

Body mass index and prognosis in patients hospitalized with acute exacerbation of chronic obstructive pulmonary disease

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Abstract

Background Nutritional status, weight loss and cachexia have important prognostic implications in patients with chronic obstructive pulmonary disease (COPD). Body mass index (BMI) has been implicated in COPD risk assessment, but information is mostly limited to composite scores or to patients with stable disease. We aimed to analyse the association between BMI and mortality in acute exacerbation of COPD.

Methods This retrospective survey included 968 patients hospitalized due to acute exacerbation of COPD at the University Clinic Golnik from February 2002 to June 2007. Vital status was ascertained with Central Population Registry, and database was censored on November 1, 2008. **Results** Median BMI was 25.08 kg/m² (interquartile range, 21.55–29.05 kg/m²) and 210 patients (22%) had BMI < 21 kg/m². During median follow-up of 3.26 years (1.79–4.76 years), 430 patients (44%) died. Lowest mortality was found for BMI 25.09–29.05 kg/m². When divided per BMI decile, mortality was lowest for BMI 25.09–26.56 kg/m² (33%). In univariate analysis, BMI per quartile and BMI per unit increase were predictive for all-cause mortality. In an adjusted model, BMI per 1 kg/m² unit increase was associated with 5% less chance of death (hazard ratio 0.95, 95% confidence interval 0.93–0.97). **Conclusions** Low BMI < 21 kg/m² is frequent in patients hospitalized due to acute exacerbation of COPD. Higher BMI was independently predictive of better long-term survival. A better outcome in obese patients compared to normal weight is in contrast to primary prevention data but concurs with observations of an obesity paradox in other cardiovascular diseases.

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1 Introduction

Nutritional status, weight loss and cachexia have important prognostic implications in patients with chronic disease [1, 2]. In contrast to common public beliefs and guidelines for primary preventive medicine, high body mass index (BMI) confers protective effects for patients with established

chronic diseases such as chronic obstructive pulmonary disease (COPD), heart failure (HF) and chronic kidney disease [3–5]. Similar observations have been reported for other chronic and acute disease conditions which summarized to term reverse epidemiology [6].

Along the natural course of COPD, poor nutritional status, weight loss and development of cachexia frequently occur [7] and contribute to excessive morbidity and mortality burden [8]. In clinical practice, nutritional status is most frequently estimated by BMI calculation and low BMI has been found as an independent predictor of increased mortality [3, 7, 8]. Most of the initial studies, however, were conducted in limited samples or in clinically stable ambulatory patients, and, therefore, may not reflect the full picture of COPD patients [8–11]. For hospitalized patients, less information is available and reports are divergent in their findings. Most of the studies had relatively short follow-up period, and data about association between BMI and long-term mortality after hospitalization for acute exacerbation of COPD is particularly scarce [12–14].

The aim of the present study was therefore to assess the association between BMI and long-term mortality in COPD patients after acute deterioration necessitating hospital care.

2 Methods

2.1 Study design

This study used data from a survey which revised all consecutive discharges from University Clinic Golnik from February 2002 to June 2007 [15]. Patients discharged with COPD (J44.0–J44.9 ICD 10 code) as a primary diagnosis were screened for the analysis. The study protocol was approved by the National Ethics Committee of Slovenia.

2.2 Patients and data collection

Initial review of medical records identified 1,391 potentially eligible patients. After verification of COPD as primary admission cause by an independent review of medical documentation and availability of required data such as complete pulmonary function testing and information about body height and body weight to allow for BMI calculation, we included 968 patients. Patients' demographic characteristics, smoking status, length of hospital stay, concomitant disease, discharge medication and long-term oxygen therapy (LTOT) were retrieved from index hospitalization medical records.

2.3 Study endpoints and statistical analysis

The primary outcome of this a priori analysis was all-cause mortality, which was assessed through the Central Population

Registry, and the database was censored on November 1, 2008. Secondary endpoints included BMI distribution and relative risk of death across BMI deciles.

Continuous variables are presented as mean values \pm standard deviation or as median (interquartile range—IQR). Categorical variables are presented as absolute numbers (%). Differences between the patient subgroups (e.g. per BMI quartiles) were evaluated using the Student's *t* test, chi-squared test, Mann–Whitney *U* test and analysis of variance as appropriate. Kaplan–Meier survival curves were used to present occurrence of primary endpoints during follow-up. The difference across BMI quartiles was compared using the log-rank test. The relationship between all-cause mortality and BMI per 1 kg/m² increase (model 1) or BMI quartiles (model 2) was evaluated with Cox models of proportional hazards. To identify independent predictors of mortality, age, gender, Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage, HF, cancer and asthma were forced into the multivariate model. We report hazard ratios (HR) and corresponding 95% confidence intervals (CI). SPSS 16.0 software (SPSS Inc., 2007, Chicago, IL, USA) was used for statistical calculations. For all tests, a *p* value of <0.05 was considered statistically significant.

3 Results

A total of 968 patients were included in this study, median BMI was 25.08 kg/m² (IQR 21.55–29.05 kg/m²); 210 patients (22%) had BMI > 21 kg/m², 294 patients (30%) were overweight (BMI 25–30 kg/m²) and 194 patients (20%) were obese (BMI > 30 kg/m²). Table 1 summarizes patient characteristics over BMI quartiles. For most parameters, there were no differences between patient subgroups. A significant increase was observed for prevalence of concomitant asthma and HF and forced expiratory volume in 1 s (FEV₁). By contrast, GOLD stage decreased over BMI quartiles.

During follow-up (median 3.26 years; range 1.79 to 4.76 years), 430 patients (44%) died. Mortality rates at year 1, 2, and 3 after discharge were 12% (95% confidence interval [CI] 10–15%), 25% (21–26%), and 32% (29–35%), respectively. Lowest mortality was found for patients in third BMI quartile (25.09–29.05 kg/m²) and increased to lowest BMI quartile—Table 1 and Fig. 1. When patients were divided per BMI decile, mortality was lowest for those with BMI of 25.09–26.56 kg/m² (33%). A linear increase was observed for patients below optimal BMI decile (a relative risk of 1.94 for patients with BMI < 18.42 kg/m²), whereas risk plateaued with increasing BMI—Fig. 2.

BMI was associated with all-cause mortality which was independent of other parameters (Table 2). In univariate

Table 1 Patient characteristics per body mass index quartiles

	All patients (N=968)	Body mass index <21.55 kg/m ² (N=242)	Body mass index 21.55–25.08 kg/m ² (N=242)	Body mass index 25.09–29.05 kg/m ² (N=242)	Body mass index >29.05 kg/m ² (N=242)	p
Age	70±9	69±9	70±9	70±9	69±9	0.082
Men	700 (72%)	167 (69%)	190 (78%)	174 (72%)	169 (70%)	0.100
Length of stay	12±8 days	12±8	13±10	11±9	12±7	0.351
Mortality	430 (44%)	132 (54%)	123 (51%)	82 (34%)	93 (38%)	<0.001
Current smoker	233 (24%)	74 (31%)	60 (25%)	40 (17%)	59 (24%)	0.229
GOLD	2.8±0.9	3.0±0.9	2.8±0.9	2.7±0.8	2.6±0.8	<0.001
FEV ₁	1,304±577 ml	1,145±554 ml	1,311±620	1,344±555	1,418±545	<0.001
VC	2,885±910 ml	2,843±897 ml	2,998±948	2,889±946	2,810±840	0.116
Asthma	178 (18%)	31 (13%)	39 (16%)	49 (20%)	59 (24%)	0.006
Heart failure	263 (27%)	29 (12%)	54 (22%)	70 (29%)	110 (45%)	<0.001
Cancer	108 (11%)	32 (13%)	30 (12%)	24 (10%)	22 (9%)	0.428
SABA	882 (91%)	218 (90%)	225 (93%)	223 (92%)	216 (89%)	0.458
LABA	656 (68%)	159 (66%)	161 (66%)	167 (69%)	169 (70%)	0.693
ICS	627 (65%)	145 (60%)	162 (67%)	153 (63%)	167 (69%)	0.175
Tiotropium	262 (27%)	73 (30%)	62 (25%)	71 (29%)	56 (23%)	0.255
Teophylline	497 (51%)	132 (54%)	132 (54%)	116 (48%)	117 (48%)	0.294
LTOT	194 (20%)	54 (22%)	49 (20%)	38 (16%)	53 (22%)	0.257

FEV₁ forced expiratory volume in 1 s, VC vital capacity, SABAs short-acting β₂-agonists, LABAs long-acting β₂-agonists, ICSs inhaled corticosteroids, LTOT long-term oxygen treatment, GOLD Global Initiative for Obstructive Lung Disease

survival analysis, BMI per quartile and BMI per unit increase were predictive for all-cause mortality. The associations remained significant after adjustment for other parameters that are known to predict survival in patients with COPD. In an adjusted model, BMI per 1 kg/m² increase was associated with 5% less chance of death (95% CI 0.93–0.97). Similarly, patients in two highest BMI quartiles had 48% and 46% less chance of death (95% CI 0.41–0.72) when compared to patients in lowest BMI quartile.

4 Discussion

This study found that 22% of patients hospitalized due to acute exacerbation have BMI<21 kg/m². We were able to demonstrate that BMI, either per unit increase or per quartile, is an independent predictor of long-term mortality. Importantly, higher BMI was associated with better survival. Optimal BMI with lowest risk of death was in the overweight category (BMI of 25.09–26.56 kg/m²).

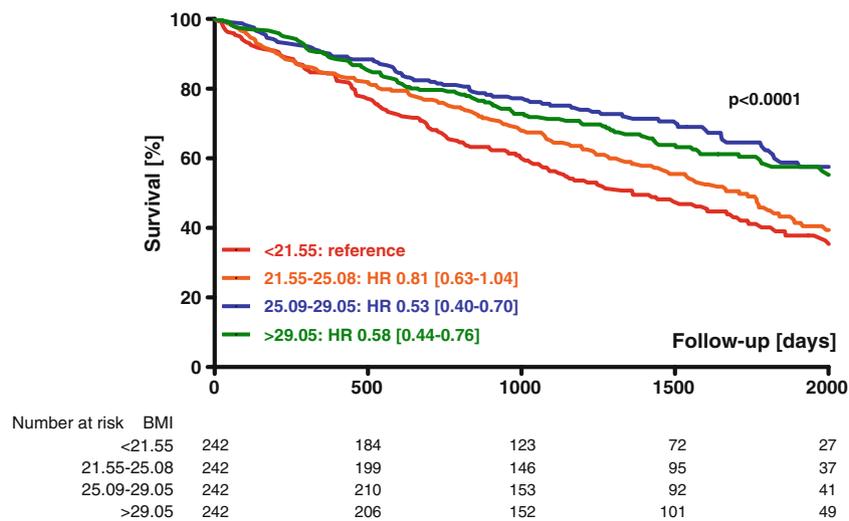


Fig. 1 Kaplan–Meier survival curves per body mass index quartiles and univariate analysis of mortality. HR hazard ratio, CI confidence interval

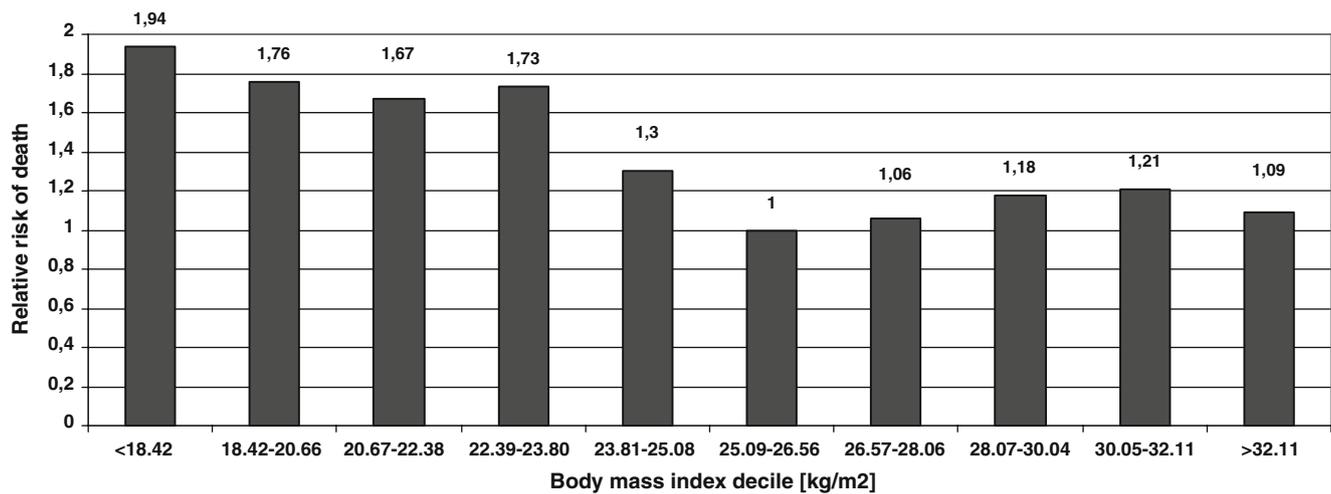


Fig. 2 Relative risk for all-cause mortality per body mass index deciles (body mass index 25.09–26.56 kg/m² as reference)

In patients with COPD, poor nutritional status as depicted with low BMI is a frequent finding [16–18]. Our results are confirming previous studies [8, 12] and extend current knowledge as we evaluated patients with acute admission due to COPD. Low BMI could also be suggestive for whole body wasting and occurrence of cachexia [19, 20]. This generally is a non-reversible condition, and no effective remedy is available to date [21, 22].

Acute exacerbation of COPD is a common and serious situation where hospital admissions are frequent [9]. Low BMI, along with some other predictors, precipitates need for hospital care [23]. In contrast to other chronic diseases, only few strategies are in place to keep COPD patients

away from hospitals and assessment of self-rated health could drive preventive measures to prevent unnecessary hospitalizations [24, 25]. This could be particularly relevant in the context of body size because risk for disability and poor/fair self-rated health was found to be lowest in overweight or even obese [26].

Our study has investigated body size in an unselected population hospitalized due to acute exacerbation of COPD. Overweight and obesity are firmly established risk factors for cardiovascular and other diseases, and increased disease severity of the disease may have been expected in this COPD population. Importantly, most of the patient characteristics that are available in daily clinical practice were not different across the BMI spectrum. Also no differences

Table 2 Cox proportional hazard models for all-cause mortality

	Univariate	Multivariate	
		Model 1	Model 2
Body mass index [per 1 kg/m ²]	0.95 [0.94–0.97]	0.95 [0.93–0.97]	NA
Body mass index			
<21.55 kg/m ²	Reference	NA	reference
21.55–25.08 kg/m ²	0.81 [0.63–1.04]	NA	0.82 [0.64–1.06]
25.09–29.05 kg/m ²	0.53 [0.40–0.70]	NA	0.52 [0.39–0.69]
>29.05 kg/m ²	0.58 [0.44–0.75]	NA	0.54 [0.41–0.72]
Age [per 1 year]	1.04 [1.03–1.05]	1.03 [1.02–1.04]	1.03 [1.02–1.04]
Gender [male vs female]	0.90 [0.73–1.12]	0.87 [0.70–1.09]	0.87 [0.70–1.09]
GOLD stage I	Reference	Reference	Reference
GOLD stage II	1.29 [0.75–2.20]	1.13 [0.66–1.95]	1.12 [0.65–1.93]
GOLD stage III	1.41 [0.83–2.40]	1.04 [0.60–1.79]	1.06 [0.62–1.83]
GOLD stage IV	2.82 [1.66–4.80]	2.07 [1.20–3.56]	2.11 [1.23–3.63]
Heart failure	1.60 [1.31–1.95]	1.72 [1.39–2.14]	1.65 [1.33–2.05]
Cancer	1.80 [1.37–2.36]	1.60 [1.21–2.11]	1.54 [1.17–2.03]
Asthma	0.61 [0.47–0.80]	0.75 [0.57–0.98]	0.75 [0.57–0.98]

Data are presented as hazard ratios and 95% confidence intervals

GOLD Global Initiative for Obstructive Lung Disease, *NA* not applicable

were found for COPD specific treatments. The prognosis was predicted by BMI independently of other established mortality predictors with better survival observed in those patients who were overweight and obese. Implications of our results are relevant for clinical practice because BMI is an easily accessible parameter, even in acutely deteriorated patients. For COPD, several scoring systems to predict prognosis were developed. The BODE score includes body-mass index (B), the degree of airflow obstruction (O) and dyspnea (D), and exercise capacity (E). The BODE composite score [23] is allegedly the most frequently used in everyday practice but it is primarily limited to patients with clinically stable disease as seen in outpatient setting. Due to its availability and clinical importance, the BMI has also been included in other scoring systems in patients with COPD [27]. Overall, the low BMI is included in the scoring systems to predict outcome in COPD patients as managed by primary and secondary care physicians [23, 27]. Our study confirms increased risk in patients with low BMI. But more importantly, we show that overweight and moderate obesity are not associated with increased mortality. Further, during acute exacerbation, however, some of the score components (e.g. forced expiratory volume in 1 second, dyspnoea score) may be particularly vulnerable to short-term changes which limit the applicability of risk assessment during patient deterioration. Our results demonstrated that BMI, even on top of other recognized risk stratifiers that are reliably accessible during course of transient clinical deterioration, is predictive of all-cause mortality in patients admitted due to COPD exacerbation. Although retrospective in design, our study has relevant advantages over previous reports. We have included a large sample of patients with reliable diagnosis of COPD, and we have followed them for long-term outcome. Importantly, we have included only patients already experiencing worsening which necessitated hospital admission. Such an event is a relevant point to both patient and caring physician in a patient's course of disease to predict future disease progression and to re-consider therapeutic strategies [25, 28]. In an era of complex patient assessment, future studies need to look into composite scores including cardiovascular therapy and treatment as well as laboratory parameters beyond COPD [29]. This could identify novel therapeutic strategies either to prevent patient deterioration or to improve rehabilitation and outcome once clinical condition has worsened [30–32]. It is important to stress that management strategies have to shift beyond the symptom relief interventions [33, 34] and to assess the global patient situation beyond COPD, where concomitant disease may play a decisive role [2, 35]. A tailored approach accounting for patient complexity and disease severity, preferably in an outpatient setting [36], could prove as particularly advantageous.

4.1 Limitations

This study has to be interpreted in view of certain limitations. Through selected methodology, we were unable to control for potential effects of parameters beyond the included variables thus there exists a risk of residual confounding by additional variables and co-morbidities beyond the study design. It is important to notice that our findings are based upon index hospitalization information which was not controlled for any changes through the follow-up period. This limitation, however, is driven per study design and is shared with many previous publications [12–14].

4.2 Clinical implications

BMI is an easily accessible parameter which carries important information for patient assessment and risk stratification. This is particularly important in the presence of chronic disease like COPD. In patients experiencing acute exacerbation of COPD, assessment of functional parameters like dyspnoea, exercise capacity and pulmonary function may be of limited value for long-term risk assessment which could importantly impact risk stratification. Our results, along with some of previous studies [3, 7–15], suggest that BMI calculation carries a potential to identify patient at risk of poor prognosis. This enables the clinicians to identify patients at risk and to plan future therapeutic efforts to prevent body wasting and to improve prognosis for patients with COPD [37, 38].

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Conflicts of interest The authors declare that they have no conflict of interest.

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