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A multidimensional risk score to predict all-cause hospitalization in community-dwelling older subjects with obstructive lung disease

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Abstract

Background—Both respiratory and non-respiratory hospitalizations are common and costly events in older subjects with obstructive lung disease. Prevention of any hospitalization in these subjects is essential. We aimed to construct a prediction model for all-cause hospitalization risk in community-dwelling older subjects with obstructive lung disease.

Methods—We studied 268 community-dwelling subjects with obstructive lung disease (defined as FEV₁/FVC < LLN) who participated in the observational Health, Aging and Body Composition Study and constructed a prediction model for 9-year all-cause hospitalization risk using a weighted linear combination based upon beta coefficients.

Results—There were 225 subjects with 1 hospitalizations and 43 subjects free from hospitalization during the follow-up. Heart and vascular disease (H), objectively measured lower

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extremity dysfunction (O), systemic inflammation (S), dyspnea (P), impaired renal function (I), and tobacco exposure (T) were independent predictors for all-cause hospitalization (ALL). These factors were combined into the HOSPITAL score (0–23 points), with an area under the curve in ROC analysis of 0.70 ($p < 0.001$). The hazard ratio for all-cause hospitalization per one-point increase in the HOSPITAL score was 1.15 (95% confidence interval, 1.11–1.19, $p = 0.001$). Increasing HOSPITAL score was further associated with shorter time to first admission, increased admission rate, and more respiratory admissions.

Conclusion—The HOSPITAL score is a multidimensional score to predict all-cause hospitalization risk in community-dwelling older subjects with obstructive lung disease, that may aid in patient counseling and prevention to reduce burden and health care costs.

Keywords

COPD; Pulmonary disease; Older age persons; Cox Proportional Hazards Modeling

Introduction

Chronic obstructive pulmonary disease (COPD) in particular is common in aged persons, and is associated with significant functional limitations^{1,2} and high health care costs.³ During the course of their disease, patients with COPD are frequently hospitalized not only for exacerbations or pneumonia,^{4,5} but also for a wide range of non-respiratory causes.^{6,7} All-cause hospitalization rates in COPD range from approximately 0.4 to 0.7 admissions per person per year, depending on the population studied.^{6–10} Whereas hospital stays drive direct costs of COPD-related care,¹¹ hospitalizations for non-respiratory reasons constitute the greatest expense in patients with COPD.³ Moreover, 72% of the 30-day readmissions after exacerbated COPD are primarily for non-respiratory problems.¹²

Irrespective of the primary reason for admission, hospitalization may trigger a progressive physical decline,^{13,14} which has recently also been shown in patients with COPD.¹⁰ Patients with COPD hospitalized for respiratory and non-respiratory causes experienced an equal rate of accelerated decline in six minute walking distance after discharge compared to non-hospitalized patients.¹⁰ Furthermore, all-cause hospitalization in COPD is associated with high mortality.¹⁵ Preventing any hospitalization in patients with COPD is therefore crucial. Although several studies have suggested that the physical activity level and exercise capacity may be predictors of all-cause hospitalization in patients with COPD,^{10,16,17} a thorough investigation of potential risk factors has not been undertaken. Moreover, these were studies conducted in secondary and tertiary care center populations, whereas strategies to prevent hospitalization should ideally commence in the pre-clinical setting.

In the current study, we analyzed baseline and 9-year follow-up data from community-dwelling older subjects with obstructive lung disease participating in the observational Health, Aging and Body Composition (ABC) Study to identify risk factors for all-cause hospitalization. We subsequently constructed a risk prediction model that may aid in patient counseling in the pre-clinical setting. The Health ABC Study cohort was selected as it provides a rich characterization of community-dwelling older subjects with long follow-up data available.

Methods

A detailed methodology can be found online in the supplemental material.

Study population

This study was performed using data from the Health ABC Study which is a longitudinal observational study of 3075 community-dwelling black and white men and women, 70 to 79 years of age, residing in Pittsburgh, Pennsylvania and Memphis, Tennessee. Participants were included if they reported no difficulty walking a quarter mile, climbing 10 steps without resting, or performing mobility-related activities of daily living. The Health ABC Study protocol was approved by the Institutional Review Boards of the clinical sites. All participants gave written informed consent.

For the current analyses we used baseline data, obtained in 1997/1998 through in-person interview and clinic based examination, and 9-year follow-up hospitalization data. We analyzed the subjects (n=268) who met the criterion for obstructive lung disease (reduced [i.e. < lower limit of normal, LLN] forced expiratory volume in 1s [FEV₁]/forced vital capacity [FVC] as determined by age, sex, and race-normalized values)¹⁸ at baseline. Pre-bronchodilator lung function was assessed according to international standards.¹⁹

Hospitalizations and survival

Subjects were asked to report any hospitalizations and every 6 months they were asked directed questions about interim events. When an event was reported, medical records were collected (admission, discharge dates, and primary reason for hospitalization (e-Table 1)).

Covariates at baseline

As previously reported,^{18,20} clinic site, gender, race (black/white), age, tobacco exposure, dyspnea, body mass index (BMI), fat free mass index (FFMI), daily physical activity, knee extensor strength, hand grip strength, Short Physical Performance Battery (SPPB), and plasma C-reactive protein (CRP) were determined following standardized methodology. Comorbid heart and vascular disease (coronary heart disease, cerebrovascular disease, and congestive heart failure), chronic kidney disease (CKD),²¹ diabetes, cancer, and cognitive impairment²² were recorded. Furthermore, all-cause hospitalizations in the year prior to inclusion were reported by Centers for Medicare and Medicaid Services.

Statistical analysis

Baseline differences between subjects with 1 hospitalizations and subjects free from hospitalizations during the follow-up were tested using Student t-test for continuous variables, χ^2 test for categorical variables and Kruskal-Wallis test for continuous variables with skewed distributions. Univariate Cox proportional hazards models using bootstrap estimation (1000 replications; resampling with replacement) were performed to identify the association of candidate variables with all-cause hospitalization. All covariates with a p-value ≤ 0.10 were considered for inclusion in a multivariable model with a backward elimination approach using bootstrap estimation again allowing variables with a p-value ≤ 0.10 to be retained in the model. FEV₁, physical activity, BMI and CRP were modeled in

categories.^{23–25} The bias-corrected beta coefficients from the final multivariate model were subsequently standardized and rounded to the closest integer in order to assign weighted scores to each of the remaining variables.²⁶ Summation of these scores led to the final risk score. Receiver-Operating Curve (ROC) analysis was performed for the newly developed risk score to estimate its sensitivity and specificity in classifying persons by means of the Cox model as either hospitalized or not. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS version 22 for Windows, SPSS Inc.).

Results

Of the 268 subjects, 225 (84%) had ≥ 1 hospitalizations and 43 (16%) were free from hospitalization during the 9-year follow-up, with a total of 1944 person years. In total, those with ≥ 1 hospitalizations were hospitalized 811 times for any cause. The majority of these hospitalizations were for non-respiratory reasons (72.3%). Subjects had a median number of 3 (interquartile range [IQR] 1–5) hospitalizations, corresponding with 0.44 (IQR 0.22–0.78) hospitalizations per year. The median length of stay per hospitalization was 5 (IQR 4–9) days, and the median time to the first all-cause hospitalization was 2.2 (IQR 1.0–4.4) years.

Compared to subjects free from hospitalization, those with ≥ 1 hospitalizations had a higher prevalence of heart and vascular disease, a lower prevalence of cancer (particularly driven by a lower prevalence of prostate cancer [data not shown]) and a tendency towards a higher prevalence of CKD (Table 1). The latter group also had higher CRP levels and were more often ever-smokers, while no differences were found in body composition or muscle strength.

Univariate Cox proportional hazards analysis indicated that all-cause hospitalization was significantly predicted by clinic site, previous all-cause hospitalization, heart and vascular disease, FEV₁, dyspnea, CRP, daily physical activity level, SPPB, CKD, and tobacco exposure (Table 2).

In the multivariate Cox regression model heart and vascular disease, SPPB, CRP, dyspnea, CKD, and tobacco exposure were retained as significant predictors (Table 3). These variables were subsequently combined into the HOSPITALL score (HHeart and vascular disease [H], Objectively measured lower extremity dysfunction [O], Systemic inflammation [S], dysPnea [P], Impaired renal function [I], and Tobacco exposure [T] predict ALL-cause hospitalization [ALL]). Each subject received points based on the presence of heart and vascular disease, SPPB (<10 or ≥ 10), CRP (<5.0 or ≥ 5.0 $\mu\text{g/ml}$), dyspnea (none/mild or moderate), the presence of CKD, and tobacco exposure (ever- or never smokers) (Table 3). None or mild dyspnea as well as current and former smoking were taken together as their beta-coefficients were comparable (data not shown). The final HOSPITALL score for each subject was obtained by summing the points corresponding to each variable. HOSPITALL scores ranged from 0 to 23. As expected, subjects with ≥ 1 hospitalizations had higher HOSPITALL scores than those free from hospitalization (6.2 ± 2.7 vs 4.4 ± 2.1 , $p < 0.001$). Per one point increase of the HOSPITALL score the all-cause hospitalization risk increased by 15% (HR 1.15 [95% CI 1.11–1.19], $p = 0.001$). The final model did not substantially change when additionally adjusting for clinic site (data not shown).

The AUC of the ROC curve for the HOSPITAL score was 0.70 (95% CI 0.62–0.78, $p < 0.001$). For comparison, we also analyzed the AUC's for two previously validated mortality predictor scores in COPD and for FEV₁ alone. In the same Health ABC Study cohort, Mehrotra *et al.* described the PILE index (a combination score of FEV₁, IL-6, and knee extensor strength) and a modified version of the BODE index (mBODE, a combination score of BMI, FEV₁, dyspnea, and time to complete 400 meter walking).²⁰ The AUC's for the PILE index, mBODE index and FEV₁ to predict time to first all-cause hospitalization were 0.60 (95% CI 0.50–0.70, $p = 0.052$), 0.58 (95% CI 0.49–0.67, $p = 0.105$), and 0.44 (95% CI 0.35–0.53, $p = 0.216$), respectively, indicating superiority of the HOSPITAL score in this population.

When we divided the subjects into three HOSPITAL score risk strata (low, average and high risk with HOSPITAL scores of 0–4, 5–8, and 9, respectively), we identified significant differences between these groups not only in their risk for all-cause hospitalization (Figure 1), but also in time to the first admission, hospitalization rate, and primary cause for hospitalization (Table 4).

Discussion

Preventing hospitalizations is key in the management of patients with obstructive lung disease. The alarming admission and readmission rates urge physicians to break and preferably prevent this vicious cycle of hospitalizations. In community-dwelling older subjects with obstructive lung disease participating in the Health ABC Study, we have constructed the HOSPITAL score to predict all-cause hospitalization. The score comprises heart and vascular disease, lower extremity dysfunction, systemic inflammation, dyspnea, CKD, and tobacco exposure. The score may aid in the guidance for risk reduction in a population of older obstructive lung disease patients in the pre-clinical setting. The HOSPITAL score was more discriminative in predicting all-cause hospitalization than existing multidimensional risk scores. While the HOSPITAL risk factors may not necessarily be disease-specific and may also predict hospitalization and associated poor outcomes in general populations, the score underlines the broad multidimensional scope needed in obstructive lung disease care.

Moderate dyspnea was the strongest predictor amongst the HOSPITAL risk factors. Mild dyspnea did not increase the risk above no dyspnea. The definition of moderate dyspnea as applied in the Health ABC Study is comparable to a modified Medical Research Council grade of 2.²⁷ In our population the percentage of subjects with moderate dyspnea was relatively low with 10.3% as was to be expected given the community-dwelling nature of the population and that subjects needed to be well-functioning upon inclusion. Our results stress the need for documenting dyspnea severity in primary care obstructive lung disease subjects as it is a simple and sensitive measure that provides insight into the risk of a variety of poor outcomes including all-cause hospitalization.

Heart and vascular disease is the most prevalent comorbidity in COPD in the majority of studies, ranging from 28–70%.^{28,29} Furthermore, a recent meta-analysis showed a two to five times higher risk of major cardiovascular diseases in patients with COPD compared

with a non-COPD population.³⁰ Further stressing the clinical importance of comorbid heart and vascular disease in COPD, we found that it was a strong predictor in the HOSPITAL score. This suggests that preventing the development of heart and vascular disease in COPD may decrease the risk of hospitalization. Early identification of cardiovascular risk factors in COPD is therefore essential. Not only should we focus on common risk factors such as smoking and age, but metabolic syndrome status, systemic inflammation, adipose tissue distribution, and skeletal muscle oxidative capacity have been proposed as key mediators in COPD,³¹ that need further investigation in future studies. Also, interventions to modify cardiovascular risk in COPD are urgently warranted.

We found that objectively measured lower extremity dysfunction measured by the SPPB was a strong predictor for all-cause hospitalization. The SPPB is commonly used in older age populations but has recently also been shown to be a valid and simple assessment tool to measure functional impairment in COPD, independent of FEV₁.³² SPPB scores <10 have been associated with disability in aged persons,³³ with hyperinflation and with an increased proportion of type 2 quadriceps muscle fibers in COPD patients indicative of decreased oxidative capacity in skeletal muscle.³² Also, SPPB scores at discharge after hospitalization have been inversely correlated with the rate of decline in activity of daily living performance in older persons.³⁴ Clinical use of the SPPB test in COPD patients warrants further investigation.

It is well established that persistent low-grade systemic inflammation is present in some patients with COPD but its origin is still unclear.³⁵ Recent studies indicate that plasma levels of the clinical inflammatory marker CRP are at least partly influenced by adipose tissue mass,^{36,37} which is modifiable by lifestyle adaptations. In addition to previously reported associations between high CRP and low exercise capacity,³⁸ respiratory hospitalizations and increased mortality,³⁹ the current study also shows that high levels of CRP are predictive of all-cause hospitalization risk.

Although CKD is less common in COPD patients than heart and vascular disease, it has recently been shown that COPD patients with CKD had the highest incidence of all-cause ER visits which led to hospitalizations, and had the highest incidence of all-cause hospitalizations.²⁸ In addition, that study also showed that all-cause total healthcare costs were highest in COPD patients with CKD compared with other comorbidities.²⁸ Therefore, future studies need to increase the understanding of the relation between COPD and CKD. In our study, CKD was defined based on the CKD-Epidemiology Collaboration creatinine-cystatin C equation, which, in comparison to equations based on creatinine or cystatin C alone, has been shown to be more precisely and accurately in estimating the glomerular filtration rate (GFR) across the range of GFR.²¹

It is well-known that smoking is a major risk factor for developing COPD and many other chronic diseases, but smokers in this population still had an additional risk for all-cause hospitalization. This may be related to known effects of smoking on other organ systems and could reflect the influence of an overall unhealthy lifestyle.

Strengths and weaknesses

The unique design of the Health ABC Study enabled us to thoroughly investigate risk factors for all-cause hospitalization during a long follow-up of 9 years in community-dwelling older subjects with obstructive lung disease. An advantage of the long follow-up duration was that we could identify subjects free from any hospitalization during the entire follow-up. By comparing their characteristics to those with at least one all-cause hospitalization we were able to construct a solid risk score. Also, it was possible to compare the HOSPITALL score with other existing multidimensional risk scores showing superiority of the HOSPITALL score.

A limitation of this study is that no COPD diagnosis based on Global Initiative of Obstructive Lung Disease criteria could be given because post-bronchodilator pulmonary function was not available. To define obstructive lung disease, we used stringent criteria based on age-, sex-, and race-adjusted LLN cutoffs, as recommended by previous studies.⁴⁰ Nevertheless, it would be of interest to validate the HOSPITALL score in comparable cohorts with post-bronchodilator spirometry. Furthermore, it should be noted that the Health ABC Study included subjects without disability or mobility impairment which has implications for the generalizability of our results.

Conclusion

The HOSPITALL score is a multidimensional score to predict the risk of all-cause hospitalization in community-dwelling older subjects with obstructive lung disease. The HOSPITALL score may aid in patient counseling and prevention to reduce burden and health care costs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviation list

AUC	Area under the curve
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
CI	Confidence Interval
CKD	Chronic kidney disease
CRP	C-reactive protein

FEV₁	Forced expiratory volume in 1 second
FFMI	Fat free mass index
FVC	Forced vital capacity
Health ABC Study	Health, Aging, and Body Composition Study
HR	Hazard ratio
IQR	Interquartile range
LLN	Lower limit of normal
ROC	Receiver operating curve
SPPB	Short physical performance battery

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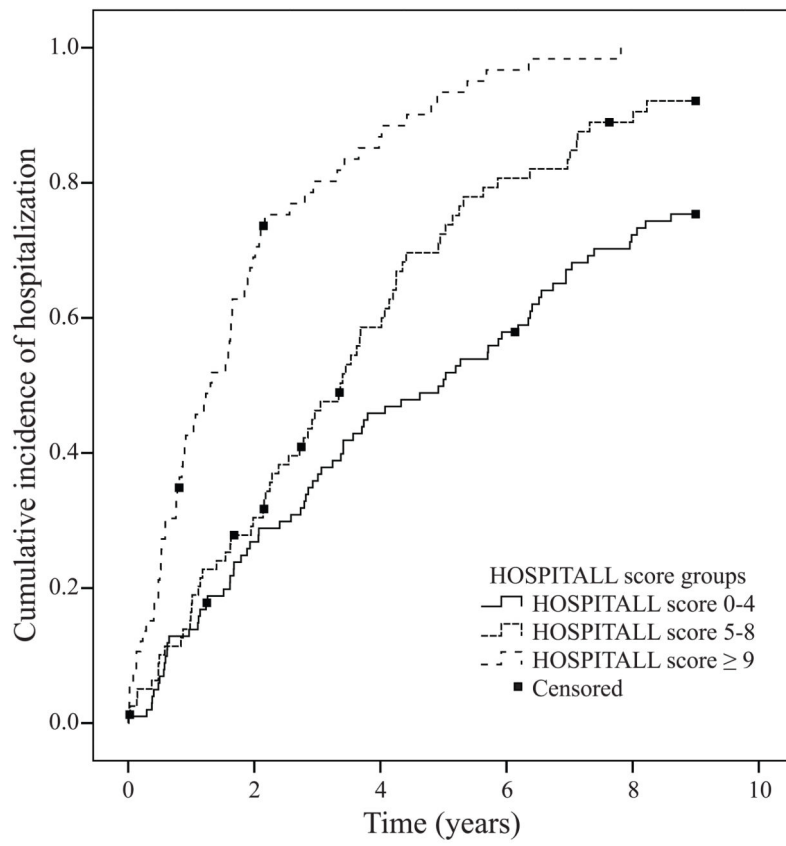


Figure 1. Kaplan Meier plot using HOSPITAL score groups as stratum ($p < 0.001$ by log-rank test).

Table 1

Baseline characteristics of the 268 subjects with obstructive lung disease

	Total (n=268)	Subjects with 1 hospitalizations (n=225)	Subjects free from hospitalization (n=43)	p-value
Age, y	73.2 ± 2.9	73.2 ± 2.8	73.0 ± 3.1	0.580
Gender, % male	57.5	58.2	53.5	0.565
Race, % white	55.6	55.1	58.1	0.714
Site, % Memphis	51.1	49.8	58.1	0.315
Previous all-cause hospitalization, %	13.1	13.8	9.3	0.419
FEV ₁ , %pred [*]	63 ± 18	62 ± 18	67 ± 20	0.121
Dyspnea				
None, %	50.6	48.6	60.5	0.245
Mild, %	39.2	40.0	34.9	
Moderate, %	10.3	11.4	4.7	
Physical activity, kcal/kg/wk [†]	65 (36–100)	62 (35–95)	77 (44–106)	0.068
Inactive	27.6	30.2	14.0	0.085
Lifestyle active	56.3	54.7	65.1	
Exercisers	16.0	15.1	20.9	
Tobacco exposure				
Ever, %	82.8	85.8	67.4	0.003
Never, %	17.2	14.2	32.6	
Quadriceps strength, Nm	103 ± 40	102 ± 40	107 ± 39	0.466
Grip strength, kg	64 ± 22	63 ± 21	66 ± 23	0.421
SPPB, % <10	31.3	33.8	21.4	0.115
BMI, kg/m ²	25.4 ± 4.7	25.3 ± 4.7	26.0 ± 4.8	0.379
FFMI, kg/m ²	17.0 ± 2.5	17.0 ± 2.5	17.1 ± 2.4	0.666
CRP, µg/ml [†]	2.06 (1.16–3.64)	2.16 (1.24–3.78)	1.17 (0.79–2.39)	<0.001
Heart and vascular disease, %	27.2	30.5	14.3	0.032
Chronic kidney disease, %	20.1	22.6	9.5	0.054
Diabetes, %	11.6	12.5	7.0	0.300
Cancer, %	17.2	15.1	27.9	0.041
Cognitive impairment, %	13.1	12.9	14.3	0.806

Abbreviations: BMI, body mass index; CRP, C-reactive protein; FEV₁, forced expiratory volume in 1 second; FFMI, fat free mass index; FMI, fat mass index; IL-6, interleukin-6; SPPB, short physical performance battery; TNF-α, tumor necrosis factor-α.

Data are mean (SD) unless indicated otherwise.

^{*} From reference equations⁴⁰

[†] Median (IQR).

Table 2

Investigated covariates in 268 subjects with obstructive lung disease as predictors for 9-year all-cause hospitalization using univariate Cox proportional hazards regression analysis

Variable	No. of hospitalizations	No. at risk	HR (95% CI)	p-value
Age, y	225	268	1.03 (0.98–1.07)	0.258
Gender				
Female	94	114	1.00	
Male	131	154	1.05 (0.81–1.37)	0.708
Race				
White	124	149	1.00	
Black	101	119	1.19 (0.91–1.55)	0.214
Site				
Memphis	112	137	1.00	
Pittsburgh	113	131	1.38 (1.06–1.79)	0.012
Previous all-cause hospitalization				
No	193	232	1.00	
Yes	31	35	1.58 (1.08–2.31)	0.048
FEV ₁ %pred				
Mild	38	47	1.00	
Moderate	125	149	1.29 (0.89–1.85)	0.142
Severe	62	72	1.56 (1.04–2.34)	0.037
Dyspnea				
None	107	133	1.00	
Mild	99	103	1.20 (0.90–1.59)	0.238
Moderate	25	27	2.49 (1.60–3.86)	0.004
Physical activity				
Exercisers	34	43	1.00	
Lifestyle active	123	151	1.02 (0.70–1.49)	0.914
Inactive	68	74	1.63 (1.08–2.47)	0.020
Tobacco exposure				
Never	32	46	1.00	
Ever	193	222	1.69 (1.16–2.47)	0.019
Quadriceps strength	198	236	1.00 (0.99–1.00)	0.154
Grip strength	223	265	1.00 (0.99–1.00)	0.216
SPPB				
10	147	180	1.00	
<10	75	84	1.78 (1.34–2.35)	0.001
BMI				
20.0 kg/m ²	21	24	1.21 (0.75–1.94)	0.377

Variable	No. of hospitalizations	No. at risk	HR (95% CI)	p-value
20.0–24.9 kg/m ²	99	115	1.00	
25.0–29.9 kg/m ²	67	85	0.90 (0.66–1.22)	0.479
30.0 kg/m ²	38	44	1.07 (0.74–1.55)	0.704
FFMI	222	265	1.00 (0.95–1.06)	0.904
CRP				
<5.0 µg/ml	186	224	1.00	
5.0 µg/ml	35	38	1.70 (1.18–2.44)	0.010
Heart and vascular disease				
No	153	189	1.00	
Yes	67	73	1.86 (1.39–2.48)	0.002
Chronic kidney disease				
No	171	209	1.00	
Yes	50	54	1.49 (1.08–2.04)	0.013
Diabetes				
No	196	236	1.00	
Yes	28	31	1.27 (0.85–1.88)	0.263
Cancer				
No	191	222	1.00	
Yes	34	46	0.86 (0.59–1.23)	0.441
Cognitive impairment				
No	196	232	1.00	
Yes	29	35	1.13 (0.76–1.67)	0.546

Abbreviations: BMI, body mass index; CRP, C-reactive protein; CI, confidence interval; FEV₁, forced expiratory volume in 1 second; FFMI, fat free mass index; HR, hazard ratio; SPPB, short physical performance battery.

Table 3

Final multivariable model as 9-year risk predictor for all-cause hospitalization: HOSPITAL score

Covariate	Coefficient	Hazard Ratio (95% CI)	P-value	HOSPITAL points
Heart and vascular disease				
No		1.00		0
Yes	0.44	1.55 (1.14–2.10)	0.011	3
Short Physical Performance Battery				
10		1.00		0
<10	0.55	1.73 (1.28–2.35)	0.001	4
CRP				
<5.0 µg/ml		1.00		0
5.0 µg/ml	0.37	1.45 (0.99–2.13)	0.058	3
Dyspnea				
None or mild		1.00		0
Moderate	0.98	1.71 (1.71–4.17)	0.001	7
Chronic kidney disease				
No		1.00		0
Yes	0.30	1.34 (0.96–1.88)	0.070	2
Tobacco exposure				
Never		1.00		0
Ever	0.55	1.73 (1.16–2.58)	0.018	4

Abbreviation: CRP, C-reactive protein.

Table 4

Stratification of HOSPITAL scores

	HOSPITAL score groups			p-value
	Low risk	Average risk	High risk	
HOSPITAL score	0–4	5–8	9	
n	101	80	66	
Risk of all-cause hospitalization, HR (95%CI)	0.60 (0.43–0.84) [†]	1	2.36 (1.66–3.34) [‡]	-
Time to first all-cause hospitalization, y (IQR) [*]	3.06 (1.26–5.87)	2.92 (1.16–4.38)	1.27 (0.52–2.15)	<0.001
All-cause hospitalizations per person per year, n (IQR) [*]	0.11 (0.00–0.39)	0.40 (0.13–0.73)	0.66 (0.35–1.23)	<0.001
Primary cause of first hospitalization				
Respiratory, n (%)	8 (10.7)	17 (24.6)	21 (32.8)	0.006
Non-respiratory, n (%)	67 (89.3)	52 (75.4)	43 (67.2)	

^{*} Median (IQR)[†] p=0.002[‡] p<0.001