RESEARCH ARTICLE

The Outcome of an Emergency Respiratory Admission Predicted by Forced Expiratory Flow ($FEF_{25–75}$)

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ABSTRACT

Background: Respiratory admissions are over-represented in emergency medical admissions; we tested whether forced expiratory flow at 25 to 75% of vital capacity (FEF_{25-75}) reflecting small airways function, was predictive of 30-day mortality outcomes.

Methods: Between 2002 and 2017, there were 25,274 emergency admission episodes in 8071 patients with a primary respiratory diagnosis. We employed a logistic multiple variable regression model, to determine whether a pre-existing lung function measurement of ($FEF_{25–75}$) was prognostic for 30-day hospital mortality, having adjusted for other outcome predictors including Acute Illness Severity and Case Co-morbidity / Complexity.

Results: Respiratory admissions represented 23.7% of all admissions but 33.3% of readmissions. $FEF_{25–75}$ values linearly and inversely predicted 30-day hospital mortality outcomes - OR 0.88 (95% CI: 0.85, 0.91); consecutive deciles (falling values) of $FEF_{25–75}$ demonstrated progressively rising mortality rates. Respiratory admissions with a lower $FEF_{25–75}$ status were older 70.3 yr. (IQR: 60.9, 77.7) vs. 64.5 yr. (IQR: 50.3, 76.2), had a longer hospital length of stay – 6.2 days (IQR: 3.2, 10.9) vs. 5.8 days (IQR: 2.7, 7.3%) and a higher 30-day hospital episode mortality – 3.2% vs. 2.6%. The range of per patient mortality prediction was from decile 1 (lowest $FEF_{25–75}$ function) 17.0% (95% CI: 14.9%, 19.1%), decile 5 of 11.7% (95% CI: 10.8%, 12.5%), and decile 10 of 7.0% (95% CI: 5.8%, 8.1%). Comorbidity interacted with the lung function estimate – the threshold to influence outcome negatively was reduced in those with lower $FEF_{25–75}$ values.

Conclusion: Baseline $FEF_{25–75}$ linearly and inversely predicted 30-day hospital mortality outcomes. Outcomes in those with lower $FEF_{25–75}$ parameter showed Comorbidity dependence.

Key Words: Lung function, $FEF_{25–75}$, Mortality Outcomes, Comorbidity Score.

1. Introduction:

Acute Medicine focuses on the immediate and early specialist management of adult patients requiring urgent care for acute medical conditions[1]; reforms to care delivery via the establishment of acute medical admissions units (AMAU)[2,3], and other structural change such as consultant inputs[4] have improved outcomes over recent years. Patients presenting with respiratory admissions contribute greatly to the total AMAU workload; they represent 23.7% of all our emergency medical admissions and 33.3% of readmissions. St. James's Hospital may not be entirely representative in this regard as we serve and inner city catchment area with high levels of social deprivation.[5]

Respiratory function data on ventilation and gas exchange are vital in the diagnosis, monitoring and prognostication of obstructive and restrictive lung diseases.[6-9] They also play a central role in therapeutic decision making.[10] Pulmonary function tests (PFT's) have demonstrated mixed results as surrogate markers for risk associated with interventional and surgical procedures. For example, reduction in FEV_1 values strongly predicted an increased length of stay and in-hospital mortality following cardiac surgery.[11] DLCO values, prior to cardiac surgery, also predicted post-operative outcomes.[12] However, in heart failure patients pulmonary function tests including FEV_1 and DLCO did not predict mortality in continuous flow LVAD implantation.[13]

Small airway obstruction is an early feature of many obstructive lung diseases. Flow parameters reflecting disturbance at this anatomic level (less than 2 mm caliber) may hence also be useful. Forced mid expiratory flow between 25% and 75% of forced vital capacity (FEF_{25-75}) is considered more reflective of distal airflow obstruction than FEV1.[14] Compared with FEV1, that is an established standard measure of airflow obstruction, FEF_{25-75} has been under investigated in the epidemiologic and clinical literature. This is thought to be due to difficulties with its reproducibility.[15] Also variability of FEF_{25-75} index limits definition of an optimal threshold to diagnose distal airflow obstruction.[16] Threshold values of less than 65% of predicted have been used to identify distal airflow obstruction in asthmatic children.[17] Nonetheless, studies have suggested significant value of FEF_{25-75} in management of childhood asthma[18], as well as in examining the aetiology of poor lung function in both adults and children.[15] Additionally, there is evidence that FEF_{25-75} may have a clinical relevance especially when FEV1 values are normal[19] and it has been suggested that FEF_{25-75} may precede

FEV1 impairment, so potentially signifying early disease and poor prognosis.[20]

With regards to all cause hospital mortality, we have previously shown a clear correlation between declining FEV1 and DLCO values and increased 30 day mortality following acute hospital admission. Both function parameters independently predicted worse outcomes, after adjustment for acute illness severity and comorbidities and case complexity.[21] In this study therefore we examined data relating to 25,274 emergency respiratory episodes to St James's Hospital, Dublin over a 16-year period (2002-2017) to evaluate how FEF_{25-75} of vital capacity might predict the 30-day mortality outcomes of emergency medical admissions with a primary respiratory disorder.

2. Methods:

2.1 Background: St James's Hospital, Dublin serves as a secondary care center for emergency admissions in a catchment area with a population of 270,000 adults. All emergency medical admissions were admitted from the ED to an Acute Medical Admission Unit, the operation and outcome of which have been described elsewhere.[22,23] As a city center hospital St James's admits persons resident elsewhere but working in the capital in addition to visitors to Dublin who became acutely ill. The number of emergency medical admissions resident in the catchment area was 74.5%; this compares with a figure of 59% for ED presentations where the social influences on emergency department visitations on two London hospitals have been examined.[24]

2.2 Data collection: An anonymous patient database was employed, collating core information of clinical episodes from the Patient Administration System (PAS), the national hospital in-patient enquiry (HIPE) scheme, the patient electronic record, the emergency room and laboratory systems. HIPE is a national database of coded discharge summaries from acute public hospitals in Ireland.[25,26] International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) has been used for both diagnosis and procedure coding from 1990 to 2005 with ICD-10-CM used since then. Data included parameters such as the unique hospital number, admitting consultant, date of birth, gender, area of residence, principal and up to nine additional secondary diagnoses, principal and up to nine additional secondary procedures, and admission and discharge dates. Additional information cross-linked and automatically uploaded to the database includes physiological, haematological and biochemical parameters. We in 2002 designed programs to extract the HIPE data and admission biochemical and haematological variables (linked via the Medical Record Number) to monitor the performance of the Acute Medical Admission Unit.

This study had no interventional component, used anonymised routinely collected data and complied with data protection legislation.

2.3 Acute Illness Severity Score: Derangement of biochemical parameters may be utilized to predict clinical outcome. We derived an Acute Illness Score based on laboratory data – this is an

age adjusted 30-day in-hospital mortality risk estimator, derived from an aggregrate laboratory score of admission parameters.[27-29] This Risk Score is exponentially related to the 30-day episodes mortality outcome with a range of model adjusted mortality outcomes from 2.5% (2.3%– 2.6%) to 32.1% (30.4% - 33.8%).

2.4 Measurement of spirometry values: Spirometry parameters (FVC and FEV1 and $FEF_{25/75}$) were measured using the Vmax® Encore system (Vyaire Medical, 26125 North Riverwoods Blvd, Mettawa, IL 60045, USA). All assessments were carried out by Respiratory Physiology staff to European Respiratory Society (ERS) standards.[30] Predicted values were calculated using European Community of Coal and Steel (ECCS) reference values.[31,32]

2.5 Comorbidity Instrument: Hospital HIPE codes[25,26] were interrogated to construct a measure of multi-morbidity. To devise the score, we searched ICD9 hospital episode discharge codes (back-mapping ICD10 codes to ICD9 as appropriate) based on the definition proposed by the US Department of Health and Human Services for chronic physical or mental health disorders, that limit people 'in activities that they generally would be expected to be able to perform'. These ICD codes were similar to those proposed by the Canadian group for multi-morbidity[33] and the work of Quan[34,35]; they were grouped by system into the following ten groups: (i) cardiovascular, (ii) respiratory, (iii) neurological, (iv) gastrointestinal, (v) diabetes, (vi) renal, (vii) neoplastic disease, (viii) others (including rheumatologic disabilities), (ix) ventilatory assistance required and (x) transfusion requirement. We have previously detailed the ICD9 codes for chronic physical or mental health disorders utilized as a supplementary Table.[36] In addition, we searched other hospital databases for evidence of diabetes (Diamond database), respiratory insufficiency (FEV1 < 2 L data pulmonary function laboratory), troponin status (high sensitivity troponin > 25 ng/L), low albumin (<35 G/dL) and anaemia (haemoglobin levels < 10 G/dL) or chronic renal insufficiency - MDRD < 60 mL/min*1.73 m^2.[37] The 'morbidity score or total burden' for each individual's clinical episode during the study, was weighted by its relative importance against the 30-day mortality outcome in the multiple variable regression analysis.

2.6 Statistical methods: Descriptive statistics were calculated for demographic data, including means/standard deviations (SD), medians/interquartile ranges (IQR), or percentages. We examined 30-day in-hospital mortality as the primary outcome. We performed comparisons between categorical variables and 30-day in hospital mortality using chi-square tests; multiple comparisons were adjusted for multiplicity using Scheffe's comparison statistic. Mortality results have been presented either by episode (all admissions counted) or by patient (only one episode considered – last admission if more than one). In an extended time series (16 years), 48.7% of patients were readmitted at least once, 9.3% > 5 times and 20 patients > 50 times each. Whether per episode or per patient mortality analysis is optimal is uncertain. Mortality estimates by episode (with the

numerator the same in both methods) yield results at least 50% lower than per patient calculations obviously.

Logistic regression analysis was employed to examine significant outcome predictors ($p<0.10$ by Wald test from the univariate analysis) of 30-day in hospital mortality to ensure that the model included all variables with predictive power. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated for those significant model predictors. A stepwise logistic regression analysis examined the association between 30-day mortality and the following predictor variables: Acute Illness Severity[38-40], Charlson Co-Morbidity Index[41], Chronic Disabling Disease[42], Sepsis status[43] and Deprivation index according to the Quintiles of the SAHRU (Irish National) deprivation number.[44]

We used the margins command in Stata to estimate and interpret adjusted predictions for sub-groups, while controlling for other variables such as time, using computations of average marginal effects. Margins are statistics calculated from predictions of a previously fitted model at fixed values of some covariates and averaging or otherwise over the remaining covariates. In the multiple variable logistic model we adjusted univariate estimates of effect using the previously described outcome predictor variables. The model parameters were stored; post-estimation intra-model and cross-model hypotheses could thereby be tested.

Statistical significance at $P<0.05$ was assumed throughout. Stata v.15 (Stata Corporation, College Station, Texas) statistical software was used for analysis.

3. Results:

3.1 Patient Demographics (Table I): During the 16-year study period (2002-2017), there were a total of 106,586 episodes of medical emergencies in 54,928 unique patients admitted through the Emergency Department. Those with a primary respiratory classification were 23.7% but 33.3% of readmissions. The proportion of males was 47.8%. Their median length of stay (LOS) was 6.0 days (IQR: 2.9, 10.7) and median age was 68.0 years (IQR: 55.7, 77.0).

The demographic characteristics (Table 1), below or above the median $FEF_{25–75}$, are tabulated by Acute Illness Severity[27,28], Morbidity Score, Charlson Co-morbidity Index[41] and Sepsis status.[43] Respiratory admissions with a lower $FEF_{25–75}$ status were older - 70.3 years (IQR: 60.9, 77.7) vs. 64.5 years (IQR: 50.3, 76.2), had a longer hospital length of stay – 6.2 days (IQR: 3.2, 10.9) vs. 5.8 days (IQR: 2.7, 7.3%) and a higher 30-day hospital episode mortality – 3.2% vs. 2.6%. Respiratory admissions were clearly at higher risk as evidenced by higher levels of Acute Illness Severity, Morbidity Score, Charlson Index and Sepsis Grade. Those below the $FEF_{25–75}$ median were more likely to have higher Acute Illness Severity (> Gr 4: 78.5% vs. 64.3%), Co-Morbidity Scores (>= 8 points - 35.4% ; >= 12 points - 9.7% vs >= 8 points - 32.1% ; >= 12 points - 8.7%), have a higher frequency greater Charlson Index (Grade 2 - 38.7% vs. 30.8%) but similar Sepsis levels (culture positive 2.8% vs. 2.9%).

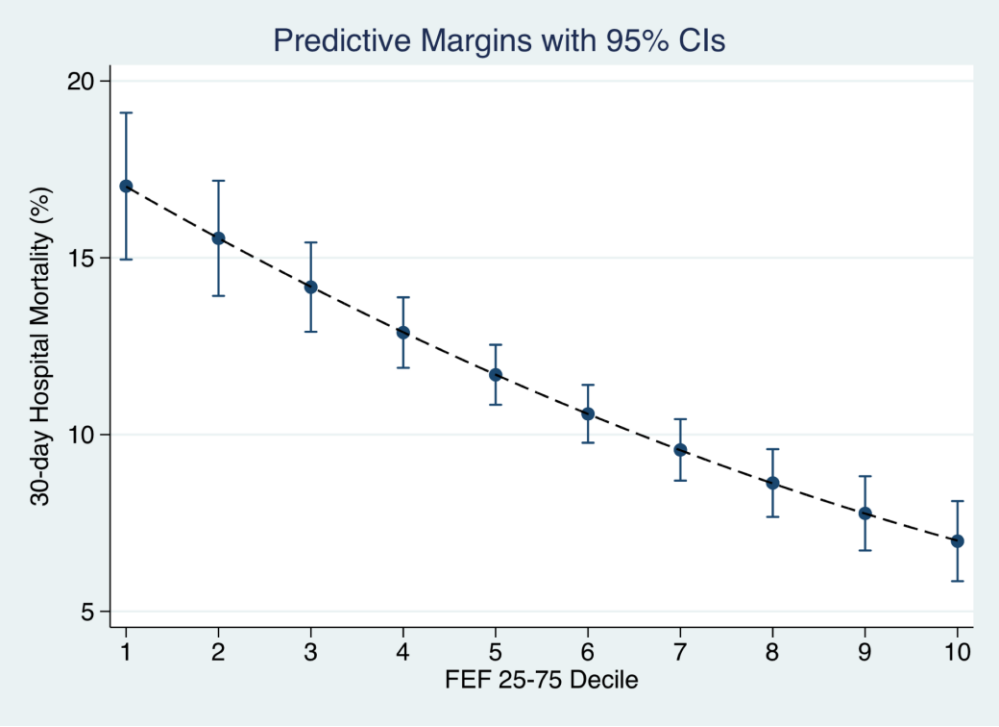
Table I: Characteristics of Respiratory Episodes by median FEF_{25-75} cut-point

	Lower (N = 11618)	Upper (N = 11286)	p-value
Age (yr.)			
Mean (SD)	68.3 (12.90)	62.3 (17.29)	<0.001
Median (Q1, Q3)	70.3 (60.9, 77.7)	64.5 (50.3, 76.2)	
Length Stay (day)			
Mean (SD)	7.98 (6.41)	7.56 (6.52)	<0.001
Median (Q1, Q3)	6.2 (3.2, 10.9)	5.8 (2.7, 10.3)	
Gender			
Male	5509 (47.4%)	5272 (46.7%)	0.285
Female	6109 (52.6%)	6014 (53.3%)	
30-day Hospital Mortality			
Alive	11242 (96.8%)	10997 (97.4%)	0.002
Dead	376 (3.2%)	289 (2.6%)	
Illness Severity Score			
1	24 (0.2%)	137 (1.3%)	<0.001
2	115 (1.1%)	471 (4.5%)	
3	593 (5.5%)	1158 (11.1%)	
4	1593 (14.7%)	1967 (18.8%)	
5	2686 (24.8%)	2376 (22.7%)	
6	5820 (53.7%)	4358 (41.6%)	
Morbidity Score			
< 6	3270 (31.4%)	2891 (32.7%)	<0.001
>=6 < 8	2433 (23.4%)	2336 (26.5%)	
>=8 < 12	3684 (35.4%)	2834 (32.1%)	
>=12 < 20	1013 (9.7%)	767 (8.7%)	
Charlson Index			
0	1948 (16.8%)	4181 (37.1%)	<0.001
1	5164 (44.5%)	3612 (32.1%)	
2	4492 (38.7%)	3474 (30.8%)	
Sepsis Group			
1	8742 (75.2%)	8866 (78.6%)	<0.001
2	2548 (21.9%)	2098 (18.6%)	

3	328 (2.8%)	322 (2.9%)

3.2 Logistic multiple variable model of 30-day hospital mortality outcomes (Fig 1): The 30-day hospital episode mortality outcome was essentially linearly and inversely related to the underlying $FEF_{25–75}$ value (Fig 1); adjusted for other outcome predictors of Acute Illness Severity, Charlson Co-Morbidity Score, and Sepsis Status, falling $FEF_{25–75}$ values predicted adverse outcomes – OR 0.88 (95% CI: 0.85, 0.91). The range of per patient mortality prediction was from decile 1 (lowest $FEF_{25–75}$) 17.0% (95% CI: 14.9%, 19.1%), decile 5 of 11.7% (95% CI: 10.8%, 12.5%), and decile 10 of 7.0% (95% CI: 5.8%, 8.1%).

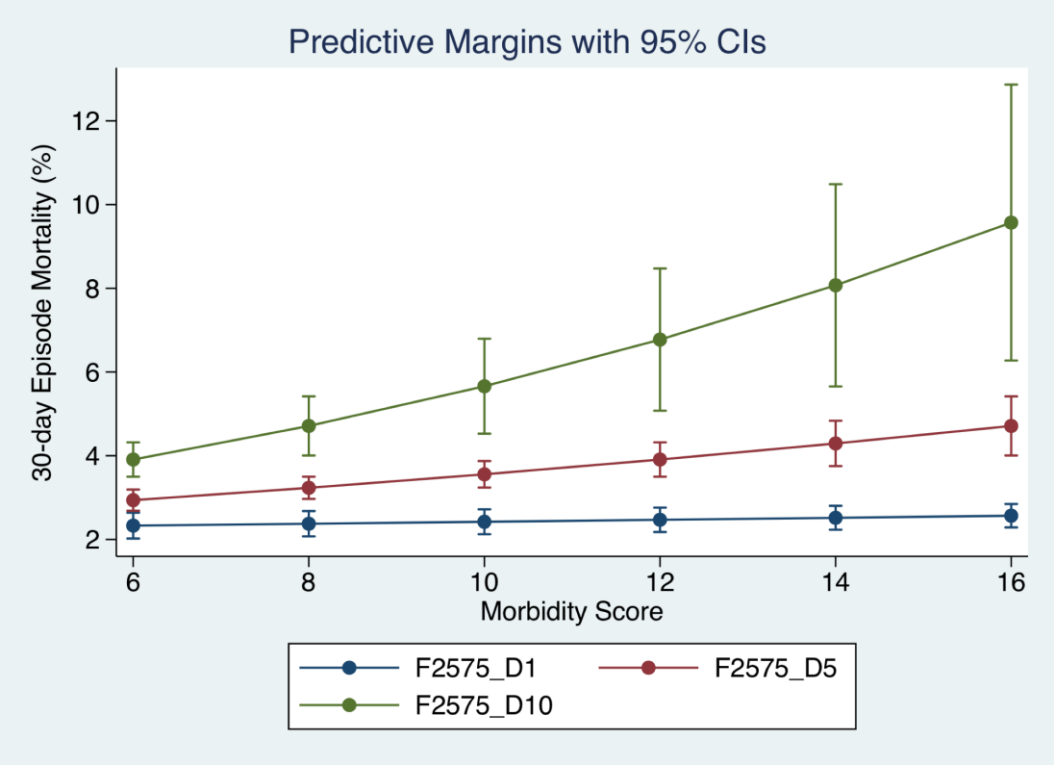
Figure 1: The 30-day per patient mortality risk increased essentially as a linear function with a falling FEF_{25-75} Decile (cut points 10, 14, 18, 24, 31, 39, 49, 61 and 79 percent predicted). The mortality outcome plotted against the baseline FEF_{25-75} level was adjusted in the model for Acute Illness Severity, Charlson Co-Morbidity Score, and Sepsis Status.



3.3 Comorbidity and $FEF_{25–75}$ interactions as determinants of outcome (Fig 2): One might anticipate that, all other things being equal, at any given level of lung function as estimated by FEF_{25-75}, the 30-day hospital mortality might be worse in patients with a high comorbidity burden compared with lesser disease. We therefore

tested this hypothesis, by studying the interaction of our Comorbidity Score with the FEF_{25-75} parameter (Fig 2). Increasing Comorbidity Scores, in those with better function had limited impact; however, with falling FEF_{25-75} levels, the slope of the relationship increased such that respiratory patients with lower FEF_{25-75} had worse outcomes at any Comorbidity Score. At a Comorbidity Score of 10 points, for example, the model predicted 30-day hospital mortality for Deciles 1, 5 and 10 (declining function) of 2.3%, 2.4% and 5.1% rising at a Comorbidity Score of 16 points to 5.1%, 6.4% and 12.3% respectively. Those with worse FEF_{25-75} function showed considerable dependence on the Comorbidity burden.

Figure 2: The 30-day mortality risk for any hospital episode in a respiratory admission showed a linear increase with Comorbidity status. Comorbidity Score interacted with respiratory function, as determined by FEF_{25-75} pre-admission level; respiratory patients with lower FEF_{25-75} had worse outcomes at any Comorbidity Score



4. Discussion: These data demonstrate that the FEF_{25-75} parameter, recorded at a point prior to an acute emergency medical admission linearly and inversely predicted 30-day hospital mortality outcomes; the prediction model demonstrated that falling

values of $FEF_{25–75}$ were associated with a rising probability of an in-hospital death. The mortality outcome showed conditional dependence on the summative Comorbidity Score; the $FEF_{25–75}$ parameter interacted with the latter so that for worse lung function, the threshold at which Comorbidity influenced mortality outcomes was reduced. The slope of the relationship between the Comorbidity Score and mortality outcome was notably steeper with declining lung function.

FEV_1 and DLCO are well established, validated and reproducible parameters for the characterisation and prognostication of pulmonary disease[11,12,21] and are a valuable tool in clinical decision making. $FEF_{25–75}$ more closely reflects small airway flow.[45] Despite the fact that small airway obstruction is an early feature of many obstructive lung diseases, $FEF_{25–75}$ has not been extensively utilized due to its greater variability in comparison with FEV1.[46] Indeed, the view has been expressed that maximum mid-expiratory flow and flow towards the end of the forced expiratory maneuvers do not contribute usefully to clinical decision making over and above information from FEV1, FVC and FEV1/FVC ratio.[47]

There is however ample evidence in the literature supporting the utility of $FEF_{25–75}$ as a sensitive marker of pulmonary disease. For example, a reduced level of FEF_{25-75} has been associated with an increased risk of long-term asthma persistence. In children this association has been shown to be independent of FEV1.[15] Lower values of $FEF_{25–75}$ have been demonstrated in non-smoking first degree relatives of patients with early onset COPD.[48] This suggests that $FEF_{25–75}$ may be an important variable in the early detection of phenotypes with an inherited tendency to develop COPD, and is potentially worthy of inclusion in genetic epidemiological studies.[48] Low $FEF_{25–75}$ has also been shown to be a useful criterion for diagnosing distal airflow obstruction in patients treated for pulmonary tuberculosis who otherwise have a normal FEV1/FVC ratio.[49] Additionally, in patients with bronchiolitis obliterans following lung transplantation, a reduction in FEF_{25-75} values have been shown to precede decreases in FEV1.[50] This may indicate that $FEF_{25–75}$ values in this setting could be a useful prognostic marker.

Interestingly, some studies have also shown that FEF_{25-75} may be more sensitive to the early detection of adverse effects of environmental pollutants on lung function than FEV1. For example, a reduction in long term exposure to particulate matter pollution was associated with a greater attenuation in annual FEF_{25-75} decrease compared with FEV1.[51] Also, reduced $FEF_{25–75}$ values were associated with occupational exposure to aerosols, gases, and dusts independently of large-airways obstruction.[52]

Our results, reflecting a large sample of unselected respiratory admission over a 16 year period, suggest that baseline $FEF_{25–75}$ is a robust predictor of mortality following acute hospital admission. In fact, previous evaluation of the FEV_1 and the DLCO in the same population showed near identical findings.[21] We have not formally compared the FEV_1, the DLCO and the $FEF_{25–75}$ values but superficially these appear very

similar and one cannot be in any doubt that they all predict mortality outcomes. Declining lung function has mortality consequences and provided the Pulmonary Function Tests can be accurately measured, as a generality, they all should have adequate predictive capacity. Our pulmonary function laboratory performs nearly 5000 spirometry measurements per year. It is our experience that with such sustained volumes of work, good $FEF_{25–75}$ reproducibility can be achieved.

In this study we have allowed for other confounding outcome influences. In emergency medical admissions, the Acute Illness Severity[27,53], Comorbidity[41], Chronic Disabling Disease[42], Sepsis status[43] all have a major impact on 30-day hospital mortality outcome. The Acute Illness Severity is an objective and summative measure of six biochemical parameters recorded in the Emergency Department[29] and predicts over a mortality range of 2.5% (2.3%– 2.6%) to 32.1% (30.4% - 33.8%). Its strength in prediction can be gauged from the OR of 3.98 (95% CI: 3.15, 5.12) compared with Comorbidity Index OR 1.58 (95% CI: 1.37, 1.82), Sepsis OR 2.10 (95% CI: 1.81, 2.45) or Disabling Disease 1.33 (95% CI: 1.17, 1.50). Even the SES (Socio-Economic Status) of the patients, determined by the local area of residence is a potential confounder – OR 1.11 (95% CI: 0.99, 1.24). Taking the $FEF_{25–75}$ prediction as a univariate parameter or even with basic demographic patient data available has limitations particularly if the dataset is limited to dozens of even several hundred patients. Our data however was collected over 16 years with over 25,274 emergency medical episodes in 8071 patients constituting a powerful dataset.

Our study also attempts to examine the extent to which there might be interaction between the level of pulmonary function and the burden of disease. We compute the Comorbidity Burden based on a Chronic Disabling Disease classification method as defined by US Department of Health and Human Services for chronic physical or mental health disorders.[36] We demonstrate that the mortality outcome showed conditional dependence on the underlying lung function; declining lung function was associated with a lowering of the threshold at which the Comorbidity burden could be shown to influence the outcome.

The generalizability of our results may be limited by the fact this study was conducted in a single inner city centre with a catchment population characterised by high levels of social deprivation and higher than average levels of air pollution. Also, variations in pulmonary anatomical involvement could have different physiological consequence and that the predictive values of different pulmonary function parameters could differ in specific respiratory subsets. This is worthy of further study.

In conclusion, we have shown that after correcting for other important predictor variables (particularly illness acuity and complexity / comorbidity) that $FEF_{25–75}$ predicts 30-day mortality outcomes. The predictive value is similar to standard measures of airflow obstruction and alveolar efficiency such as FEV1 and DLCO. These findings are novel and

support the view that $FEF_{25–75}$ is an underutilised measure of pulmonary function with a role to play in pulmonary disease prognostication.

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