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Randomized Control Trials

Validation of modified GLIM criteria to predict adverse clinical outcome and response to nutritional treatment: A secondary analysis of a randomized clinical trial

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SUMMARY

Background & aims: The Global Leadership Initiative on Malnutrition (GLIM) recently suggested specific criteria to standardize the diagnosis of malnutrition. There is need for validation of these criteria regarding response to nutrition treatment. Our aim was to validate modified GLIM (mGLIM) criteria among medical inpatients at risk of disease related malnutrition for prediction of outcome and response to nutritional therapy.

Methods: This is a secondary analysis of the Effect of Early Nutritional Support on Frailty, Functional Outcomes, and Recovery of Malnourished Medical Inpatients Trial (EFFORT), a multicenter randomized controlled trial conducted between April 2014 and February 2018. Adult medical inpatients at nutritional risk (Nutrition Risk Score 2002 $\geq$ 3 points) were randomly assigned to receive nutritional therapy according to an algorithm based on individualized nutritional requirements (intervention group) or standard hospital food (control group). We included all participants with available information regarding mGLIM criteria. The primary outcome was adverse clinical outcome, which was a composite of 30-day all-cause mortality, ICU-admission, rehospitalization rate, major complications and decline in functional status.

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Results: Of 1917 eligible participants at nutritional risk, 1181 (61.6%) met the diagnosis of malnutrition based on mGLIM criteria. The incidence of adverse clinical outcome was significantly higher in mGLIM-positive participants compared with mGLIM-negative participants [330/1181 (27.9%) versus 140/736 (19.0%); multivariable adjusted odds ratio [OR] 1.53; 95% CI 1.22–1.93; p < 0.001]. Regarding the effect of nutritional therapy, the reduction in adverse clinical outcomes was higher in mGLIM-positive participants [180/581 (31.0%) vs. 150/600 (25.0%), OR 0.69; 95% CI 0.53–0.9, p = 0.007], compared with mGLIM-negative participants [75/379 (19.8%) versus 65/357 (18.2%), OR 0.95; 95% CI 0.65–1.40, p = 0.797], a finding that was, however, not significant in interaction analysis (p for interaction = 0.217).
Conclusion: Data from this secondary analysis of a multicenter randomized trial involving medical inpatients at nutritional risk validate the strong prognostic value of mGLIM criteria regarding adverse clinical outcomes and other long-term outcomes. However, further research is needed to improve the ability of GLIM criteria to predict therapeutic response to nutritional interventions.
Trial registration: ClinicalTrials.gov Identifier: NCT02517476.

1. Introduction

Disease-related malnutrition (DRM) is highly prevalent, particularly among polymorbid medical inpatients, and is a major public health issue [1]. Around 30% of patients admitted to hospitals are at nutritional risk or even malnourished [2–5], a condition which is strongly associated with increased morbidity, disability, short- and long-term mortality, impaired recovery from illness, and increased costs of care [6]. Recently, there has been progress in the understanding of the complex pathophysiology underlying malnutrition and in the treatment of patients with this condition with several trials and meta-analyses showing that nutritional therapy is effective in reducing complication rates and mortality associated with DRM [2,7,8].

Still, achieving consensus diagnostic criteria for the diagnosis of DRM has been challenging over the years [9]. Initially, malnutrition was defined as a lack of intake or uptake of nutrients that leads to altered body composition and body cell mass, which in turn cause decreased physical and mental function as well as adverse clinical outcomes from disease [10]. Yet, this definition, and other similar ones, lacked specificity and practical ease for routine patient care [11,12]. Recently, global experts have proposed specific variables to be included in a consensus definition for DRM [10]. More specifically, in 2019 the Global Leadership Initiative on Malnutrition (GLIM) criteria [13,14] were published as new minimal operational criteria for the diagnosis of malnutrition. The authors proposed that DRM should be diagnosed in a two-phased approach: first with nutritional screening to identify patients at risk of malnutrition and second with the application of more specific criteria to confirm malnutrition [13]. These include three phenotypic criteria (unintentional weight loss, low body mass index (BMI), and reduced muscle mass), and two etiological criteria (reduced food intake or assimilation, and inflammation or disease burden). These GLIM criteria have been derived based on a strong pathophysiological rationale and their prognostic value has been well documented in several studies [15–22]. However, there is a lack of studies validating the value of these criteria to predict response to nutritional therapy, and it remains uncertain whether nutritional therapy should be focused primarily on GLIM-positive patients (i.e., those who meet at least one criterion from the phenotypic and one from the etiological group), or to the overall population of patients at risk for malnutrition.

We validated the GLIM criteria regarding prediction of adverse clinical outcomes and nutritional treatment response among prescreened medical inpatients at risk for disease-related malnutrition included in a recent multicenter randomized controlled *Effect of early nutritional support on Frailty, Functional Outcomes and Recovery of malnourished medical inpatients Trial* (EFFORT) [2].

2. Material & methods

2.1. Study design and setting

This study is a secondary analysis of EFFORT [2], a pragmatic, investigator-initiated, open-label, multicenter trial that was undertaken in eight Swiss hospitals from April 2014 to February 2018. Reporting of the results follows the guidelines of the CONSORT statement for randomized trials [23]. The Ethics Committee of Northwestern Switzerland (EKNZ; 2014_001) approved the study protocol and all participants, or their authorized representatives, provided written informed consent. The trial was registered at ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT02517476). The main aim was to assess the effects of early nutritional therapy on patient outcomes in the medical inpatient setting. The rationale for the trial, design details, eligibility features as well as the main results have been published previously [2,24].

2.2. Patient population and management

EFFORT enrolled adult participants (≥18 years of age) at nutritional risk with a Nutritional Risk Screening (NRS 2002) total score of at least 3 points and with an expected hospital stay of more than 4 days who were willing to provide informed consent within the first 48 h after admission. The NRS 2002 comprises two main parts: impaired nutritional status and severity of disease (≈stress metabolism), each with a scoring system from 0 (absent) to 3 (severe). An age-corrected total score ≥3 indicates "nutritionally at risk", and nutritional therapy should be considered [4]. Exclusion criteria were admission to intensive care or surgical units, inability to ingest food, pre-existing artificial nutritional therapy at admission, terminal condition, contraindications for nutritional supplements and several diseases such as anorexia nervosa, acute pancreatitis, acute liver failure, cystic fibrosis, stem-cell transplantation, and bariatric surgery. Randomization (1:1) was done with an interactive web-response system, with variable block sizes and stratified according to site and severity of malnutrition. Participants in the intervention group received individualized nutritional therapy initiated in the first 48 h after admission. A trained registered dietician calculated individual energy and protein goals and developed a treatment plan, initially based on oral nutrition (food adjustment according to participants' preferences, food fortification, snacks between meals and oral nutritional supplement). If less than 75% of caloric and protein targets were reached within 5 days, an escalation to enteral tube feeding or parenteral feeding was

discussed. Participants in the control group received standard hospital food. Upon admission, medical diagnosis according to ICD 10-codes, socio-demographic and anthropometric data, baseline muscle strength and functional status using the Barthel's Index [25] were assessed in all participants based on the trial protocol. Following discharge, blinded study nurses contacted participants after 30 and 180 days for a structured telephone interview. Prespecified health-related outcomes were systematically assessed at these time points.

2.3. Modified GLIM criteria (mGLIM)

We categorized participants as mGLIM-positive (i.e., malnourished) or mGLIM-negative as proposed by the GLIM criteria [13], based on admission information available of participants in the trial. In brief, we used the three phenotypical criteria (i.e., unintentional weight loss, low BMI, reduced muscle mass) and the two etiologic criteria (reduced food intake or assimilation, inflammation/disease burden). mGLIM-positive participants had at least one criterion from each group. Detailed information about the different components of mGLIM criteria and NRS 2002 is summarized in the appendix (eMethods 1 in the Supplement). Importantly, because GLIM criteria were not available at the time point of the planning of the EFFORT trial, we did not prospectively assess GLIM criteria in participants but used the available clinical information collected during the trial on participants to classify them. We used handgrip strength as a proxy for reduced muscle mass, and we applied cutoffs of 8 kg for female and 16 kg for male participants according to results from a former study [26], Inflammation was defined as an admission serum C-reactive protein concentration $\geq$10 mg/l as used in previous studies [27]. For some criteria, we adjusted the definition slightly due to lack of more specific information. Specifically, we used weight loss of >5% of the body weight within the last 6 months but we had no information about weight loss >10% over more than 6 months as proposed by GLIM. As our data about food intake were limited to the last week, we defined reduced food intake as "<50% of energy requirements during the last week" and used the presence of gastrointestinal admission diagnosis to define "a GI condition that adversely impacts food assimilation or absorption". An overview of definitions of criteria used in our sample is presented in the appendix (eTable 1 in the Supplement). Missing variables were treated as missing and we thus excluded participants with unknown mGLIM status due to missing variables.

2.4. Outcomes

The primary endpoint was a composite endpoint defined as adverse clinical outcome within 30 days including the following outcomes: all-cause mortality, admission to the intensive care unit from the medical ward, nonelective hospital readmission after discharge, major complications (adjudicated nosocomial infection, respiratory failure, a major cardiovascular event, acute renal failure, gastrointestinal failure), or a decline in functional status of 10% or more from admission to day 30 as measured by the Barthel's index (scores range from 0 to 100, with higher scores indicating better functional status) [2,24].

Secondary short-term outcomes were each individual component of the primary endpoint and length of hospital stay. Secondary long-term outcomes were all cause-mortality within 180 days and 5 years as well as quality of life assessed after 180 days through the 5-level European Quality of life 5 Dimensions index including the self-assessment visual analogue scale (EQ5D-VAS) [2,24]. Detailed information for each outcome is summarized in the appendix (eMethods 2 in the Supplement).

2.5. Statistical analysis

Continuous data are expressed as means and standard deviations; binary and categorical variables are shown as counts and percentages. Baseline characteristics were compared between mGLIM-positive and mGLIM-negative participants by means of Student t-test (continuous) and Pearson χ^2 test (binary, categorical). In a first step, we assessed the association between mGLIM definition and clinical outcomes by calculation of logistic regression analysis and reported odds ratios (OR) and 95% confidence intervals (CI). We adjusted the analyses for the following predefined covariates: age, sex, main diagnosis, comorbidities, randomization, and study center. Further, we studied the association of the different components mGLIM criteria with clinical outcomes. In a second step, we studied the effect of nutritional therapy in association with mGLIM criteria by comparing outcomes in participants receiving nutritional therapy with control participants not receiving additional support within the population of mGLIM-positive and mGLIM-negative participants. We included interaction terms into the statistical models to investigate if there was evidence for effect modification due to mGLIM criteria. Similar to the initial trial, we used a multivariable model adjusted for age, sex, main diagnosis, comorbidities, and study center. Statistical analyses were performed with STATA 17.0 (STATA Corp., College Station, TX). Results were considered statistically significant at $p < 0.05$.

3. Results

From the 2028 participants at nutritional risk originally included in the EFFORT trial, we excluded 111 due to incomplete information about the single components of mGLIM criteria. We thus had 1917 eligible participants included in the final analysis. Figure 1 shows the participant flow throughout the trial based on the original trial.

A total of 1181 (61.6%) participants met mGLIM criteria for the diagnosis of malnutrition and were classified as mGLIM-positive, while 736 (38.4%) were mGLIM-negative. Baseline characteristics for the overall cohort and stratified by mGLIM criteria are shown in Table 1. The mean overall age was 72.4 years and 52.4% were male. There were several differences between the mGLIM-positive and mGLIM-negative participants with regard to anthropometric data, nutritional data, admission diagnoses and comorbidities. Comparing our cohort with the original cohort of the EFFORT trial, the participants we had to exclude because of missing GLIM status were older, had a higher BMI and had more hypertension and congestive heart failure but less malignant comorbidities (eTable 2).

3.1. Association of mGLIM definition and clinical outcome

In a first step, we investigated the association of mGLIM criteria and adverse clinical outcomes to understand its prognostic implications. eTable 3 shows primary and secondary outcomes for mGLIM-positive and the mGLIM-negative participants.

Overall, the incidence of adverse clinical outcomes was higher in mGLIM-positive participants [330/1181 (27.9%) versus 140/736 (19.0%)] resulting in an OR of 1.65 (95% CI 1.32–2.06; $p < 0.001$) and an even more pronounced association was found for 30-day mortality [127/1181 (10.8%) versus 35/736 (4.8%), OR of 2.41 (95% CI 1.64–3.55; $p < 0.001$)]. These associations remained significant after adjusting for age, gender, main diagnosis, comorbidities, randomization, and study center.

Furthermore, we found a higher mortality rate in mGLIM-positive participants when compared with mGLIM-negative ones

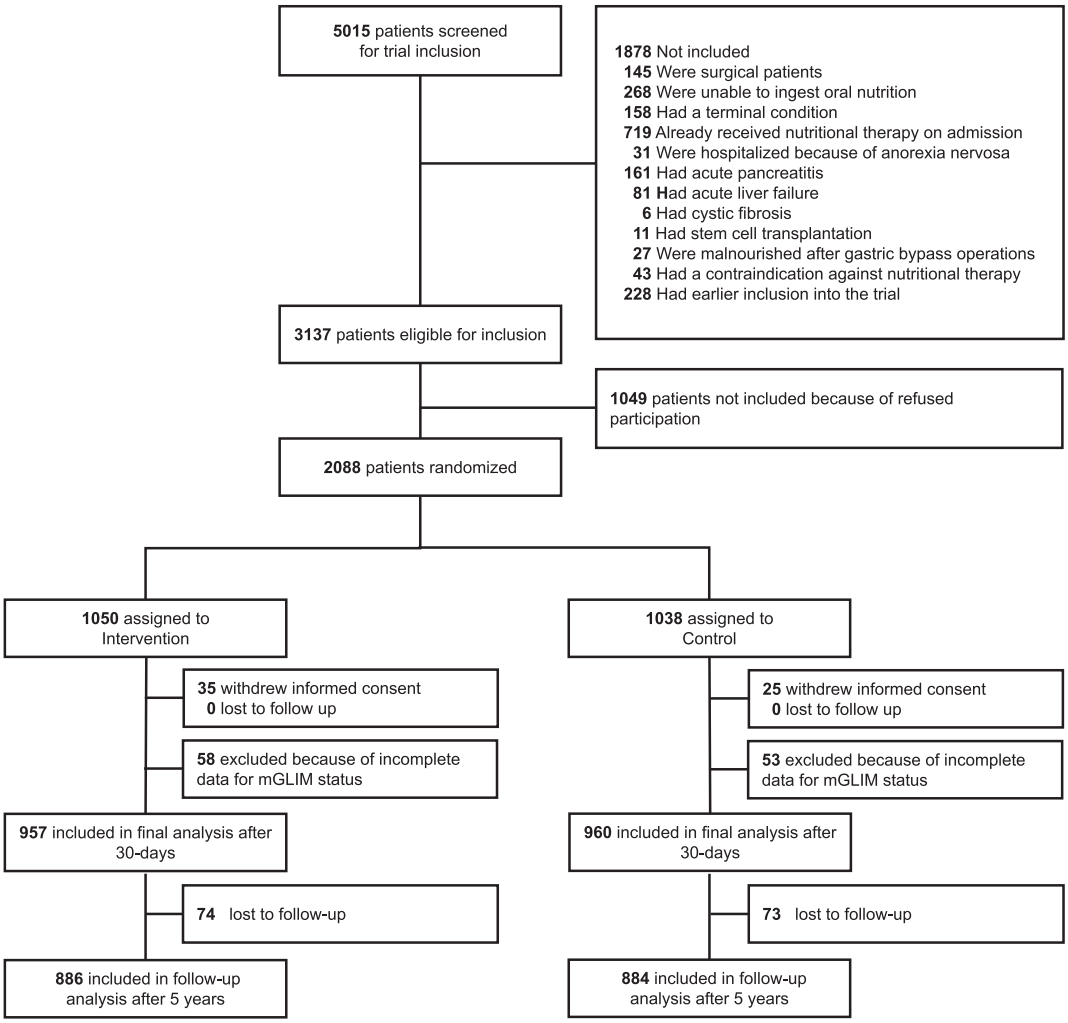

Fig. 1. Study flow diagram.

after 180 days [336/1181 (28.5%) versus 107/736 (14.5%), adjusted OR 2.23; 95% CI 1.71–2.90; $p < 0.001$] and 5 years [642/1096 (58.6%) versus 292/674 (43.3%); adjusted OR 1.81; 95% CI 1.45–2.25; $p < 0.001$]. Kaplan Meier estimate (Fig. 2) shows the difference in long-term mortality within 5 years for the mGLIM-positive and the mGLIM-negative group (adjusted HR, 1.59; 95% CI 1.38–1.83; $p < 0.001$).

As for the other secondary outcomes, we found that the percentage of participants with significant loss of function at 30-days was higher in the mGLIM-positive group (adjusted OR 1.82; 95% CI 1.32–2.51; $p < 0.001$) when compared with the mGLIM-negative group. Mean length of hospital stay was longer in mGLIM-positive participants (10.5 days) compared with mGLIM-negative ones (9.6 days). No differences were found in ICU admission, non-elective hospital readmission after discharge and major complications. Quality of life after 180 days was significantly lower in the mGLIM-positive group (adjusted difference, −3.21; 95% CI −5.44 to −0.97; $p = 0.005$).

3.2. Association of individual mGLIM components and clinical outcome

Regarding the prognostic value of the specific components of the single mGLIM criteria, we found the incidence of adverse clinical outcome to be significantly higher in participants who experienced >5% weight loss in the last 6 months (adjusted OR 1.29; 95% CI 1.02–1.62, $p = 0.032$), in participants with CRP ≥10 mg/l (adjusted OR 1.9; 95% CI 1.45–2.51, $p < 0.001$) and in participants with at least one etiologic mGLIM criterion (adjusted OR 2.21; 95% CI 1.5–3.27; $p < 0.001$) compared with participants not meeting these criteria. Even more pronounced associations were found for the secondary endpoints short- and long-term mortality and functional decline. Considering these endpoints, a reduction of food intake and/or a gastrointestinal problem, a HGS ≤8 kg for female or ≤16 kg for male as well as the presence of at least one phenotypic criterion do also have significant prognostic implications.

Detailed information about the results of the association between the individual mGLIM components and clinical outcomes is shown in Table 2.

3.3. Effect of nutritional therapy in association of mGLIM criteria

In a second step, we studied the effect of nutritional therapy in association with mGLIM criteria to understand whether GLIM criteria were helpful in identifying participants benefitting from nutritional therapy. Figure 3 displays the effect of nutritional therapy on adverse clinical outcome rate stratified in mGLIM-positive and mGLIM-negative participants as well as stratified by the characteristics of the single components of mGLIM criteria.

Table 1
Baseline characteristics.

	Overall	mGLIM-negative	mGLIM-positive	p value
n	1917	736	1181	
Sociodemographics				
Age, mean (SD) years	72.4 (14.1)	72.1 (14.4)	72.6 (13.9)	0.5
Male sex	1004 (52.4%)	382 (51.9%)	622 (52.7%)	0.74
Nutritional assessment				
BMI, mean (SD) kg/m^2	24.7 (5.3)	26.4 (5.4)	23.6 (4.9)	<0.001
Weight at admission, mean (SD) kg	70.7 (16.6)	75.4 (16.9)	67.6 (15.7)	<0.001
Height, mean (SD) cm	167.7 (9.3)	167.8 (9.1)	167.7 (9.4)	0.82
NRS 2002 total score				
3	585 (30.5%)	343 (46.6%)	242 (20.5%)	<0.001
4	734 (38.3%)	266 (36.1%)	468 (39.6%)	
5	497 (25.9%)	101 (13.7%)	396 (33.5%)	
6	101 (5.3%)	26 (3.5%)	75 (6.4%)	
mGLIM criteria				
Phenotypic criteria	1358 (71.0%)	177 (24.1%)	1181 (100.0%)	<0.001
Weight loss >5% in 6 months	1135 (60.0%)	139 (19.1%)	996 (85.6%)	<0.001
BMI < 20 kg/m^2 (<70 y) or BMI < 22 kg/m^2 (≥70 y)	495 (25.8%)	82 (11.1%)	413 (35.0%)	<0.001
Low HGS, ≤8 kg (female) or ≤16 kg (male)	218 (12.4%)	22 (3.1%)	196 (18.8%)	<0.001
Etiologic criteria	1673 (87.8%)	492 (67.9%)	1181 (100.0%)	<0.001
Reduced food intake or gastrointestinal problem	1175 (61.4%)	320 (43.5%)	855 (72.6%)	<0.001
Inflammation, CRP ≥ 10 mg/l	1339 (71.8%)	419 (58.4%)	920 (80.1%)	<0.001
Admission diagnosis				
Infection	571 (29.8%)	236 (32.1%)	335 (28.4%)	0.085
Cancer	361 (18.8%)	112 (15.2%)	249 (21.1%)	0.001
Cardiovascular disease	190 (9.9%)	82 (11.1%)	108 (9.1%)	0.15
Failure to thrive	187 (9.8%)	72 (9.8%)	115 (9.7%)	0.97
Lung disease	117 (6.1%)	49 (6.7%)	68 (5.8%)	0.42
Gastrointestinal disease	159 (8.3%)	38 (5.2%)	121 (10.2%)	<0.001
Neurological disease	91 (4.7%)	54 (7.3%)	37 (3.1%)	<0.001
Renal disease	63 (3.3%)	19 (2.6%)	44 (3.7%)	0.17
Metabolic disease	60 (3.1%)	30 (4.1%)	30 (2.5%)	0.06
Other	48 (2.5%)	17 (2.3%)	31 (2.6%)	0.67
Comorbidities				
Hypertension	1037 (54.1%)	399 (54.2%)	638 (54.0%)	0.94
Malignant disease	642 (33.5%)	199 (27.0%)	443 (37.5%)	<0.001
Chronic kidney disease	597 (31.1%)	222 (30.2%)	375 (31.8%)	0.46
Coronary heart disease	538 (28.1%)	216 (29.3%)	322 (27.3%)	0.32
Diabetes	402 (21.0%)	164 (22.3%)	238 (20.2%)	0.27
Congestive heart failure	325 (17.0%)	135 (18.3%)	190 (16.1%)	0.2
Chronic obstructive pulmonary disease	288 (15.0%)	109 (14.8%)	179 (15.2%)	0.84
Peripheral arterial disease	177 (9.2%)	63 (8.6%)	114 (9.7%)	0.42
Cerebrovascular disease	155 (8.1%)	65 (8.8%)	90 (7.6%)	0.34
Dementia	68 (3.5%)	23 (3.1%)	45 (3.8%)	0.43

Abbreviations: GLIM, Global Leadership Initiative on Malnutrition (mGLIM-negative meaning not fulfilling modified GLIM criteria; mGLIM-positive meaning fulfilling modified GLIM criteria); BMI, body mass index; NRS, Nutritional risk screening; SD, standard deviation.

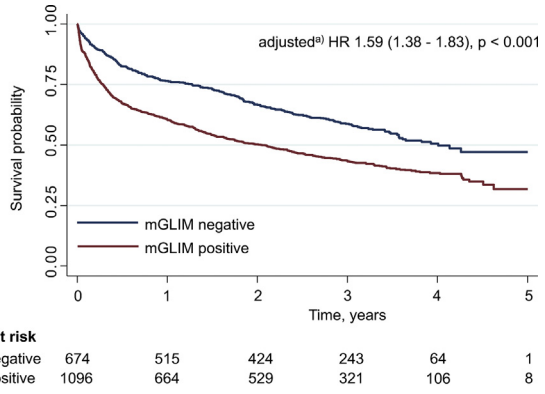

Fig. 2. Kaplan Meier estimate for time to death within 5 years. Abbreviations: HR, hazard ratio; GLIM, Global Leadership Initiative on Malnutrition (mGLIM-negative meaning not fulfilling modified GLIM criteria; mGLIM-positive meaning fulfilling modified GLIM criteria). [a]Adjusted for age, sex, main diagnosis, comorbidities, randomization, study center.

Regarding the effect of nutritional therapy, there was a stronger reduction of adverse clinical outcomes in mGLIM-positive participants [180/581 (31%) vs. 150/600 (25%), adjusted OR 0.69; 95% CI 0.53–0.9] compared with mGLIM-negative ones [75/379 (19.8%) vs 65/357 (18.2%), adjusted OR 0.95; 95% CI 0.65–1.4]. However, this difference was not significant in interaction analysis (p for interaction = 0.217). In the analyses of the association of nutritional therapy and secondary endpoints (eFigs. 1–5), we consistently found GLIM-positive participants to have a stronger reduction of events compared with GLIM-negative participants but the difference in the effect was not statistically significant except for ICU admission (eFig. 2). However, the event rates for ICU admission were low and the effect of nutritional support was rather due to increased risk of ICU admission in GLIM-negative participants.

As for the single components of mGLIM, we found a trend for pronounced effect of nutritional therapy on adverse clinical outcomes in participants with low handgrip strength (HGS >8 kg for female or >16 kg for male: OR 0.85; 95% CI 0.67–1.09 and HGS ≤8 kg or 16 kg respectively: OR 0.48; 95% CI 0.25–0.91; p for

Table 2
Association of individual mGLIM criteria and clinical outcome.

	Patients meeting the criterion	Patients without the criterion	Unadjusted		Adjusted[a]	
	Events/total (%)	Events/total (%)	OR or coefficient (95% CI)	p-value	OR or coefficient (95% CI)	p-value
Adverse clinical outcome within 30-days						
Phenotypic criteria						
Weight loss > 5% in 6 months	306/1135 (27)	159/757 (21)	1.39 (1.12–1.73)	0.003	1.29 (1.02–1.62)	0.032
BMI < 20 kg/m^2 (<70 y) or BMI < 22 kg/m^2 (≥70 y)	130/495 (26.3)	340/1420 (23.9)	1.13 (0.89–1.43)	0.302	1.14 (0.89–1.46)	0.305
HGS ≤8 kg (female) or ≤16 kg (male)	63/218 (28.9)	352/1543 (22.8)	1.38 (1–1.89)	0.048	1.16 (0.83–1.63)	0.38
Etiologic criteria						
Food intake <50% or gastrointestinal problem	299/1175 (25.5)	171/739 (23.1)	1.13 (0.91–1.41)	0.254	1.23 (0.98–1.54)	0.068
Inflammation (CRP ≥ 10 mg/l)	362/1339 (27)	89/526 (16.9)	1.82 (1.41–2.35)	<0.001	1.9 (1.45–2.51)	<0.001
Overall						
≥1 phenotypic criterion	358/1358 (26.4)	112/556 (20.1)	1.42 (1.12–1.8)	0.004	1.27 (0.99–1.63)	0.057
≥1 etiologic criterion	434/1673 (25.9)	34/233 (14.6)	2.05 (1.4–3)	<0.001	2.21 (1.5–3.27)	<0.001
30-days all-cause mortality						
Phenotypic criteria						
>5% in 6 months	115/1135 (10.1)	45/757 (5.9)	1.78 (1.25–2.55)	0.002	1.74 (1.2–2.53)	0.004
BMI < 20 kg/m^2 (<70 y) or BMI < 22 kg/m^2 (≥70 y)	49/495 (9.9)	113/1420 (8)	1.27 (0.89–1.81)	0.182	1.34 (0.92–1.94)	0.125
HGS ≤8 kg (female) or ≤16 kg (male)	25/218 (11.5)	105/1543 (6.8)	1.77 (1.12–2.81)	0.015	1.45 (0.88–2.39)	0.148
Etiologic criteria						
Food intake <50% or gastrointestinal problem	109/1175 (9.3)	53/739 (7.2)	1.32 (0.94–1.86)	0.108	1.57 (1.1–2.24)	0.013
Inflammation (CRP ≥ 10 mg/l)	135/1339 (10.1)	18/526 (3.4)	3.16 (1.91–5.23)	<0.001	3.16 (1.88–5.33)	<0.001
Overall						
≥1 phenotypic criterion	132/1358 (9.7)	30/556 (5.4)	1.89 (1.25–2.84)	0.002	1.72 (1.13–2.62)	0.012
≥1 etiologic criterion	154/1673 (9.2)	7/233 (3)	3.27 (1.52–7.07)	0.003	3.54 (1.61–7.78)	0.002
Admission to ICU						
Phenotypic criteria						
>5% in 6 months	29/1135 (2.6)	15/757 (2)	1.3 (0.69–2.44)	0.419	1.24 (0.65–2.38)	0.51
BMI < 20 kg/m^2 (<70 y) or BMI < 22 kg/m^2 (≥70 y)	14/495 (2.8)	30/1420 (2.1)	1.35 (0.71–2.56)	0.362	1.4 (0.72–2.73)	0.323
HGS ≤8 kg (female) or ≤16 kg (male)	6/218 (2.8)	33/1543 (2.1)	1.3 (0.54–3.13)	0.565	1.26 (0.5–3.2)	0.628
Etiologic criteria						
Food intake <50% or gastrointestinal problem	32/1175 (2.7)	12/739 (1.6)	1.7 (0.87–3.31)	0.122	1.56 (0.79–3.09)	0.204
Inflammation (CRP ≥ 10 mg/l)	30/1339 (2.2)	11/526 (2.1)	1.07 (0.53–2.16)	0.843	1.31 (0.62–2.76)	0.477
Overall						
≥1 phenotypic criterion	37/1358 (2.7)	7/556 (1.3)	2.2 (0.97–4.96)	0.058	2.19 (0.96–5.01)	0.063
≥1 etiologic criterion	40/1673 (2.4)	4/233 (1.7)	1.4 (0.5–3.96)	0.523	1.53 (0.54–4.38)	0.426
Non-elective hospital readmission						
Phenotypic criteria						
>5% in 6 months	110/1135 (9.7)	56/757 (7.4)	1.34 (0.96–1.88)	0.085	1.18 (0.83–1.67)	0.352
BMI < 20 kg/m^2 (<70 y) or BMI < 22 kg/m^2 (≥70 y)	46/495 (9.3)	123/1420 (8.7)	1.08 (0.76–1.54)	0.67	1.08 (0.75–1.56)	0.677
HGS ≤8 kg (female) or ≤16 kg (male)	12/218 (5.5)	146/1543 (9.5)	0.56 (0.3–1.02)	0.059	0.55 (0.29–1.02)	0.058
Etiologic criteria						
Food intake <50% or gastrointestinal problem	101/1175 (8.6)	68/739 (9.2)	0.93 (0.67–1.28)	0.649	0.89 (0.64–1.24)	0.505
Inflammation (CRP ≥ 10 mg/l)	123/1339 (9.2)	38/526 (7.2)	1.3 (0.89–1.9)	0.176	1.42 (0.95–2.12)	0.085
Overall						
≥1 phenotypic criterion	125/1358 (9.2)	44/556 (7.9)	1.18 (0.82–1.69)	0.367	1.05 (0.73–1.52)	0.792
≥1 etiologic criterion	152/1673 (9.1)	16/233 (6.9)	1.36 (0.79–2.31)	0.265	1.41 (0.82–2.43)	0.213
Major complications[b]						
Phenotypic criteria						
>5% in 6 months	81/1135 (7.1)	61/757 (8.1)	0.88 (0.62–1.24)	0.456	0.86 (0.6–1.24)	0.42
BMI < 20 kg/m^2 (<70 y) or BMI < 22 kg/m^2 (≥70 y)	36/495 (7.3)	106/1420 (7.5)	0.97 (0.66–1.44)	0.888	0.96 (0.64–1.45)	0.857
HGS ≤8 kg (female) or ≤16 kg (male)	23/218 (10.6)	106/1543 (6.9)	1.6 (0.99–2.57)	0.053	1.18 (0.71–1.96)	0.516
Etiologic criteria						
Food intake <50% or gastrointestinal problem	84/1175 (7.2)	58/739 (7.9)	0.9 (0.64–1.28)	0.57	0.97 (0.68–1.38)	0.846
Inflammation (CRP ≥ 10 mg/l)	116/1339 (8.7)	23/526 (4.4)	2.07 (1.31–3.28)	0.002	2.08 (1.29–3.37)	0.003
Overall						
≥1 phenotypic criterion	98/1358 (7.2)	44/556 (7.9)	0.91 (0.63–1.31)	0.597	0.86 (0.59–1.26)	0.428
≥1 etiologic criterion	132/1673 (7.9)	10/233 (4.3)	1.91 (0.99–3.69)	0.054	1.95 (1–3.81)	0.05
Decline in functional status ≥ 10%[c]						
Phenotypic criteria						
>5% in 6 months	155/1135 (13.7)	72/757 (9.5)	1.5 (1.12–2.02)	0.007	1.48 (1.08–2.02)	0.014
BMI < 20 kg/m^2 (<70 y) or BMI < 22 kg/m^2 (≥70 y)	65/495 (13.1)	164/1420 (11.6)	1.16 (0.85–1.57)	0.351	1.16 (0.84–1.61)	0.361
HGS ≤8 kg (female) or ≤16 kg (male)	37/218 (17)	162/1543 (10.5)	1.74 (1.18–2.57)	0.005	1.42 (0.93–2.16)	0.103
Etiologic criteria						
Food intake <50% or gastrointestinal problem	150/1175 (12.8)	79/739 (10.7)	1.22 (0.92–1.63)	0.174	1.45 (1.07–1.96)	0.016
Inflammation (CRP ≥ 10 mg/l)	186/1339 (13.9)	36/526 (6.8)	2.2 (1.51–3.19)	<0.001	2.22 (1.5–3.28)	<0.001
Overall						
≥1 phenotypic criterion	183/1358 (13.5)	46/556 (8.3)	1.73 (1.23–2.42)	0.002	1.6 (1.12–2.27)	0.009
≥1 etiologic criterion	212/1673 (12.7)	16/233 (6.9)	1.97 (1.16–3.34)	0.012	2.15 (1.25–3.7)	0.006
180-days all-cause mortality						
Phenotypic criteria						
>5% in 6 months	307/1135 (27.1)	132/757 (17.4)	1.76 (1.4–2.21)	<0.001	1.63 (1.26–2.1)	<0.001
BMI < 20 kg/m^2 (<70 y) or BMI < 22 kg/m^2 (≥70 y)	124/495 (25.1)	319/1420 (22.5)	1.15 (0.91–1.46)	0.24	1.23 (0.94–1.62)	0.128
HGS ≤8 kg (female) or ≤16 kg (male)	2.70146	218/20.22 (312)	1543 (0–1.46)	4.37	1.74 (1.22–2.48)	0.002

Table 2 (*continued*)

	Patients meeting the criterion	Patients without the criterion	Unadjusted		Adjusted[a]	
	Events/total (%)	Events/total (%)	OR or coefficient (95% CI)	p-value	OR or coefficient (95% CI)	p-value
Etiologic criteria						
Food intake <50% or gastrointestinal problem	300/1175 (25.5)	143/739 (19.4)	1.43 (1.14–1.79)	0.002	1.9 (1.47–2.45)	<0.001
Inflammation (CRP ≥ 10 mg/l)	356/1339 (26.6)	68/526 (12.9)	2.44 (1.84–3.23)	<0.001	2.61 (1.9–3.57)	<0.001
Overall						
≥1 phenotypic criterion	355/1358 (26.1)	87/556 (15.7)	1.91 (1.47–2.47)	<0.001	1.7 (1.28–2.26)	<0.001
≥1 etiologic criterion	414/1673 (24.8)	26/233 (11.2)	2.62 (1.72–4)	<0.001	3.22 (2.04–5.1)	<0.001
5-year all-cause mortality						
Phenotypic criteria						
>5% in 6 months	593/1058 (56.1)	324/690 (47)	1.44 (1.19–1.75)	<0.001	1.37 (1.1–1.71)	0.005
BMI < 20 kg/m^2 (<70 y) or BMI < 22 kg/m^2 (≥70 y)	268/455 (58.9)	666/1314 (50.7)	1.39 (1.12–1.73)	0.003	1.55 (1.21–1.99)	0.001
HGS ≤8 kg (female) or ≤16 kg (male)	134/191 (70.2)	696/1436 (48.5)	2.5 (1.8–3.47)	<0.001	2.01 (1.4–2.89)	<0.001
Etiologic criteria						
Food intake <50% or gastrointestinal problem	569/1080 (52.7)	363/687 (52.8)	0.99 (0.82–1.2)	0.95	1.24 (1–1.54)	0.052
Inflammation (CRP ≥ 10 mg/l)	702/1248 (56.3)	203/475 (42.7)	1.72 (1.39–2.13)	<0.001	1.9 (1.48–2.45)	<0.001
Overall						
≥1 phenotypic criterion	714/1258 (56.8)	217/509 (42.6)	1.77 (1.43–2.17)	<0.001	1.66 (1.31–2.1)	<0.001
≥1 etiologic criterion	831/1544 (53.8)	96/216 (44.4)	1.46 (1.09–1.94)	0.01	1.76 (1.28–2.43)	0.001

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; NRS, nutritional risk screening; GLIM, Global Leadership Initiative on Malnutrition (GLIM negative meaning not fulfilling GLIM criteria; GLIM positive meaning fulfilling GLIM criteria); BMI, body mass index (weight in kilograms divided by height in meters squared); HGS, hand grip strength; UAC, upper arm circumference; CRP, C-reactive protein.

[a] Adjusted for age, sex, main diagnosis, comorbidities, randomization center.

[b] Major complications include nosocomial infection or abscess, respiratory failure with requiring ventilation (invasive or non-invasive), major cardiovascular event (e.g., cardiac arrest, myocardial infarction, stroke, intracranial bleeding, pulmonary embolism), acute renal failure (two times increase of baseline creatinine or new requirement of dialysis, e.g., due to volume overload or electrolyte disturbance), gastro-intestinal failure (e.g. hemorrhage, intestinal perforation and acute pancreatitis).

[c] To estimate decline in functional status, we used the Barthel index (scores range from 0 to 100, with higher scores indicating better functional status) and compared initial scores on admission with scores at day 30.

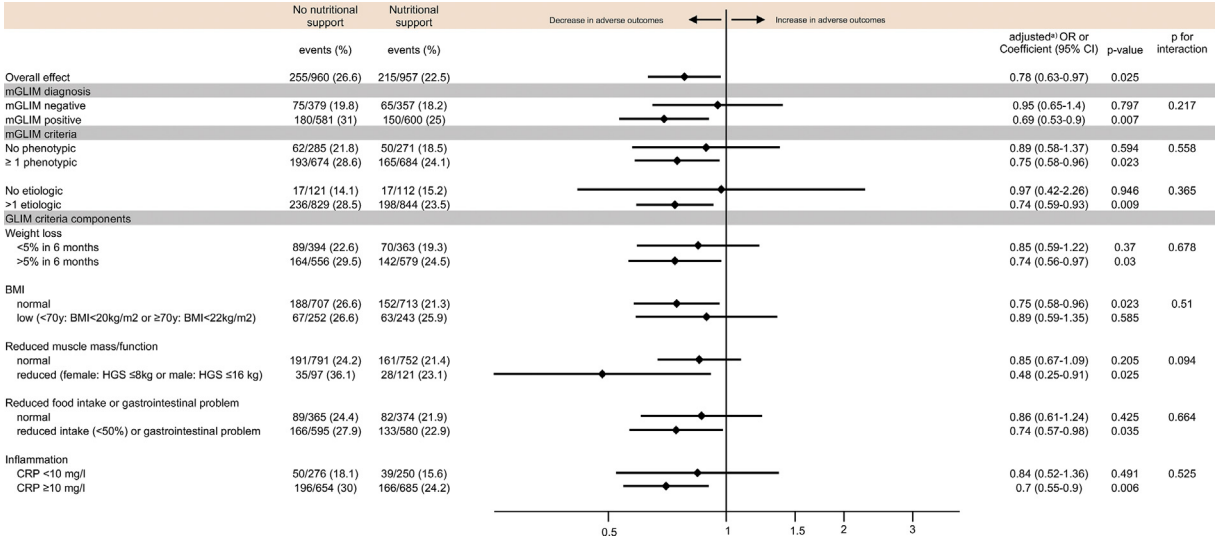

Fig. 3. Forest plot for adverse clinical outcome: Response to nutritional therapy according to mGLIM status and mGLIM components. Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; NRS, nutritional risk screening; GLIM, Global Leadership Initiative on Malnutrition (mGLIM-negative meaning not fulfilling modified GLIM criteria; mGLIM-positive meaning fulfilling modified GLIM criteria); BMI, body mass index (weight in kilograms divided by height in meters squared); HGS, hand grip strength; UAC, upper arm circumference; CRP, C-reactive protein. [a]Adjusted for age, sex, main diagnosis, comorbidities, study center. Values are presented on a logarithmic scale for better visualization.

interaction = 0.094). Additionally, low HGS did significantly modify the effect of nutritional therapy on 30-day mortality (HGS >8 kg for female or >16 kg for male: OR 0.97; 95% CI 0.64–1.45 and HGS ≤8 kg or 16 kg respectively: OR 0.21; 95% CI 0.07–0.59; p for interaction = 0.011) and on reduction of functional decline (HGS >8 kg for female or >16 kg for male: OR 0.76; 95% CI 0.54–1.06 and HGS ≤8 kg or 16 kg respectively: OR 0.29; 95% CI 0.13–0.65; p for interaction = 0.038).

4. Discussion

The key findings of this secondary analysis investigating the effect of nutritional therapy in a population of participants at nutritional risk according to the newly proposed GLIM criteria are threefold. First, about 62% of the participants identified as nutritionally at-risk by means of the NRS 2002 fulfilled the modified GLIM criteria. Second, we found that mGLIM-positive participants

had an important increase in risk for adverse clinical outcomes, demonstrating that GLIM criteria help identify the highly vulnerable among participants prescreened with a nutritional screening tool. Third, when comparing the effects of nutritional therapy among mGLIM-positive and mGLIM-negative participants, there was a higher risk reduction in GLIM-positive participants, but without being statistically significant.

In 2019, GLIM criteria were proposed as new minimal operational criteria for the diagnosis of malnutrition after an initial risk screening with any validated screening tool. Importantly, these criteria are largely based on pathophysiological rationales and observational studies regarding association of the different components and clinical outcomes, and the authors called for validation among different cohorts in order to further advance the science. Herein, the large set of NRS-prescreened, multimorbid medical participants included in the prospective, randomized EFFORT trial [2] suits this purpose well. To our knowledge, validation in a similar population from an interventional trial has not been done yet. Importantly, our population did not include surgical patients, ICU patients, outpatients, and patients from health care of the older person wards where similar validation studies are still needed.

Our data regarding the frequency of participants at nutritional risk meeting the mGLIM criteria are in concordance a study from Italy reporting 62.3% GLIM-positive participants [28] in the NRS 2002 prescreened group; two studies from China showed slightly lower percentages (52.8% [29] and 47.3% [30] respectively).

Similarly, in line with other studies, mGLIM criteria in our cohort were a strong predictor for short-term adverse clinical outcomes, quality of life, as well as long-term survival. For example, Hirose et al. [21] investigated elderly patients with heart failure and found patients diagnosed with malnutrition according to GLIM to have a significantly higher 1-year mortality rate. Similar associations were found in a cohort of hospitalized medical and surgical patients [22], patients with lung cancer [18], elderly patients with cancer [17], and in patients undergoing abdominal surgery [16,30]. Severe malnutrition defined by GLIM criteria was also associated with reduced survival in patients with amyotrophic lateral sclerosis [20] and hospitalized patients with type 2 diabetes [19]. Importantly, our sample size was much larger when compared with most previous studies and we focused on a population that underwent prescreening for risk of malnutrition by means of NRS 2002. When looking at single components of mGLIM, we found that phenotypic criteria, such as long-term weight loss (>5% in 6 months) and reduced HGS, as well as etiologic criteria, such as reduced food intake and inflammation, showed significant associations with adverse clinical outcomes, mortality or functional decline. Overall, the etiologic criteria, especially inflammation, showed a stronger prognostic value as compared with phenotypic criteria. Yet, it remains somewhat undefined whether the etiologic component is rather reflecting disease severity than undernutrition, which both are strongly linked. However, long-term weight loss and low HGS were also consistently associated with worse clinical outcomes particularly long-term mortality and thus provide additional prognostic information. There is need for additional research to better define etiologic criteria in the future.

As a key finding from our study, nutritional interventions in mGLIM-positive participants resulted in a stronger reduction of the risk for adverse outcome compared with the mGLIM-negative participants – but this result was not significant in the interaction analysis. Importantly, findings were similar for most of the clinical outcomes investigated with a higher risk reduction in mGLIM positive participants but non-significant results in the interaction analysis. There are two possible explanations for the lack of significance. First, our sample may be underpowered and in a larger study this would become significant. Second, GLIM criteria lack specificity to select patients for nutritional interventions. While this is, to our knowledge, the first validation of GLIM criteria in a randomized controlled trial, other observational studies have looked at the potential of GLIM to predict treatment response. Particularly, two previous cohort studies performed in China and the United States suggested that GLIM status was not predictive for the response to nutritional therapy with regard to reduction in infectious complications [30,31]. However, there is still room for further improvement regarding patient selection for nutritional therapy. We previously found kidney function [32], specific comorbidities such as chronic heart failure [33] and tumor diagnosis [34] to be associated with a stronger treatment response.

As a reduction in muscle mass is a key component of the concept of malnutrition, the GLIM committee recommends the assessment of this criterion using body composition techniques such as X-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), computed tomography (CT), or magnetic resonance tomography (MRI). Functional assessments of muscle strength such as handgrip measurement are mentioned only as a supportive measure [13]. However, other committees such as the European Working Group on Sarcopenia in older people (EWGCOP) stated that "*sarcopenia is now considered a muscle disease (muscle failure), with low muscle strength overtaking the role of low muscle mass as a principal determinant*" [35]. As a limitation we did not have data on body composition techniques in our set, and used handgrip strength as a proxy for reduced muscle mass. Reduced handgrip strength proved to have good prognostic and predictive value for poor clinical outcome and also for response to nutritional therapy, respectively, as recently demonstrated [26]. Also, Contreras-Bolivar et al. [36] showed that GLIM criteria using handgrip strength were a good predictor of 6-months-mortality in hospitalized patients with cancer and Li et al. [37] found that patients with gastric cancer diagnosed with severe malnutrition by GLIM criteria based on either midarm circumference or body weight-standardized handgrip strength to had a shorter median survival time. Few other studies also validated GLIM criteria but often excluded the criterion of reduced muscle mass in their analyses due to lack of data and/or lack of diagnostic standards [16,30]. We suggest, especially for retrospective analyses, the measurement of reduced muscle strength using hand grip strength as a relevant proxy for the phenotypic criteria of reduced muscle mass. This simple and inexpensive test which is broadly applicable in daily practice even in low- and middle-income countries should be performed as a natural part of the nutritional assessment in all patients, and also in order to recognize sarcopenia. Such a recognition indicates that muscle resistance exercises should be part of the nutritional therapy.

4.1. Strengths and limitations

Strength of this analysis includes the large and heterogeneous patient population including medical inpatients with multiple morbidities from a previous randomized trial with thus high external validity. We followed the guidance on validation published by GLIM by testing criterion validity, comprising both concurrent and predictive validity and by involving several of the proposed health outcomes [38].

There are also several limitations. First, because this is a secondary analysis, we defined mGLIM criteria in retrospect with the available data, which were collected prospectively during the trial. We excluded 5.4% of the participants of the initial trial due to missing data, which makes a sampling bias possible. In fact, the participants with missing GLIM status were significantly older, had higher BMI and some differences in comorbidities, which

could influence external validity. Additionally, we lacked information regarding weight loss of over 6 months and food intake of >1 week and, therefore, malnutrition according to mGLIM criteria might be slightly underdiagnosed. Still, the prevalence of mGLIM-positive participants was similar to other studies using the NRS 2002 as a prescreening tool. Secondly, we did not adjust our analysis for multiple testing and results should, thus, be considered exploratory.

Thirdly, due to the prescreening by means of the NRS 2002, which was also originally developed to detect patients likely to respond to nutritional therapy, the results should be interpreted only for this specific prescreened cohort. However, there are data showing that the NRS 2002 does not detect all GLIM-positive participants in a cohort of unknown nutritional status. In one paper that used GLIM as gold standard, the sensitivity of the NRS 2002 was only 47.1% [28]. That study found better sensitivity for Malnutrition Universal Screening Tool (MUST) and Subjective Global Assessment Form (SGA). Another study compared the NRS 2002, MUST and Mini Nutritional Assessment-Short Form (MNA-SF) for the diagnostic process proposed by GLIM and found only MNA-SF prescreened patients to show a significant association of GLIM and increased in-hospital mortality [29]. Which of these screening tools shows best performance remains unclear today, but using the NRS 2002 we were able to show a significant prognostic benefit of GLIM criteria.

Finally, we were not able to reconstruct the severity grading of GLIM criteria because of missing data on over 6-month weight loss and because of missing cut-off values for hand grip strength measurements. While there are data for GLIM severity grade to have prognostic implications [17], further studies are needed to investigate the value of GLIM severity grade on prediction of therapeutic effect. This would be interesting, because in the original EFFORT trial [2], no significant effect modification was found for the different severity grades according to NRS 2002.

5. Conclusion

Data from this secondary analysis of a multicenter randomized trial involving medical inpatients at nutritional risk validate the strong prognostic value of mGLIM criteria regarding adverse clinical outcomes and other long-term outcomes. However, further research is needed to improve the ability of GLIM criteria to predict therapeutic response to nutritional interventions.

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Role of the funder/sponsor

The funders had no rule in the design and conduct of this study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Author contributions

Prof Schuetz had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Kaegi-Braun and Ms Boesiger are equally contributing co-first authors.

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Acquisition and analysis of data: Kaegi-Braun, Boesiger, Schuetz, Tribolet.

Interpretation of data: Kaegi-Braun, Boesiger, Tribolet, Gomes, Kutz, Hoess, Pavlicek, Bilz, Sigrist, Brändle, Henzen, Thomann, Rutishauser, Aujesky, Rodondi, Donzé, Stanga, Lobo, Mueller, Schuetz.

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Statistical analysis: Kaegi-Braun, Boesiger, Schuetz.

Obtained funding: Stanga, Mueller, Schuetz.

Supervision: Schuetz, Mueller.

Additional contributions

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Conflict of interest

Prof. Stanga reported grants from Nestlé Health Science, Abbott Nutrition, Fresenius Kabi and Baxter not related to this project. Prof. Schuetz reported grants from Nestlé Health Science, Thermofisher, BioMerieux, Abbott Nutrition and Roche Diagnostics not related to this project. No other disclosures where reported.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2022.02.009.

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