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The impact of nutritional support on malnourished inpatients with aging-related vulnerability

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PII: S0899-9007(21)00141-6
DOI: https://doi.org/10.1016/j.nut.2021.111279
Reference: NUT 111279

To appear in: *Nutrition*

Received date: 22 January 2021
Revised date: 4 March 2021
Accepted date: 1 April 2021

Please cite this article as: Annic Baumgartner MD , Daphne Pachnis , Lucie Parra , Lara Hersberger MD , Annika Bargetzi MD , Laura Bargetzi MD , Nina Kaegi-Braun MD , Pascal Tribolet RD , Filomena Gomes PhD , Claus Hoess MD , Vojtech Pavlicek MD , Stefan Bilz MD , Sarah Sigrist MD , Michael Braendle Prof. , Christoph Henzen Prof. , Robert Thomann MD , Jonas Rutishauser Prof. , Drahomir Aujesky Prof. , Nicolas Rodondi Prof. , Jacques Donzé Prof. , Zeno Stanga Prof. , Beat Mueller Prof. , Philipp Schuetz Prof. , The impact of nutritional support on malnourished inpatients with aging-related vulnerability, *Nutrition* (2021), doi: https://doi.org/10.1016/j.nut.2021.111279

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source: https://doi.org/10.48350/156120 | downloaded: 26.4.2024

Highlights

- This secondary analysis of the randomized clinical EFFORT trial found a more than 50%-reduction in mortality at 30 days in hospitalized patients with aging-related vulnerability at nutritional risk receiving protocol-guided individualized nutritional support to reach specific protein and energy goals compared to patients receiving standard usual hospital food
- Significant improvements in patients receiving nutritional support were also found for longer term mortality at 180 days
- Individualized nutritional support also improved functional outcomes and quality of life over 30 and 180 days
- These data support the early screening of hospitalized patients with aging-related vulnerability for nutritional risk, followed by the implementation of individualized nutritional interventions.

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The impact of nutritional support on malnourished inpatients with aging-related vulnerability

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Conflict of interest: The study was investigator-initiated and supported by a grant from the Swiss National Science Foundation to Mr. P. Schuetz (SNSF Professorship, PP00P3_150531) and the Research Committee of the Kantonsspital Aarau (1410.000.058 and 1410.000.044). Mr. P. Schuetz's institute received unrestricted grant money from Nestlé Health Science and Abbott Nutrition. All other authors report no conflicts of interest.

Impact statement:

We certify that this work is novel. Our results state the importance of nutritional support in this patient population. Mortality of these patients in the acute setting is improved by the implementation of a screening for malnutrition and consecutive provision of individualized nutritional support.

Abstract

Introduction: Malnutrition is highly prevalent in patients with aging-related vulnerability, defined by very old age (≥80 years), physical frailty or cognitive impairment, and increases risks for morbidity and mortality. The effects of individualized nutritional support in the acute hospital setting on mortality and other clinical outcomes remains understudied.

Methods: For this secondary analysis of the randomized-controlled EFFORT trial, we analyzed data of patients at nutritional risk (Nutritional Risk Screening 2002 [NRS] score ≥3 points) with aging-related vulnerability randomized to receive protocol-guided individualized nutritional support to reach specific protein and energy goals (intervention group), or to standard usual hospital food (control group). The primary endpoint was all-cause 30-day mortality.

Results: Of 881 patients with aging-related vulnerability, 23.4% presented with a frailty syndrome, 81.8% were ≥80 years of age and 15.3% showed cognitive impairment. Patients with aging-related vulnerability receiving individualized nutritional support compared to usual hospital food showed a more than 50%

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reduction in the risk of 30-day mortality (60/442 [13.6%] *vs.* 31/439 [7.1%], odds ratio 0.48 (95%CI 0.31 to 0.76), p=0.002). Significant improvements were also found for long-term mortality at 180 days, as well as functional improvements and quality of life measures.

Conclusion: Malnourished patients with aging-related vulnerability show a significant and clinically relevant reduction in the risk of mortality and other adverse clinical outcomes following individualized in-hospital nutritional support. These data support the early screening of patients with aging-related vulnerability for nutritional risk, followed by a nutritional assessment and implementation of individualized nutritional interventions.

(**Total word count:** 249)

Keywords: malnutrition, nutritional support, frailty, dementia, geriatric

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Introduction

As a result of the continuously increasing global life expectancy there is a growing number of people aged 65 years or older.[1, 2] Older age is a relevant risk factor, which affects multiple diseases, yet until recently, clinical research has not focused on the associated accelerated aging-related health deficits.*[3]* Aging leads to a gradual decline in physiological reserve and increased vulnerability to stressors. An acceleration of this process leads to a decline in physiological reserves in multiple organ systems and eventually results in impaired homeostatic mechanisms.[1, 4, 5] The clinical presentation of this increased vulnerability is known as frailty syndrome.[1, 2, 4, 5] Pathophysiology of this accelerated aging process leading to frailty seems to be influenced by the interaction of numerous factors not sufficiently understood to date. Frailty, as well as older age, has independently been associated with higher risk of complications, morbidity, as well as mortality in the presence of an additional acute medical condition.[1, 4-7]

There is no consensus-based definition of frailty syndrome, most likely due to insufficient understanding of its pathophysiology. There are, however, generally accepted parameters of frailty such as: age-associated decline in lean body mass, strength, endurance, balance, walking performance and activities of daily living.[3, 4] Prevalence is estimated at about 7-9% of community-dwelling older adults aged ≥60 years and reaches 30% in subjects aged 80 years or older.[1, 2] Considering the increasing number of people aged 65 or more and the associated costs that disabilities generate for society, it is imperative that we identify treatments to reverse and prevent further progression.

Apart from physical frailty as the primary phenotype of frailty syndrome, a broader concept, which includes cognitive, psychological and social factors has been

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proposed.[3, 8, 9] In epidemiological studies, mild cognitive impairment seems to be closely associated with physical frailty.[3, 9, 10] The term cognitive frailty was created as a result of simultaneous presence of both physical frailty and cognitive impairment.[3] So far, pathophysiologic understanding of the process is very limited and there is ongoing debate about its diagnostic criteria and precise definition.[11] Independent of the definition used, dementia and mild cognitive impairment have also been associated with increased morbidity and mortality.[11, 12]

The risk of malnutrition is increased for multiple reasons in frail, cognitively impaired and very old patients.[6, 12-15] In all above-mentioned conditions - as well as in the general, multimorbid medical population - malnutrition *per se* is independently associated with increased mortality.[12, 14, 16] It remains unclear, however, if frail, cognitively impaired or very old patients hospitalized for acute medical conditions benefit from individualized nutritional support during their hospital stay, and if it helps preventing further decline in performance status, cumulative morbidity and overall mortality.

We therefore performed the preplanned secondary analysis of the *Effect of early nutritional support on Frailty, Functional Outcomes and Recovery of malnourished medical inpatients Trial* (EFFORT) - looking specifically at patients with aging-related vulnerabilities including frailty syndrome, cognitive impairment of any extent, and with very old age ≥80 years.[16] We hypothesized that protocol-guided individualized nutritional support to reach protein and energy goals reduces the risk of mortality and other adverse clinical outcomes in the subgroup with increased aging-related vulnerability.

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Materials and Methods

Study Design and Setting

This is a secondary analysis of the EFFORT trial - a pragmatic, investigator-initiated, open-label, non-blinded, multicenter, randomized, controlled trial. The trial protocol and main results*[16, 17]* have been published previously.*[18-24]* The ethics committee of Northwestern Switzerland (EKNZ; 2014_001) approved the trial and it was registered at ClinicalTrials.gov in August 2015 (https://clinicaltrials.gov/ct2/show/NCT02517476).

A total of eight secondary and tertiary care hospitals in Switzerland participated, including the University Clinic in Aarau, the University Hospital in Bern, cantonal hospitals in Lucerne, Solothurn, St. Gallen, Muensterlingen and Baselland, as well as the hospital in Lachen.

Patient Population

We screened medical patients upon hospital admission for malnutrition based on the Nutritional Risk Screening 2002 (NRS).[25] This score includes multiple aspects concerning current nutritional status, age and severity of the underlying disease. Principal inclusion criteria for the trial were nutritional risk defined as NRS total score ≥ 3 points, expected length of stay of >4 days and written informed consent. We excluded patients initially treated in intensive care or a surgical unit with one or more of the following conditions: inability to orally ingest food orally, pre-existing nutritional support, terminal illness, past history of gastric bypass, anorexia nervosa, cystic fibrosis and stem cell transplantation, hospitalization for acute pancreatitis or liver failure, or any individuals with contraindications for nutritional support. We randomized patients using an interactive online system in a 1:1 ratio to either the intervention group which received individualized nutritional support according to

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nutritional requirements; or to the control group which was served usual hospital food.

For this subgroup analysis we included only patients with increased aging-related vulnerability. This was defined as the presence of either frailty syndrome, very old age ≥80 years or cognitive impairment. Patients were classified as frail according to criteria published by Fried et al.[4] Assessment of frailty syndrome classification was performed at time of hospital admission by the responsible medical team at each participating study center. Patients were classified as cognitively impaired if they had been diagnosed with dementia according to patient history, or if they evoked suspicion of a cognitive impairment clinically that led to specific screening during the index hospitalization. In these cases, the Mini Mental Status Examination (MMSE) by Folstein or the Montreal Cognitive Assessment («MoCA»-Score) was used.[26, 27]

Study Intervention

Details of the nutritional intervention, which are in line with current ESPEN guidelines for polymorbid patients, have been published previously.[16, 17, 28, 29] In brief, patients randomized to the intervention group received individualized nutritional support supervised by a registered dietician. The weight-adjusted Harris-Benedict equation was used to predict energy goals. Daily protein intake of 1.2–1.5 g/kg body weight was recommended for the general population, with lower targets for those with acute renal failure (0.8 g per kg of body weight). Achievement of nutritional plan goals was reassessed every 24 to 48 hours during the hospital stay. If at least 75% of the energy and protein goals could not be reached within 5 days through oral ingestion, an escalation of the nutritional support to enteral or parenteral feeding was made. Upon discharge, dietary counselling was offered in combination with a

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prescription for oral nutritional supplements, as needed. Patients in the control group received standard Swiss hospital food according to their individual preferences.

Outcomes

The primary endpoint of this analysis was all-cause mortality up to day 30 after inclusion in the trial. Trained study nurses (blinded to the allocated intervention) performed structured telephone interviews with all patients 30 days after inclusion to collect outcome information. If the patient was unable to provide information, a family member or the family doctor confirmed their survival status.

Secondary endpoints included major adverse events, major complications, non-elective hospital readmission within the first 30 days, mean length of hospital stay as well as mortality at 180 days. In line with the initial EFFORT trial, major adverse events included all-cause mortality, admission to the intensive care unit from the medical ward and non-elective hospital readmission after discharge. Major complications included adjudicated nosocomial infection, respiratory failure, major cardiovascular event (i.e. stroke, intracranial bleeding, cardiac arrest, myocardial infarction) or pulmonary embolism, acute renal failure, gastro-intestinal events (including hemorrhage, intestinal perforation, acute pancreatitis) or a decline in functional status of 10% or more from admission to day 30 measured by the Barthel's Index (scores range from 0 to 100, with higher scores indicating better functional status).[16, 17, 30]

Statistical Analyses

We hypothesized that individualized nutritional support was superior to usual hospital food in the patient subgroup with aging-related vulnerability. We performed all

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analyses in the intention-to-treat population, which included all patients with aging-related vulnerability who had undergone randomization (unless they withdrew consent). To elucidate the primary outcome, we compared frequencies using a chi-square test, and also fitted a logistic regression model adjusted for main prognostic factors (Barthel's Index and NRS at baseline) and study center, as predefined in the study protocol. We reported adjusted odds ratios (OR) and corresponding 95% confidence intervals (CI's). A similar statistical approach was applied for secondary endpoints, utilizing Student's t-test and linear regression models for continuous outcomes. The Kaplan–Meier method was employed to calculate probability of all-cause mortality within 30 days of randomization. As this subgroup was small and not powered for our primary endpoint, we compared effects with findings from the main trial by calculating interaction analyses (test for effect modification).

We performed all statistical analyses using STATA 15.1 (Stata Corp, College Station, TX, USA). Statistical significance was considered for a P value <0.05 (for a 2-sided test).

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Results

We analyzed data of 881 patients with aging-related vulnerability from an initial cohort of 2,028 patients (43.4%). **Figure 1** shows the patient flow in the overall trial. Patients had a mean age of 82.4 years. There was a high level of comorbidities within the cohort. Polymorbidity, defined as >2 chronic conditions, was present in 438 (49.7%) patients. The mean number of chronic comorbidities was 2.4, which was

slightly higher than the 2.1 of the main trial cohort. Detailed baseline characteristics are presented in **Table 1** and were well balanced between the intervention and control group.

The subgroup with aging-related vulnerability contained patients with three partially overlapping characteristics: frailty syndrome, very old age ≥80 years and any type of cognitive impairment. 23.4% (206/881) presented with a frailty syndrome. 81.8% (721/881) were ≥80 years of age and 15.3% (135/881) showed cognitive impairment.

Protocol adherence was high and energy and protein goals were met in 79% and 76% in the intervention group, respectively. Energy and protein intake in the intervention group was significantly higher compared to control group patients. Patients in the intervention group had 286 kcal more energy intake (95% CI 226 to 541) and 13g more protein intake (95%CI 6 to 20) per day than patients of the control group.

Clinical outcomes

Primary endpoint

Patients with aging-related vulnerability receiving nutritional support showed more than 50% reduction in risk of 30-day mortality (60/442 [13.6%] vs. 31/439 [7.1%], adjusted OR 0.48 (95%CI 0.31 to 0.76), p=0.002) (**Table 2**). **Figure 2** shows endpoints in the overall EFFORT trial and in patients with aging-related vulnerability as well as patients with frailty, age ≥80 years and patients with cognitive impairment. Results were similar in all subgroups but only significant in the largest of the predefined subgroups of very old patients aged ≥80 years (55/363 [15.2%] vs. 30/358 [8.4%], adjusted OR 0.51 (95%CI 0.31 to 0.83)).

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Figure 3A illustrates the time to death in patients with aging-related vulnerability with significant short time in control group patients compared to the intervention group.

The risk reduction of 30-day mortality in patients with aging-related vulnerability was more pronounced compared to results in the main trial (adjusted OR of the main trial 0.65 [95%CI 0.47 to 0.91], p of interaction analysis: 0.002). The difference remained robust after adjustment for polymorbidity (adjusted OR 0.46 [95%CI 0.24 to 0.89]).

Secondary endpoint

We also found strong improvements regarding several secondary endpoints including adverse outcome (90/439 [20.5%] vs. 131/442 [29.62%], adjusted OR 0.61 [95%CI 0.45 to 0.83]), which was similar to the initial trial (p of interaction analysis = 0.095). Also, functional outcome – defined as a decline in Barthel's Index of >10% at 30 days - showed significant improvement in the intervention group. These results, again, were more pronounced than in the original EFFORT. In line with the main trial results, quality of life within the first 30 days, as well as 180 days after hospitalization, improved significantly in the intervention group. In addition, long-term mortality over 180 results was significantly improved in the intervention group (**Figure 3B**).

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Discussion

This secondary analysis of a large randomized clinical trial investigated the effects of individualized nutritional support on mortality and other important clinical outcomes in the subgroup of malnourished patients with aging-related vulnerability due to frailty syndrome, very old age ≥80 years or cognitive impairment. We found a 50% decrease in 30-day mortality and a significant reduction in the risk of adverse outcome associated with nutritional support. These results were more pronounced than those of the main trial (EFFORT) and persisted even after adjustment for polymorbidity. In light of the increasing number of patients with aging-related vulnerability in general medical wards, we believe our findings could substantially impact treatment and improve therapeutic success in acute settings.

Malnutrition is an established risk factor for mortality in older and frail patients.[31, 32] Due to limited physiologic reserves related to homeostatic mechanisms, its effect is more pronounced in this patient population than in the non-frail, general polymorbid patient on a medical ward.[33] Any additional acute medical event rapidly jeopardizes successful treatment *per se.[34]* In such cases, individual nutritional support could potentially strengthen physical resilience. Furthermore, intervention trials have reversed physical frailty by improving nutritional status.[35] The beneficial impact of nutritional support on mortality, though, has only been shown in a few smaller studies in malnourished elderly patients on medical wards.[36, 37] Data from selected patient populations of very old patients aged ≥80 years with frailty syndrome, or cognitively impaired patients has been lacking. Apart from reducing mortality, maintenance of the greatest possible autonomy as well as quality of life in the mid- to long-term are equally important medical care aims for geriatric cohorts.[12] Our data indicates that individualized nutritional support improves long-

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term outcome, e.g. 180-day-mortality (OR 0.76 [95% CI 0.59, 0.99], also see **Figure 3B**) as well as quality of life at 180 days. Continuing nutritional support in the out-patient setting might be necessary to further improve clinical, functional and qualitative outcome. Adding exercise and cognitive training may also improve outcomes. [35, 36]

There is abundant research on the interplay of malnutrition with advancing age, physical frailty and cognitive impairment. Malnutrition aggravates physical frailty as well as cognitive function, but may itself also result from physical frailty or cognitive impairment.[38] This interaction often leads to a vicious cycle, which is difficult to control if dynamics have time to accelerate. It is therefore crucial to intervene early to maintain quality of life, functional status and autonomy. [39] Strict screening for risk of malnutrition at time of hospital admission and nutritional care plans to guide the provision of nutritional support must be established and broadly implemented. From a wider perspective, we anticipate that costs of nutritional support (even if administered and professionally supervised over a longer period of time in both inpatients and outpatients) will be balanced with the expected benefits for society, especially considering the costs saved by avoiding earlier entry into nursing homes.

In the EFFORT trial, nutritional support was provided according to a previously established nutritional protocol[29, 40], which is based on guidelines from the European Society for Clinical Nutrition and Metabolism (ESPEN)[6]. For each patient, individualized nutritional energy were defined upon hospital admission according to the weight-adjusted Harris-Benedict equation.[41, 42] A recent metanalysis investigating the prediction accuracy of the predicted resting energy expenditure (REE) in healthy elderly subjects found the Mifflin equation at group level and the

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Harris-Benedict equation at individual level to perform best. [43] Still, the review highlights that none of the prediction equations provides accurate and precise resting energy expenditure estimates in healthy older adults and further research is thus needed to improve estimation of energy needs.

This is a secondary analysis of a previous trial which was powered to detect a difference in the risk for adverse clinical outcome among patients receiving nutritional support as compared to patients receiving routine hospital food. The primary hypothesis of EFFORT was that early nutritional therapy would reduce adverse clinical outcome and mortality within a follow up period of 30 days after the index hospitalization. We estimated that 40% of the target patient population would reach the primary endpoint within 30 days and hypothesized that the nutritional intervention will decrease this risk by an absolute number of 6% (relative decrease of 15%). Based on these numbers, we estimated that a sample size of 1016 per group (total number 2032) would have a power of at least 80% to find a reduction in the likelihood of the primary endpoint. Regarding this analysis, a post-hoc power analysis shows a power of 89% to detect a difference in 30-day mortality of 13.6% (control group) compared to 7.1% (intervention group).

Our analysis has several limitations worth mentioning. Firstly, the prevalence of cognitive impairment might be underestimated in our sample due to a lack of systematic screening of all patients at admission. Secondly, we had to group all affected patients in the subgroup of cognitive impairment due to low numbers of individuals with dementia or mild cognitive impairment *sensu strictu*. Variability in the clinical phenotype of mild cognitive impairment is already high due to missing diagnostic consensus, yet was even higher in our sample. Risk of death might

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diverge as well, but more probably as a result of associated parameters than due to cognitive status alone.[44] Based on the publication of Orsitto et al. the risk of malnutrition seems comparable.[14] High heterogeneity within the subgroup harbors high potential for bias, yet as the numbers remained relatively small, its effect on the result of the overall cohort of aging-related vulnerable patients is unlikely to be noteworthy. Thirdly, due to the nature of a subgroup analysis, the power of our results is limited by relatively small patient numbers and low event rates for most of the end points. Concerning mortality, however, the effect of nutritional support was more pronounced than in the overall cohort. We therefore expect this strong signal to persist in a sufficiently powered analysis. Lastly, based on the differences in prevalence of the inclusion criteria used for aging-related vulnerability (age ≥80 years, frailty syndrome and cognitive impairment), it is unclear whether the beneficial effect of nutritional support is equally important in all three, or if predominance of age ≥80 years is responsible for our results. Based on our analysis, an additional impact on frail patients can be suggested, whereas the effect on cognitive impaired subjects remains unknown. Our results encourage further research on the impact of nutritional support in old and very old patients with aging-related vulnerability, as well as physical and cognitive frailty.

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Conclusion

Malnourished patients with aging-related vulnerability due to frailty syndrome, very old age ≥80 years or cognitive impairment show a strong reduction in mortality following in-hospital nutritional support at short-term and at long-term. In light of the increasing number of patients with aging-related vulnerability on general medical wards, our analysis suggests that individualized nutritional support provided to this population could substantially impact overall treatment, improve therapeutic success,

maintain individuals' autonomy and reduce institutionalization - in particular after hospitalization for a medical illness. These data thus support the early screening of patients with aging-related vulnerability upon hospital admission for nutritional risk, followed by a nutritional assessment and implementation of individualized nutritional interventions in at-risk patients.

Acknowledgments

We thank all patients and hospital staff for their support of our trial.

Author contributions: AB, DP, LP and PS were responsible for the data analysis and interpretation of the present secondary analysis. AB, DP, LP and PS drafted the final manuscript and authors contributed to the critical revision of the manuscript. PS was responsible for obtaining funding. LH, AB, LB, NK, PT were involved in data collection and approved the final version of the manuscript.

FG, CH, VP, SB, SS, MB, CH, RT, JR, DA, NR, JD were involved in drafting the trial protocol, supervision of study sites, drafting of the final manuscript and approving the final version of the original EFFORT trial.

ZS and BM were involved in obtaining funding, drafting the trial protocol, supervising study sites, drafting the final manuscript of the original EFFORT trial and approving the final version of the current manuscript. The corresponding authors had full access to all the data used and shared the final responsibility for the accuracy of the analyzed data.

Sponsor's role: The sponsor had no influence on the study design.

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Parameter		Intervention (*n = 439*)	Control (*n = 442*)	*p value*
Sociodemographics				
Mean age, years (SD)		82.2 (9.0)	82.5 (8.8)	*0.57*
Subgroups of age				
	<50 years	15 (3.4%)	13 (2.9%)	*0.92*
	50-75 years	43 (9.8%)	44 (10.0%)	
	>75 years	381 (86.8%)	385 (87.1%)	
Male sex (%)		208 (47.4%)	218 (49.3%)	*0.56*
Components of aging-relative vulnerability				
	Frailty	107 (24.4%)	99 (22.4%)	*0.49*
	Cognitive Impairment	70 (15.9%)	65 (14.7%)	*0.61*
	≥80 years	358 (81.5%)	363 (82.1%)	*0.82*
Comorbidities				
Coronary heart disease		185 (42.1%)	182 (41.2%)	*0.77*
Congestive heart failure		165 (37.6%)	174 (39.4%)	*0.59*
Arterial hypertension		286 (65.1%)	290 (65.6%)	*0.89*
Stroke		48 (10.9%)	41 (9.3%)	*0.41*
Peripheral artery disease		62 (14.1%)	76 (17.2%)	*0.21*
Chronic kidney failure		191 (43.5%)	186 (42.1%)	*0.67*
Diabetes mellitus		101 (23.0%)	102 (23.1%)	*0.98*
Malignancy		159 (36.2%)	176 (39.9%)	*0.26*
Chronic obstructive pulmonary disease		67 (15.3%)	73 (16.5%)	*0.61*
Polymorbidity				
Mean number of comorbidities (SD)		2.4 (1.4)	2.4 (1.5)	*0.51*
Number of comorbidities (%)	1-2	131 (29.8%)	130 (29.4%)	*0.74*
	3-4	222 (50.6%)	216 (48.9%)	

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	≥5	86 (19.6%)	96 (21.7%)	
Nutritional factors				
Mean BMI (kg/m2)		24.4 (4.9)	24.0 (4.4)	*0.21*
Nutritional Risk Score 2002				
	3 points	134 (30.5%)	126 (28.5%)	*0.57*
	4 points	158 (36.0%)	167 (37.8%)	
	5 points	128 (29.2%)	122 (27.6%)	
	6 points	19 (4.3%)	27 (6.1%)	
Weight loss	none	233 (53.1%)	246 (55.7%)	*0.85*
	>5% during last 3 months	74 (16.9%)	66 (14.9%)	
	>5% during last 2 months	54 (12.3%)	53 (12.0%)	
	>5% during last month	78 (17.8%)	77 (17.4%)	
Loss of appetite	absent	39 (8.9%)	41 (9.3%)	*0.84*
	present	400 (91.1%)	401 (90.7%)	
Oral intake (% of daily needs) during last week	>75% of	32 (7.3%)	34 (7.7%)	*0.6*
	50-75%	176 (40.1%)	162 (36.7%)	
	25-50%	178 (40.5%)	181 (41.0%)	
	<25%	53 (12.1%)	65 (14.7%)	
Severity of illness	mild	13 (3.0%)	17 (3.8%)	*0.86*
	moderate	322 (73.3%)	322 (72.9%)	
	severe	102 (23.2%)	100 (22.6%)	
	unknown	2 (0.5%)	3 (0.7%)	

Table 1. Baseline characteristics of patients with aging-related vulnerability

Abbreviations: BMI = body mass index, SD = standard deviation

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Parameters	Intervention group (N=439)	Control group (N=442)	Adjusted odds ratio (OR), hazard ratio+ (HR) coefficient) (95% CI)	*p value*
Mortality				
All-cause mortality at 30 days	31 (7.1%)	60 (13.6%)	0.48 (0.31, 0.76)	*0.002*
All-cause mortality at 180 days	102 (23.2%)	127 (28.7%)	0.76+ (0.59, 0.99)	*0.040*
All-cause mortality at discharge	18 (4.1%)	32 (7.2%)	0.55 (0.3, 0.99)	*0.047*
Additional outcomes of the in-hospital and early out-hospital phase				
Adverse outcome within 30 days*	90 (20.5%)	131 (29.6%)	0.61 (0.45, 0.83)	*0.002*
Any major complications within 30 days	29 (6.6%)	41 (9.3%)	0.69 (0.42, 1.13)	*0.145*
Non-elective hospital readmission within 30 days	32 (7.3%)	35 (7.9%)	0.95 (0.58, 1.58)	*0.857*
Mean length of hospital stay****	10 (6.4)	10 (5.7)	-0.05 (-0.83, 0.73)	*0.902*

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Functional outcomes**				
Low functional status at 30 days (Barthel's Index of ≤30 points), diseased included****	87 (26)	80 (33)	6.42 (2.48, 10.37)	*0.001*
Decline in functional status (Barthel's Index) >10% at 30 days	47 (10.7%)	80 (18.1%)	0.54 (0.37, 0.8)	*0.002*
New institutionalization after hospital discharge	152 (35.1%)	144 (32.8%)	0.02 (-0.04, 0.08)	*0.562*
Falls at 180 days	60 (13.9%)	55 (12.5%)	1.09 (0.73, 1.61)	*0.686*
Bone fractures at 180 days	8 (1.8%)	3 (0.7%)	2.64 (0.68, 10.16)	*0.159*
Quality of life***				
Mean EQ-5D Index at 30 days****	0.7 (0.31)	0.7 (0.36)	0.07 (0.02, 0.11)	*0.003*
Mean EQ-5D Index at 180 days****	0.8 (0.21)	0.8 (0.22)	0.83 (0.82, 0.84)	*<0.001*
Mean EQ-5D VAS****	60 (26)	53 (30)	7.18 (3.16, 11.21)	*<0.001*

Table 2. Outcomes of patients with aging-related vulnerability

Abbreviations: EQ-5D= Questionnaire with 5 dimensions by the EURO-Qol Group; VAS = visual analog scale

Data are number of events (%), unless otherwise stated. All odds ratios were calculated with a logistic regression for binary data and linear regression for continuous data. Models were adjusted for predefined prognostic factors (initial nutritional risk screening score and baseline Barthel's Index) and study centre.

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* Composite endpoint, consisting of all-cause mortality at 30 days, major complications within 30 days, admission to the intensive care unit from the medical ward and non-elective readmissions after discharge

** To estimate decline in functional status, we used Barthel's Index (score ranging from 0 to 100, with higher scores indicating better functional status) and compared scores at admission with scores at 30 days. Only surviving patients were included in this analysis

*** To estimate quality of life, we used the European quality of Life 5 Dimensions index (EQ-5D; values range from

–0·205 to 1, with higher scores indicating better quality of life) including the visual-analogue scale (EQ-5D VAS;

scores range from 0 to 100, with higher scores indicating better health status)

**** Coefficient

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Figure Legends:

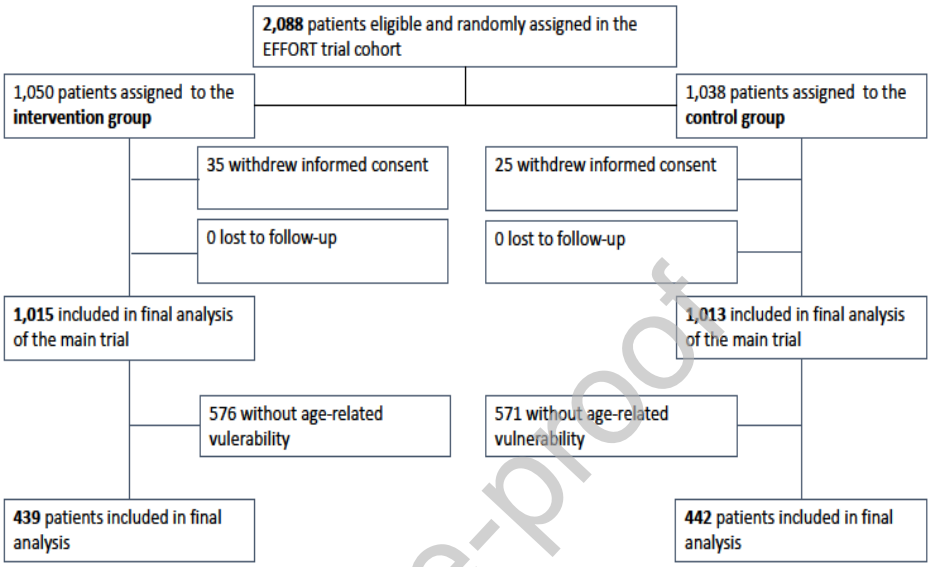

Figure 1. Patient flow

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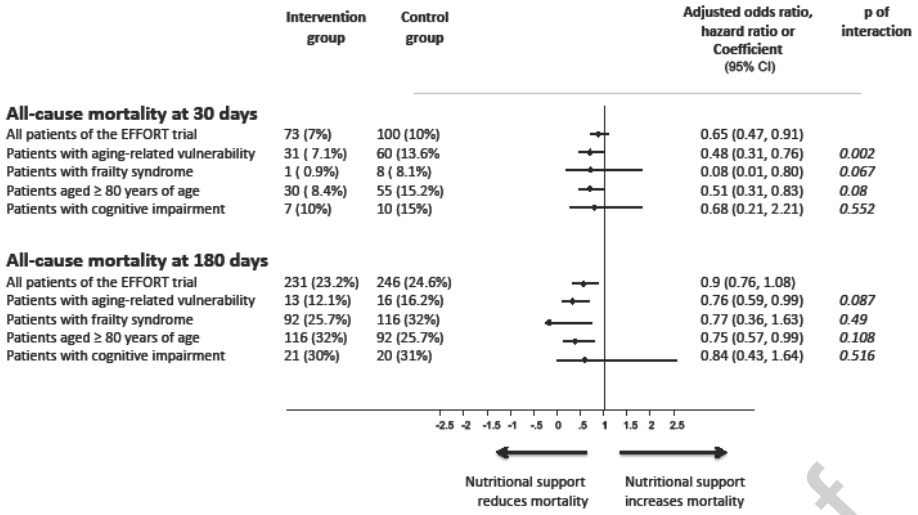

Figure 2. Adjusted odds ratios for primary and secondary outcomes in pre-specified subgroups (Forest plot)

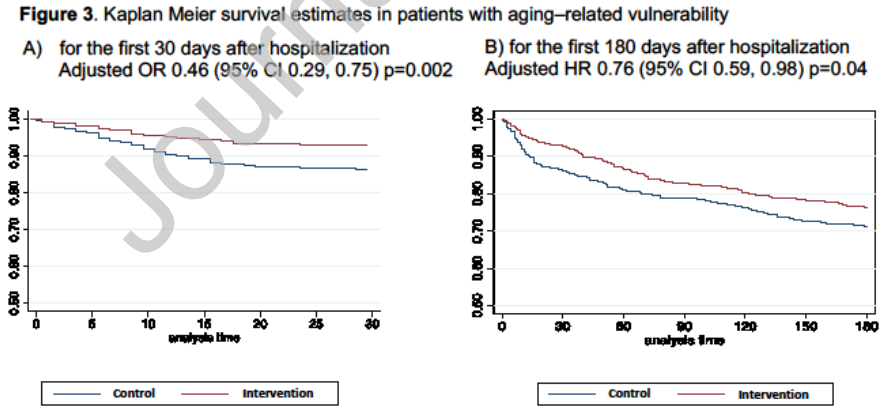

Figure 3. Kaplan Meier survival estimates in patients with aging–related vulnerability. A) for the first 30 days after hospitalization B) for the first 180 days after hospitalization

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