD/EN (148) muscl/COPD/ON (12) walk/COPD/ON (64) walk/COPD/ON (122) tox/cancer/EN (139) LOS/femur/EN (9) surv/cirrh/ON (50) surv/cirrh/EN (11) surv/HIV/PN (104)	CI/GI surg/PN (135) walk/COPD/ON (116)	inf/GI surg/PN (47) compl/GI surg/PN (7) survival/GI surg/PN (48)	compl/ATIN/PN (40)	None	None

Note: For each study are shown main outcome variable/diagnostic group/mode of feeding. Most studies investigated more than one outcome variable, but only one variable for each study is listed: the most clinically significant outcome variable in the positive trials and the variable most likely to be sensitive to nutritional support in the studies with no effect. Abbreviations: ADL: activity of daily living; CI: a clinical index explained in the study; compl: complications to therapy, e.g. surgery; enc: hepatic encephalopathy; inf: infections; LOS: length of stay; muscl: muscle function; QL: quality of life; resp: response to chemo- or radiotherapy; surv: survival; tox: toxicity to chemotherapy; walk: walking distance; wound: wound healing. canc: cancer; cirrh: cirrhosis/alcoholic hepatitis; fem: femoral fracture; geria: geriatric patients; GI surg: gastrointestinal surgery; pancr: pancreatitis. EN: enteral nutrition, i.e. tube feeding; ON: oral nutrition, i.e. sip feeding in most cases; PN: parenteral nutrition.

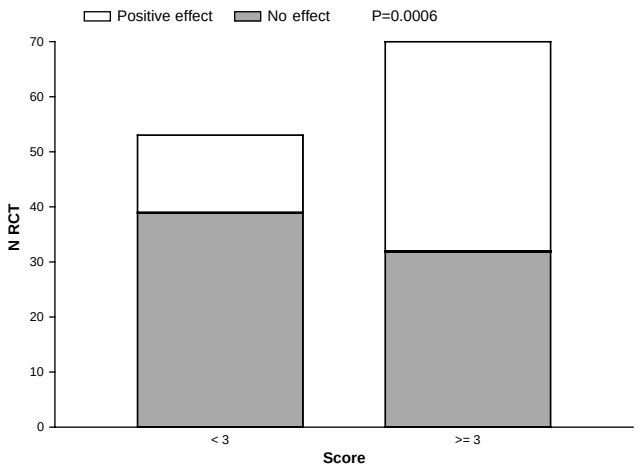

Fig. 1 Nutritional risk score and clinical outcome. All studies were classified according to nutritional risk of the patients studied, cf. Table 1, i.e. total score <3 or ≥ 3 and clinical outcome, i.e. a positive effect or no effect of nutritional support.

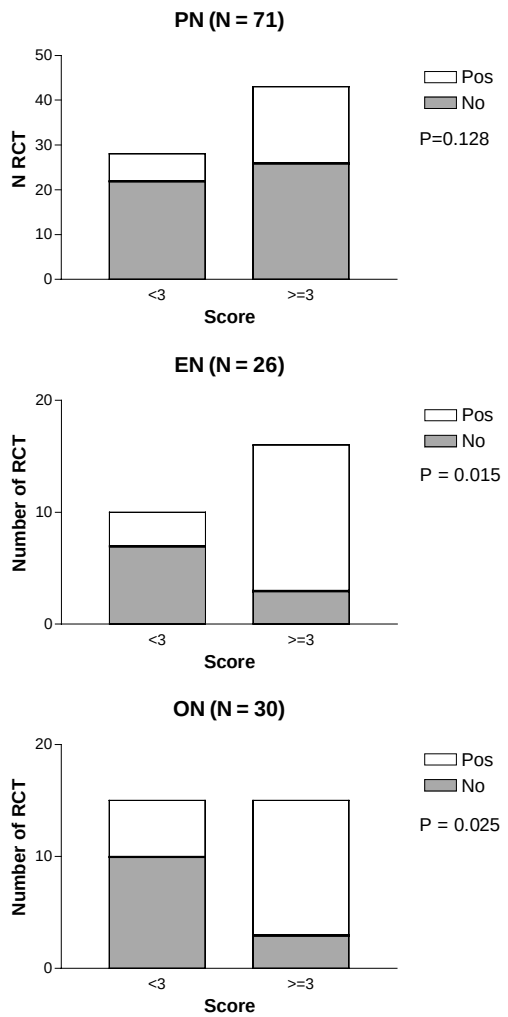

Fig. 2 Nutritional risk score and clinical outcome: relation to feeding mode. Same data as in Fig. 1 categorized according to feeding mode: parenteral nutrition (PN), enteral nutrition (EN) or oral nutrition (ON).

the studies without concise information about nutritional status ($N=20$, see above), the P value was 0.015.

Studies with a score ≥ 3 with a positive result reached a significant proportion for EN and ON studies, but not for PN studies (Fig. 2). The sum of PN, EN and ON studies is 1 less that the total number of studies, because one study (146) randomized patients to PN or EN/ON. This study is therefore excluded from all separate analyses of PN and EN/ON. Sensitivity and specificity were 74% and 46%, 81% and 70%, and 71% and 77% for PN, EN and ON studies, respectively. The scores for severity of disease in studies employing PN, EN or ON were 1.8 (1.3–2.0), 1.8 (1.1–2.1) and 1.0 (1.0–1.5), respectively (median & interquartile range); one way ANOVA with Tukey's post-test: PN vs EN: ns; PN vs ON: $P<0.001$; EN vs ON: $P<0.001$), suggesting that a difference in severity of disease was not responsible for the reduced predictive value in studies employing PN. The scores for nutritional status in studies employing PN, EN or ON were 1.3 (1.0–1.8), 1.0 (0.4–1.8) and 1.8 (1.0–2.0), respectively (median & interquartile range), without any significant differences among the groups.

Ten studies dealt with patients at age ≥ 70 (9, 16, 60, 75, 141, 142, 145, 149, 151, 196). Eight of these studies showed a positive effect of nutritional support and the only two studies without effect employed PN (75, 151). Scores for severity of disease and undernutrition in the 8 positive studies of elderly not given PN were 1.1 (1.0–1.6) and 1.1 (0.8–1.5), respectively (median & interquartile range). These values are much lower than the median values for all studies showing an effect on clinical outcome (see below). Four studies had total scores for severity of disease and undernutrition ≥ 3, and 4 had a score <3.

Figure 3 shows that the proportion of studies with a positive outcome increased with increasing score. Figure 4 shows a *receiver operating characteristic* curve (ROC analysis) for the same cut-off points as in Figure 3, indicating that the cut-off point of 3 gave the best

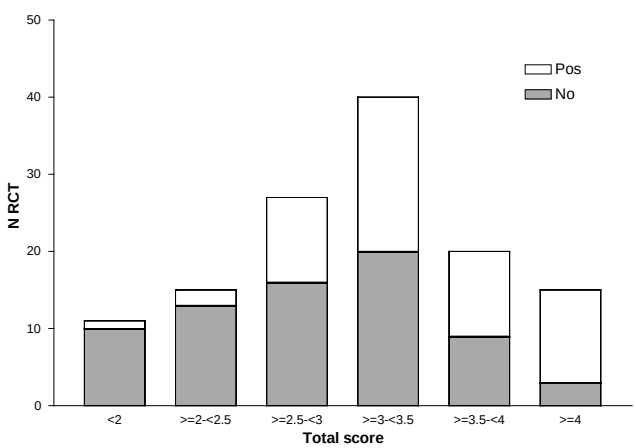

Fig. 3 Variation in nutritional risk score and clinical outcome. The studies were categorized according to total score and for each category, the number of studies with no effect or with a positive effect on clinical outcome are shown.

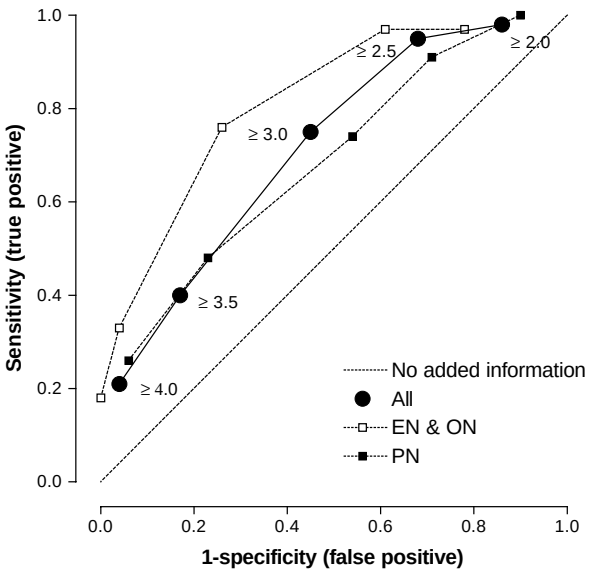

Fig. 4 ROC analysis. Same data as in Fig. 2, but cumulated at the various cut-off points, to illustrate the performance of the nutritional risk screening at various cut-off points. The point with largest distance from the line of 'no added information' of the test is considered the most discriminative cut-off point.

Table 3 Likelihood ratios for a positive effect of nutritional intervention at various cut-off points of score for nutritional risk screening (95% CI

	All ($N=128$)	Enteral or oral ($N=56$)	Parenteral ($N=71$)
≥ 2.0	1.1 (1.3–1.0)		
≥ 2.5	1.4 (1.7–1.2)	1.6 (2.2–1.1)	1.3 (1.6–1.0)
≥ 3.0	1.7 (2.3–1.2)	2.9 (5.9–1.4)	1.4 (1.9–1.0)
≥ 3.5	2.4 (4.4–1.3)	7.7 (55.3–1.1)	2.1 (4.4–1.1)
≥ 4.0	5.0 (16.8–1.5)	∞ [a]	4.2 (15.2–1.1)

[a] All 6 studies in this category were positive.

distinction for EN & ON studies while it was 3.5, and less discriminative, for PN studies. Table 3 shows the likelihood ratios (= true positive/false positive, i.e. y/x of Fig. 4). When all studies are considered, a score ≥ 2.5 was associated with a 95% confidence interval of the likelihood ratio above 1 for a postive clinical effect, and for EN & ON or PN separately, the similar scores were 2.5 and 3.5, respectively.

The following part of the analysis examined how studies with a positive outcome distinguished themselves from those without effect on outcome. Medians and interquartile ranges for the total scores of studies with a positive outcome compared to studies with no effect were 3.3 (2.9–3.8) and 2.8 (2.3–3.0), respectively ($P<0.0001$). Similar values for undernutrition were 1.8 (1.0–2.0) and 1.3 (0.8–1.8), respectively ($P=0.004$), and for severity of disease 1.8 (1.0–2.0) and 1.5 (1.0–2.0), respectively ($P=0.16$).

The results for various diagnostic groups are shown for all studies in Figure 5 or for studies using ON & EN in Figure 6. The same pattern is recognizable in all diagnostic groups: a score ≥ 3 gives a higher chance of a positive effect and this is more pronounced in studies using ON & EN. The number of studies in most diagnostic groups is too small to allow further statistical analysis. It is apparent that a large number of studies with PN and/or in cancer patients has been undertaken in groups of patients not being nutritionally at-risk, according to our screening system.

In order to analyze the data more completely than allowed by the categorical approach above, logistic regression analysis was carried out with outcome as the dependent variable and with scores for undernutrition and severity of disease as independent continous variables, and feeding (PN vs ON & EN) and age (age ≥ 70 years vs age <70 years) as independent categorical variables. The analysis showed, that response (i.e. positive outcome) $= 1.6x$[score for undernutrition] ($P<0.0005$) $+ 1.7x$[score for severity of disease] ($P<0.0005$) $-1.4x$ [TPN = yes] ($P=0.001$) $+ 2.1x$ [age ≥ 70 = yes] ($P=0.019$) -4.4 (P for the equation <0.0005). This equation suggests that severity of disease and severity of undernutrition were almost equally associated with positive outcome. It also suggested that PN was less significantly related to positive outcome compared to EN or ON, or that scores for undernutrition or severity of disease had to be higher for PN to have a positive effect, in agreement with Table 3. In addition, a positive outcome was more likely in older age. Diagnostic grouping did not affect the equation, neither when divided into two categories (medical or surgical), nor when divided into 4 categories (cancer, miscellaneous medical, GI surgery, miscellaneous surgery). It was not changed either by selecting only studies with ≥ 45 patients ($N=61$, i.e. approximately one half of the studies), by including number of patients as a variable, or by including year of publication as a variable. Finally, the mean intakes of energy and protein were calculated. When body weight was not given in the paper, it was taken to be 60 kg in studies of undernourished patients and 70 kg in studies of patients who were not undernourished, for calculation of intake/kg body weight. For studies with no effect, the mean energy (kcal/kg) and protein/amino acids (g/kg) intakes in control and treatment groups were 20 ± 2 and 0.54 ± 0.09 ($N=37$), and 33 ± 2 and 1.31 ± 0.06 ($N=59$), respectively. In studies with a positive effect, the mean energy and protein/amino acids intakes in control and treatment groups were 20 ± 2 and 0.67 ± 0.07 ($N=28$), and 37 ± 2 and 1.41 ± 0.09 ($N=49$), respectively. The intakes in the 'no effect' and positive studies were similar, suggesting that the indication with respect to severity of disease and nutritional status was more determinant for the effect of nutritional intervention, than the range of energy and protein given in these studies. The logistic regression analysis equation was not either substantially altered by including energy or protein intake, or difference in energy or protein intake between control and treatment groups, or by only analyzing studies with an intake ≥ 0.8 g protein/kg per day and ≥ 25 kcal/kg per day.

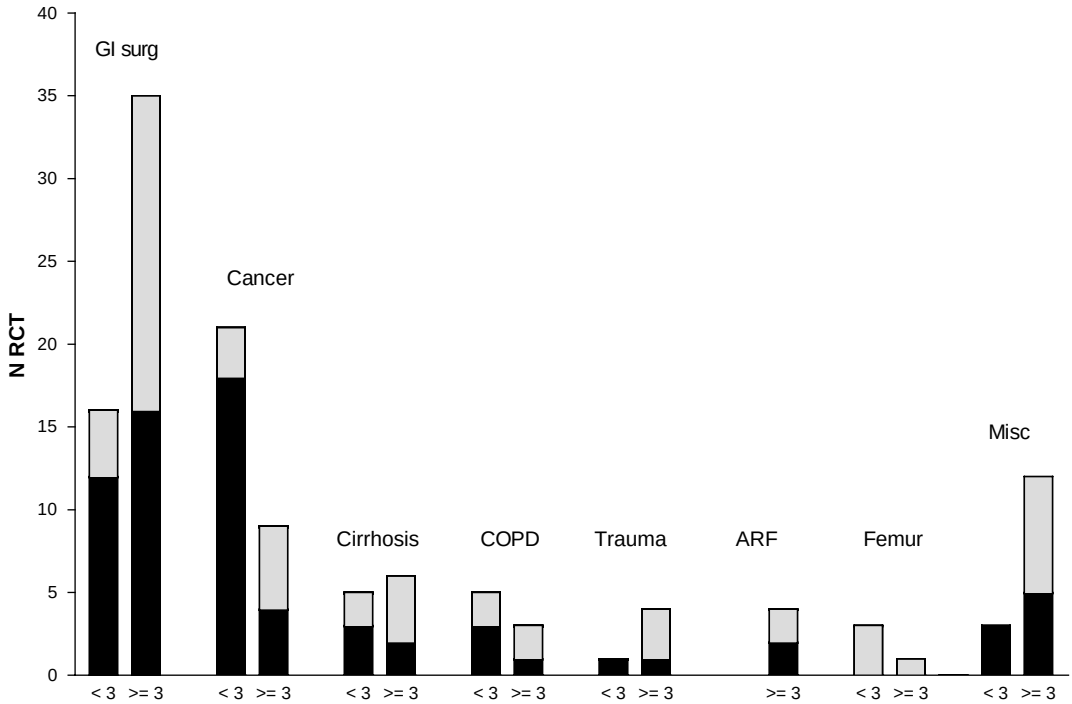

Fig. 5 Nutritional risk score and clinical outcome: results for various diagnostic groups. Same data as in Figure 1 categorized according to diagnostic group. ARF = acute renal failure. Femur = femoral fracture. Misc = miscellaneous. Shaded bars, positive effect; black bars, no effect.

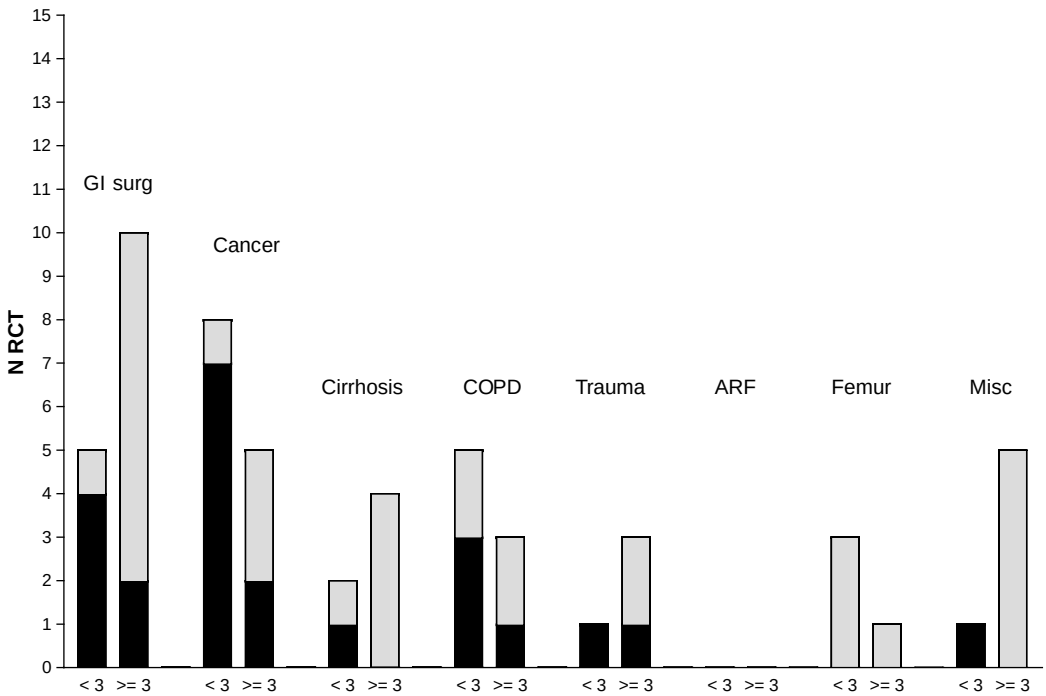

Fig. 6 Nutritional risk score and clinical outcome: results for various diagnostic groups fed enterally or orally. Same data as in Fig. 5, except that only studies with enteral or oral feeding are shown. ARF = acute renal failure. Femur = femoral fracture. Misc = miscellaneous. Shaded bars, positive effect; black bars, no effect.

Discussion

The screening system was developed on the basis of intervention studies that were illustrative of the overall concept. However, dietary history was included among the variables defining undernutrition with the same weight as the other variables, despite the fact that only few studies used dietary history as part of the initial characterization of the patients. Also, the definition of the categories of inadequate intake as mild, moderate, or severe was estimated due to lack of accurate documen-

tation. As explained in the Appendix, a number of studies with a positive outcome after nutritional support were actually characterized by a low intake in the control group, rather than by reduced actual body weight or recent weight loss. Classification of a patient as being at-risk by dietary history alone will only occur with a ≥ 1 week's history of an intake equal to 0–25% of estimated requirement, and such a history can probably be obtained with a sufficient degree of certainty in most cases. It was shown that nurses' dietary recording in quartiles agreed reasonably well with the dietitian's recording (199), and it may be assumed that a recent dietary history also will be reasonably reliable. The score for severity of disease reflects increased nutritional requirements due to stress-metabolism, and for most of the patient categories in Tables 1 and 2, several studies show increased utilization of energy and/or protein, roughly agreeing with the scores 1–3.

The adjustment for old age in Table 1 was added after the first analysis of the results. The search for a possible association with old age was prompted by the study (142) showing that a modest amount of oral supplement increased survival among 500 elderly patients during a 2 months' geriatric rehabilitation following a hospital stay. These patients had a normal body weight for height, but they did have a poor intake at the time of randomization. They did probably not have severely increased nutritional requirements, at least not more than the studies categorized as score 1 in severity of disease in Table 1. We interpreted the remarkable effect on mortality as an increased efficacy of oral supplement on the background of increased susceptibility to a mild-moderate degree of undernutrition, i.e. the inadequate intake, rather than severely increased requirements. A possible increase in efficacy of nutritional support among elderly agrees with the observation, that all the studies in elderly patients with fractured neck of femur (9, 60, 141, 196) had a positive outcome, even though only one study (9) had a score ≥ 3 when based on nutritional status and severity of disease alone, and that all 8 EN & ON studies of elderly had a positive outcome, despite the fact that their scores for nutritional status and severity of disease were rather low (see Results). After the first analysis, age ≥ 70 years was included as a categorical variable in the regression analysis, and it turned to be significantly associated with outcome (see Results). The level of significance for old age was rather low, but there were only 10 studies with a mean age of ≥ 70 years. The apparently increased efficacy of nutritional support in elderly patients, or increased susceptibility to undernutrition, may reflect a nutritional frailty of old age, possibly related to the decrease of lean body mass with age, even at constant body weight (200). When adding the value of 1 to the total score (0.5 to nutritional status and 0.5 to severity of disease) of the studies of patients of age ≥ 70 in the first analysis, the categorical effect of old age disappeared in the logistic regression analysis (data not shown). It was therefore decided to add a value of 1 to the total score obtained from nutritional status and severity of disease/stress metabolism in older patients and redo all the analyses according to the final version of Table 1. This caused only 1 study to be moved from a total score of <3 to ≥ 3 (75), employing PN, and therefore the re-calculation only caused minor changes in Table 3 and Figures 3–4, but not for other results of the analysis.

Issues to be studied further is a possible interaction of the criteria in Table 1, e.g. whether a patient with a BMI of 18.5–20.5 who also had a recent dietary intake of 25–50% should be given a higher score than a patient only fullfilling one of these citeria. At present, it is recommended to choose only the most suitable and reliable criterion for score in each component (undernutrition and severity of disease). In addition, the inter-observer variation of the screening system needs to be determined.

The main bias in our analysis is that the authors were not blinded to outcome when estimating the degree of undernutrition and severity of disease. This could influence the authors to attribute higher scores than justified by data to papers with a positive outcome. However, it was not feasible to separate these items objectively, since information on nutritional status, severity of disease and outcome often was to be sought in the text of the paper as a whole. The effect of this possible bias does not seem large, however, since median values for total score for nutritional status and severity of disease (i.e. without the age correction) in studies with positive or no effect were very close: 3.0 (2.8–3.6) and 2.8 (2.3–3.0), respectively (median and interquartile range; $P = 0.002$). Also, the smooth increases in Figure 4, and the differences between PN and EN or ON in Figure 4 and Table 3 do not suggest a threshold in the scoring induced by such a bias.

The logistic regression analysis suggested that studies with a positive outcome were characterized to a similar extent by the degree of undernutriton and severity of disease, which is compatible with the a priori assumption that indication for nutritional support rests on undernutrition combined with severity of disease. The analysis also suggested that a positive outcome was more closely associated with ON or EN than with PN, for a given degree of undernutrition and severity of disease, as is also apparent from Table 3 and Figure 4. The rather low specificity of the cut-off point ≥ 3 in the analysis of all studies including PN and of PN studies alone is a reflection of these results. This suggets that PN is less effective, or effective only when the indication for nutritional support is strong enough. The reduced efficay of PN agrees with studies directly comparing PN to EN (201, 202). The regression analysis also suggested that the association with outcome was not influenced by protein or energy intake, diagnostic category, study size or year of publication.

Clinical aspects

Studies of groups of patients considered to be nutritionally at-risk had an increased likelihood for a positive effect of nutritional intervention, and the screening system may therefore also be able to distinguish patients who are likely to benefit from nutritional support from patients who are not. This system is based on evidence to a higher degree than other systems that have only been validated by inter-observer variation such as the SGA system (6), by comparison to the SGA system (203), or by a nutritionist validating the nurse's screening (204). The present system, based on the patient's clinical condition and evidence regarding clinical outcome, may promote doctors and nurses to screen patients, since it can be argued that patients who are ignored according to this system are likely to experience a worse clinical course than would be the case with appropriate nutritional support. However, the final validation of the screening tool will be its application in a randomized study showing that patients estimated to be at-risk, who are subsequently randomized to nutritional support, have an improved outcome compared to at-risk patients not given nutritional support.

Recent meta-analyses, or systematic reviews, suggest that nutritonal support as EN or ON does improve clinical outcome (35) while PN in most cases does not (36). No attempts were made in these meta-analyses to stratify the studies according to whether or not nutritional support was indicated, in terms of nutritional status and nutritional requirements/severity of disease. As can be seen in Table 2 and Figures 5 and 6, this was, in our opinion, not the case in a large part of the studies, particularly with PN or cancer patients. The inclusion of studies of patients who may not have been nutritionally at-risk in the meta-analysis of PN studies (36), and in a systematic review of trials in cancer patients (30), may in part explain their failure to show clinical benefit of the intervention. It was in fact emphasized in both analyses that an effect among such patients could not be ruled out, due to the small number of studies dealing particularly with malnourished patients.

In the lack of a sufficient number of clinical trials in all patient categories, the right half of Table 1 is meant as examples for hospital departments to modify, according to their patient categories. This is shown for some patient groups in italics in Table 1, based on available evidence on nutritional requirements or 'clinical judgment'. As a prototype, we see patients with a score = 1 in severity of disease as patients admitted to hospital due to complications associated with a chronic disease. The patient is weak but out of bed regularly. Protein requirement is increased, but can be covered by oral diet or supplements in most cases. The prototype of score = 2 is a patient confined to bed due to illness, e.g. following major abdominal surgery or due to severe infection. Protein requirement is substantially increased but can be covered, albeit artificial feeding is required in many cases. The prototype of score = 3 is the intensive care patient with assisted ventilation, inotropic drugs, etc. Protein requirement is increased to the extent that in most cases it cannot be covered even by artificial feeding, but protein breakdown and N loss can be attenuated significantly. The categorization of patients in Table 1, as based on the randomized studies specified, should not be taken to mean that a patient with a particular diagnosis always belongs to the same category. A patient with cirrhosis, for example, who is admitted to intensive care because of a severe infection, should be given a score of 3, rather than 1. It should also be noted that a number of hospitalized patients will have a score of 0 with respect to severity of disease, and therefore hospitalization by itself does not count in the scoring system.

In cases where patients cannot be weighed, or body weight is unreliable due to accumulation of fluid, it is useful to apply measurements of MAC (9). It is difficult, however, to translate the BMI values in Table 1 to measurements of MAC, since, to our knowledge, data on simultaneous measurement of body weight and height, or % of reference weight or BMI, and MAC have not been published in a form that allows comparison of cut-off points for these measurements. In 22 of the RCTs where no edema or ascites was reported (12–14, 16, 18, 65, 82, 85, 95, 99, 100, 102, 104, 117, 118, 122, 127, 134, 137, 142, 148, 149) mean values for body weight and height (or BMI) were given together with mean values of MAC. In 12 of these studies, BMI was below 20.5 and in 10 out of these 12, mean MAC was <25 cm, and BMI was <20.5 in all studies with a mean MAC <25 cm (data not shown). It is therefore suggested that a MAC <25 cm corresponds to a BMI <20.5. These data does not allow for distinguishing between values for MAC corresponding to a BMI of <18.5 vs $18.5 >$ BMI <20.5.

Often, it is not possible to obtain an accurate height and in some cases, information on weight loss or recent dietary intake cannot be obtained from the patient or his relatives. However, the same probably applied to the trials underlying the screening and the screening procedure is not meant to be more accurate than these trials. When in doubt, it is recommended to treat the patient as an at-risk patient until it is documented that the patient by himself has an adequate dietary intake.

In departments with few at-risk patients, our screening system may seem too complex. Others developed an easy screening tool based on three simple questions (203), and if the screening was positive, a formal assessment by SGA was carried out. In the case of our system, the simple screeening questions would be: (1) is BMI <20.5? (2) has intake been reduced during the last week? (3) has there been a recent weight loss? and (4) is the patient severely ill? If the answer is yes to any of these four questions, the formal screening in Table 1 is carried out. For patients with a score <3 on admission,

it is recommended to consider whether the patient is likely to develop a score ≥ 3 in the near future, e.g. if the patient is scheduled for a major operation. In these cases, a plan for nutritional support should be decided upon right away. For the remaining patients, we recommend the screening to be repeated weekly during the hospital stay, in order to monitor and detect at an early stage whether the patients develop a risk status during the stay.

The system has been included in the National Food Agency's recommendations for food in hospitals (21) and it is being gradually introduced in hospital departments throughout Denmark. Our experience suggests that nurses and doctors can use the tool after a short introduction and a survey of three hospitals (a local, a regional and a university hospital) showed that the incidence of at-risk patients among 750 newly admitted patients was about 20% (205). This paper also shows the scores for severity of disease given to the diagnoses of the patients which may help in using Table 1. In addition, the present screening system is now recommended by ESPEN for nutritional screening in hospitals, together with the MUST system in the community and the MNA system in institutionalized elderly (206).

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The complete list of randomized trials including the scoring, outcome variables and abstracts is available on the web site of the Danish Association of Parenteral and Enteral Nutrition at www.dske.dk.

Appendix

Development of the screening system

The screening tool (Table 1) was worked out by the Danish Society for Parenteral and Enteral Nutrition with the participation of 2 of the present authors (JK and HHR), and 2 others (M Staun, Department of Gastroenterology, Rigshospitalet, Copenhagen, and K Ladefoged, Department of Gastroenterology, Koege Hospital). In brief, patients are characterized by scoring the components 'undernutrition' and 'severity of disease' in four categories (absent, mild, moderate and severe). The patient can have a score of 0–3 for each component, a total score of 0–6, and any patient with a total score ≥ 3 is considered at nutritional risk.

Undernutrition is evaluated using three variables (BMI, percent recent weight loss and recent change in food intake). The most compromised of the three variables is used to categorize the patient. History of dietary intake was included in the system in a semi-quantitative scale, despite its unmeasurable nature. History of dietary intake conveys information that is not always reflected in BMI or recent weight loss. In surgical patients, impaired wound healing was found to be more closely related to a reduction in intake of at least half of the normal intake in the week before surgery than to actual body weight or recent weight loss (207). In addition, data from some controlled trials suggest, that the observed effect of nutritional intervention was associated with recent dietary intake, rather than body habitus measurements. In an analysis of controlled trials of patients with liver cirrhosis, benefit of nutritional support appeared to be associated with low dietary intake, rather than with anthropometric measurements of undernutrition (32). In another study of elderly patients with a positive outcome from nutritional support (142), the patients were not underweight, but had a reduced dietary intake at the time of inclusion. For simplicity and practical purposes, dietary intake is categorized in quartiles of estimated requirements, and it has been shown that nurses' recording of dietary intake in quartiles agrees reasonably well with the dietitians' recording of intake (199).

Severe undernutrition (score 3, Table 1) was defined by using the study by Keys et al. of 24 weeks' semi-starvation in human volunteers (17). After 3 months, they had lost 18% of their body weight, had a BMI $\approx$18, grip strength was reduced by 17%, physical fitness by 48% and a depression score had increased by 18%. To avoid inclusion of healthy individuals with a habitually low BMI, it is emphasized that when a BMI $<$18.5 alone is to categorize a patient as being nutritionally at-risk, it must be associated with an impaired general condition that can ascribed to undernutrition, as was the case for these volunteers. The classification of a poor dietary intake defined as severe (score 3) was based on the calculation, that an intake of 0–25% of requirement would lead to a weight loss of about 5% in 2 weeks, i.e. $>$5% in 1 month.

A moderate degree of undernutrition (score 2) was defined as BMI $<$20.5, based on a study conducted in patients with chronic obstructive pulmonary disease which used body weight $<$90% of reference weight ($\approx$BMI $<$20.5), as an inclusion criterion and showed an effect of nutritional support (12). Other studies illustrating a positive effect of nutritional support in patients being moderately undernourished and having a mild degree of severity of disease are (9) and (11). In these studies, mid-arm circumference, rather than BMI, were used to characterize the degree of undernutrition and the equivalent cut-off points of BMI and MAC will be adressed in the Discussion. The magnitude of weight loss defining score 2 is an interpolation between score 3 and score 1 (see below). The category of food intake in score 2 was defined by extrapolation from score 3.

The category of mild undernutrition (score 1) does not contain a value for BMI, since a BMI 20.5 is considered adequate. The definition of this category with respect to weight loss ($>$5% in 3 months) was based on studies showing an effect of nutritional support in patients who went through moderate-major abdominal surgery, and who had experienced recent weight losses of 4–7% (13, 14). The food intake in score 1 was defined by extrapolation from Scores 3 and 2.

Within the component of severity of disease, the most severe category (Score 3) was defined by studies showing an effect of nutritional support in patients who were well-nourished before becoming severely ill. This is illustrated by studies of neurosurgical patients with head- injury who were shown to have an increased survival rate with parenteral nutrition (18), or a decreased infection rate with nasojejunal feeding (19). For the groups of patients shown in italics there are no intervention studies available documenting an effect of nutritional support vs spontaneous dietary intake, but they were inserted into the system according to 'clinical judgment' (see Discussion).

The category of moderate severity of disease (Score 2) was defined by studies suggesting that the observed effect of nutritional support was dependent on the co-existence of a mild degree of undernutrition. This applies for instance to studies with patients undergoing moderate-major abdominal surgery, since in most cases these studies have involved patients with a mild degree of undernutrition (13, 14).

The category of mild severity of disease (score 1) was defined by studies suggesting that the observed effect of nutritional support was dependent on the the co-existence of a moderate degree of undernutrition. This is illustrated by the study of patients with fractured neck of femur, since nutritional support was effective in the moderately undernourished patients but not in those who were only mildly undernourished (9). Similarly, in patients with chronic obstructive pulmonary disease, an actual body weight $<$90% of reference was an inclusion criterion (12). This category is further illustrated by studies of patients with liver cirrhosis which suggested that a positive effect of nutritional support was observed only in patients with a moderately reduced dietary intake (11, 32).

Following categorization of the patient with respect to the scores of undernutrition and severity of disease, the 2 scores are summed and a total score $\geq$3 is indicative of nutritional risk and, based on evidence given above, the patient is believed to benefit from nutritional support. As seen in Table 1, a score $\geq$3 can be obtained by being severely ill, or severely undernourished, or by having a moderate degree of severity of disease in combination with a mild degree of undernutrition, or by having a mild degree of severity of disease in combination with a moderate degree of undernutrition. With age $\geq$70 years, a value of 1 is added to the total score. This correction for frailty of old age was included in Table 1 after the validation study described. It should stressed at this point, that the studies referred to in Table 1 were selected on the grounds, that they were able to illustrate the desired categories of mild, moderate and severe in undernutrition and severity of disease, and that they seemed to be reasonably acceptable from a methodological point of view. Apart from the correction for age, there had been no efforts to undertake a complete analysis of the existing litterature when the screening system (Table 1) was worked out.

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