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Spirometric Classifications of Chronic Obstructive Pulmonary Disease Severity as Predictive Markers for Clinical Outcomes: The HUNT Study

The classification of chronic obstructive pulmonary disease (COPD) severity is important in guiding therapy and prognosis (1). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has recommended GOLD grades (1) based on post-bronchodilator percentage-predicted FEV_1 ($ppFEV_1$), which is widely used in respiratory medicine. However, $ppFEV_1$ has been criticized because of its susceptibility to physiological variation (2–4). Studies have recommended alternative expressions of FEV_1 that could be used for the classification of COPD severity (2, 3, 5–9). For the first time, we have compared the predictive abilities of a broad range of FEV_1 expressions for cause-specific mortality and hospitalization.

Some of the results of these studies have been previously reported in the form of a preprint (https://doi.org/10.1101/2020.11.03.20221432).

Methods

This study included people aged ⩾40 years who participated in the HUNT2 Study (Trøndelag Health Study 2) during 1995–1997 ($n = 44{,}384$; 75.2% participation). A 5% random sample ($n = 2{,}300$) and people reporting asthma-related symptoms, diagnosis, or use of medication ($n = 7{,}123$) were invited to perform spirometry (10). For the analysis, we included 890 people

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Author Contributions: L.B., L.L., A.L., and B.M.B. conceived and designed the study. L.B. analyzed the data. L.B. wrote the first draft of the manuscript. All authors interpreted the results and revised and approved the manuscript for submission. L.B. and B.M.B. are accountable for the accuracy and integrity of all parts of the work. As project leader for the Lung Study in HUNT2, A.L. was responsible for planning, data collection, and quality assurance of data in the lung study.

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with COPD who met both the fixed ratio (post-bronchodilator $FEV_1/FVC < 0.70$) and lower limit of normal criteria and had respiratory symptoms (daily cough in periods, cough with phlegm, wheezing, or dyspnea) and/or self-reported doctor-diagnosed COPD (1, 11).

Post-bronchodilator spirometry was performed 30 minutes after inhalation of 1 mg of terbutaline according to the 1994 American Thoracic Society guidelines (12, 13). Quality assurance of spirometric measurements is described in detail elsewhere (13, 14).

We defined expressions of FEV_1 such as $ppFEV_1$, FEV_1 *z*-score, $FEV_1 \cdot Ht^{-2}$, $FEV_1 \cdot Ht^{-3}$, and FEV_1Q (described in detail in Reference 15) as suggested by the previous studies (1–3, 5, 6, 8, 9, 16). The Global Lung Function Initiative 2012 reference equation was used to calculate $ppFEV_1$, ppFVC, FEV_1 *z*-scores, and FVC *z*-scores (11, 13). FEV_1 was standardized by the square of height in meters to calculate $FEV_1 \cdot Ht^{-2}$ (6, 9) and by the cube of height in meters to calculate $FEV_1 \cdot Ht^{-3}$ (5, 8). FEV_1 was standardized by sex-specific lowest percentile (0.5 L for men and 0.4 L for women) of FEV_1 distribution among patients to calculate FEV_1Q, as suggested by Miller and Pederson in a large European population consisting of three cohorts (5).

Follow-up and outcomes. The study outcomes were all-cause mortality, respiratory mortality, cardiovascular mortality, the first unplanned COPD hospitalization, and the first unplanned pneumonia hospitalization. Participants were followed for 5 years, and right-censoring events were emigration ($n = 3$) or end of follow-up. Cause-specific mortality and hospitalizations were identified using International Classification of Diseases codes from medical records and are described in detail elsewhere (15).

Statistical analysis. Cumulative incidence curves for all-cause mortality were constructed through Kaplan-Meier estimates, and log-rank tests were used to test differences.

A regression tree method (17) that accounts for time and multiple outcomes was applied to obtain optimal cutoffs of FEV_1Q (2.8, 4.1, and 5.2), termed FEV_1Q grades.

We applied incident/dynamic time-dependent areas under the receiver operating characteristic curves (AUCs) that account for time to compare the predictive abilities of FEV_1 expressions and their respective methods of classification of COPD severity to predict clinical outcomes (18–21). For cause-specific mortality and hospitalization, AUCs accounting for competing risks were calculated (20). We used crude models to compare AUCs because the clinical decision does not explicitly take into account other factors (5). We used 10,000 bootstrap iterations to calculate the 95% confidence interval for AUCs (22). A general bootstrap algorithm (23) was applied to compare the AUCs.

Statistical analysis was performed using R 3.6.1 software (http://www.r-project.org).

Ethics. Ethical approval was obtained from the Regional Committees for Medical and Health Research Ethics (2015/1461/REK midt). All participants gave informed written consent.

Results

During the follow-up period, 146, 30, and 56 subjects died because of all causes, respiratory diseases, and cardiovascular diseases, respectively, and 172 and 96 were hospitalized because of COPD and pneumonia, respectively. At baseline, the average age of participants was 63.8 years, 6 of 10 participants were men, and more than half (53.3%) of participants were current smokers (15). A trend for increasing cumulative incidence of all-cause mortality with worsening categories of classifications of COPD severity was observed (Figure 1).

When using FEV_1 expressions as continuous measures, the AUCs for all-cause mortality were 64.5 for $ppFEV_1$, 58.8 for FEV_1 *z*-score, 68.9 for $FEV_1 \cdot Ht^{-2}$, 69.3 for $FEV_1 \cdot Ht^{-3}$, and 70.2 for FEV_1Q (*P* value for AUCs between $ppFEV_1$ and FEV_1Q <0.001). Similar patterns of AUCs were observed for cause-specific mortality and hospitalization, except for respiratory mortality ($P = 0.062$) (Figure 2).

The FEV_1Q grades had higher AUCs compared with GOLD grades for predicting all-cause mortality ($P < 0.001$), cardiovascular mortality ($P = 0.005$), COPD hospitalization ($P < 0.001$), and pneumonia hospitalization ($P < 0.001$) but not for respiratory mortality ($P = 0.464$) (Figure 2). Similar patterns of AUCs were observed when using FEV_1 expressions as $ppFEV_1$ quartiles and FEV_1Q quartiles, except for respiratory mortality ($P = 0.848$) and cardiovascular mortality ($P = 0.381$) (Figure 2).

Discussion

In this population-based study, we found that among all FEV_1 expressions, FEV_1Q was the best predictor of clinical outcomes studied, followed by $FEV_1 \cdot Ht^{-2}$ or $FEV_1 \cdot Ht^{-3}$, across 5 years of follow-up. For respiratory mortality, the smaller sample size gives imprecise estimates, resulting in a marginally similar predictive ability for FEV_1Q and $ppFEV_1$.

FEV_1 is a continuous variable, the expression of FEV_1 is used for indicating lung function impairments in respiratory medicine, and $ppFEV_1$ is most commonly used for this purpose (1). The GOLD grades based on $ppFEV_1$ have been widely used for clinical purposes in classifying COPD severity (1). However, they have been criticized because of their susceptibility to physiological variation and poor prediction ability (2–4, 6). The FEV_1 *z*-score avoids this bias due to physiological variation (2, 3). In addition, $ppFEV_1$ and FEV_1 *z*-scores are based on reference values and depend on the choice of reference equation; therefore, performance might vary with reference values (11, 13, 24, 25). Miller and colleagues (5–7) found that FEV_1 expressions such as $FEV_1 \cdot Ht^{-2}$, $FEV_1 \cdot Ht^{-3}$, and FEV_1Q, which are independent of reference equations, were better correlated with mortality than those that are dependent on reference equations. In addition, Miller and Pedersen (5) found that FEV_1Q predicted mortality better than other FEV_1 expressions. Extending this knowledge, our study supports FEV_1Q as a stronger predictor than other FEV_1 expressions in predicting multiple clinical outcomes. This indicates that the severity in people with COPD appears to be better related to how far the FEV_1 of that person is from the "bottom line" rather than how far it is from a "predicted value."

The predictive ability of a classification of COPD severity based on a FEV_1 expression largely depends on the choice of cutoffs. For example, the GOLD grades and $ppFEV_1$ quartiles had different predictive abilities in our study. Huang and colleagues (4) observed similar results. Therefore, the optimal cutoffs of FEV_1 expressions for classification of COPD severity were investigated in this study, and we found that cutoffs for FEV_1Q (2.8, 4.1, and 5.2; FEV_1Q grades) were generally best in predicting clinical outcomes. The optimal

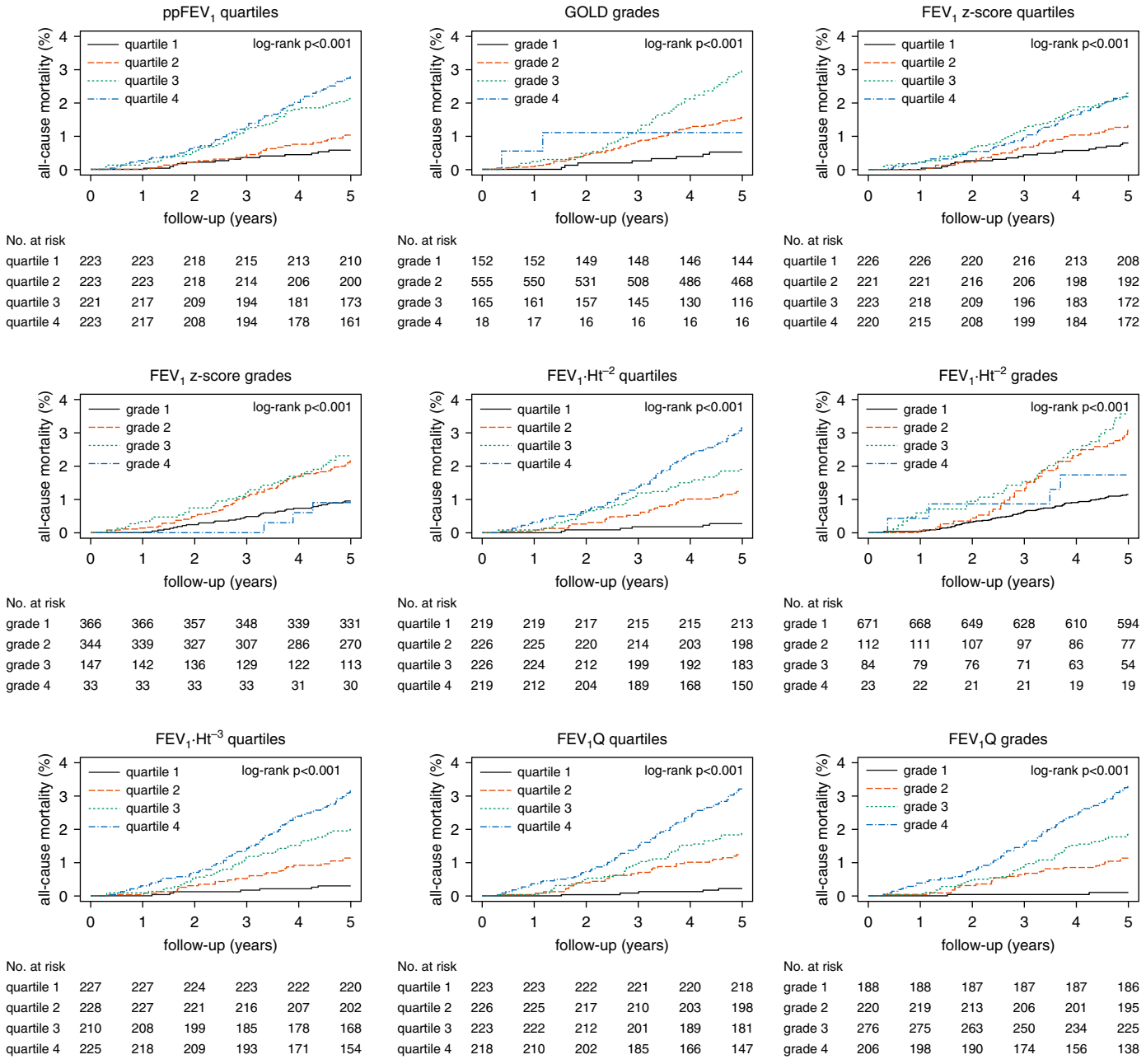

Figure 1. Cumulative incidence curves of classifications of chronic obstructive pulmonary disease (COPD) severity for all-cause mortality among participants with COPD aged ⩾40 years in the HUNT2 Study (Trøndelag Health Study 2) (1995–1997) followed for 5 years. $FEV_1 \cdot Ht^{-2} = FEV_1$ standardized by square of height in meters; $FEV_1 \cdot Ht^{-3} = FEV_1$ standardized by cube of height in meters; $FEV_1Q = FEV_1$ standardized by sex-specific lowest percentile (0.5 L for men and 0.4 L for women) of FEV_1 distribution; FEV_1 *z*-score = FEV_1 *z*-score based on the Global Lung Function Initiative 2012 equation; GOLD = Global Initiative for Chronic Obstructive Lung Disease; $ppFEV_1$ = percentage-predicted FEV_1 based on the Global Lung Function Initiative 2012 equation.

cutoffs should be further investigated in a large multiethnic population with a wide age range. In a clinical setting, information such as age, sex, and height of patients with COPD is easily available. Therefore, using FEV_1Q (or other expressions of FEV_1 that are independent of reference equations) for risk classification of patients with COPD might be easy to apply and avoid variation due to dependence on reference equations (5). Furthermore, multidimensional prognostic indices that combine reference independent FEV_1 expressions with symptoms, exacerbations, risk factors, and/or biomarkers should be investigated further.

This study also had certain limitations. Our methods may not capture nonlinear associations between FEV_1 expressions and mortality (26) or hospitalization, and further studies investigating these approaches are needed.

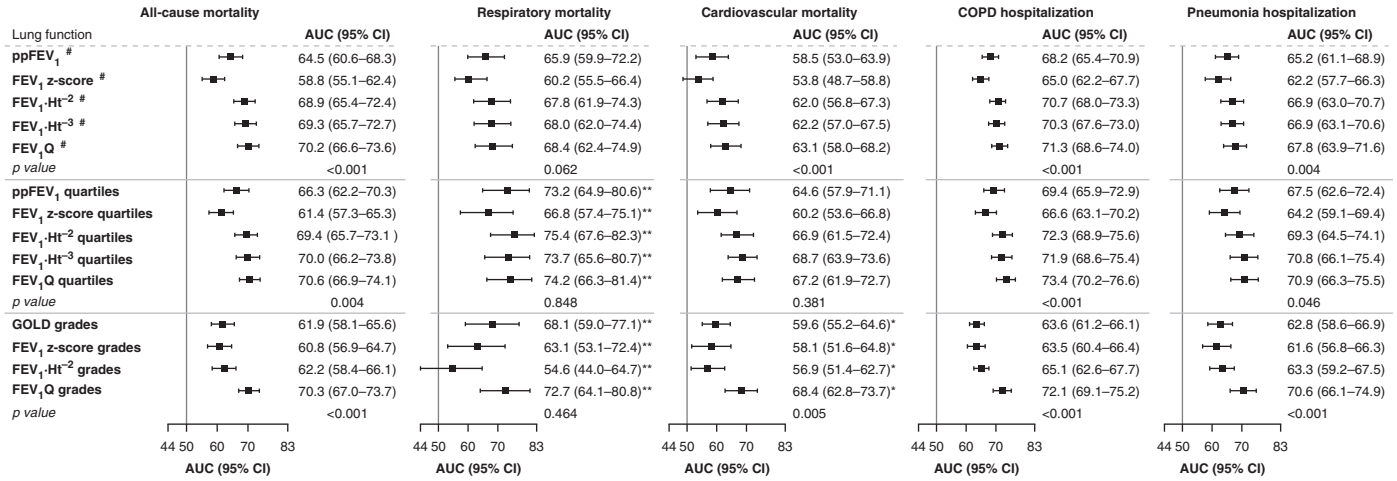

Figure 2. The areas under the receiver operating characteristic curves (AUCs) for different expressions of FEV_1 and their respective methods of classification of chronic obstructive pulmonary disease (COPD) severity for all-cause mortality ($n = 146$), respiratory mortality ($n = 30$), cardiovascular mortality ($n = 56$), COPD hospitalization ($n = 172$), and pneumonia hospitalization ($n = 96$) among participants with COPD aged ⩾40 years in the HUNT2 Study (Trøndelag Health Study 2) (1995–1997) followed for 5 years. #Continuous variables. *Grades/quartiles 3–4 were combined because of zero cases in grade/quartile 4 in Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades, FEV_1 *z*-score grades, and FEV_1 standardized by square of height in meters ($FEV_1 \cdot Ht^{-2}$) grades. **Grades/quartiles 2–4 were analyzed because of zero cases in grade/quartile 1 of GOLD grades, $FEV_1 \cdot Ht^{-2}$ quartiles, $FEV_1 \cdot Ht^{-3}$ quartiles, FEV_1 standardized by sex-specific lowest percentile (0.5 L for men and 0.4 L for women) of FEV_1 distribution (FEV_1Q) quartiles, and FEV_1Q grades. Similar differences in AUCs were observed when grade/quartiles 1–2 were combined for respiratory mortality. *P* value represents the differences between $ppFEV_1$ vs. FEV_1Q, $ppFEV_1$ quartiles versus FEV_1Q quartiles, and GOLD grades versus FEV_1Q grades. CI = confidence interval; $FEV_1 \cdot Ht^{-3} = FEV_1$ standardized by cube of height in meters; FEV_1 *z*-score = FEV_1 *z*-score based on the Global Lung Function Initiative 2012 equation; $ppFEV_1$ = percentage-predicted FEV_1 based on the Global Lung Function Initiative 2012 equation.

In summary, these findings highlight improved prediction of outcomes by the use of FEV_1Q. ■

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Preclinical Development of Virulence-attenuated *Streptococcus pneumoniae* Strains Able to Enhance Protective Immunity against Pneumococcal Infection

To the Editor:

The existing vaccination strategies for prevention of adult *Streptococcus pneumoniae* lung infections are only partially effective (1) and novel preventive approaches are required. Recent data have shown that adults develop immunity to *S. pneumoniae* through repeated episodes of asymptomatic nasopharyngeal colonization (2–6). This naturally acquired immunity includes protective responses to both protein and capsular antigens (2–6) and is boosted by recolonization events (4, 7). These data suggest that deliberate nasopharyngeal administration of live *S. pneumoniae* could prevent serious *S. pneumoniae* infections by strengthening preexisting cross-serotype protective immunity that inhibits nasopharyngeal colonization with virulent strains, increases antigen-specific systemic immunity, and perhaps strengthens alveolar macrophage–mediated innate immunity (2, 3, 6, 7). This strategy would require *S. pneumoniae* strains able to stimulate protective immunity but unable to cause disease in a population with an underlying increased susceptibility to

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