EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

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Please cite this article as: Stanojevic S, Sykes J, Stephenson AL, *et al*. Development and External Validation of 1- and 2- year Mortality Prediction Models in Cystic Fibrosis. *Eur Respir J* 2019; in press (https://doi.org/10.1183/13993003.00224-2019).

Development and External Validation of 1- and 2- year Mortality Prediction Models in Cystic Fibrosis

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Key Words: cystic fibrosis, survival, lung transplantation, prediction model

Acknowledgements: We are grateful to CF Canada and the UK CF Trust for use of the data in this study, and for the patients and families for allowing their data to be collected and used for research studies

ABSTRACT

Introduction: We aimed to develop a clinical tool for predicting 1- and 2-year risk of death for patients with cystic fibrosis (CF). The model considers patients' overall health status as well as risk of intermittent shock events in calculating the risk of death.

Methods: Canadian CF Registry data from 1982 to 2015 were used to develop a predictive risk model using threshold regression. A 2-year risk of death estimated conditional probability of surviving the second year given survival for the first year. UK CF Registry data from 2008 to 2013 were used to externally validate the model.

Results: The combined effect of CF chronic health status and CF intermittent shock risk provided a simple clinical scoring tool for assessing 1-year and 2-year risk of death for an individual CF patient. At a threshold risk of death of 20% or greater, the one-year model had a sensitivity of 74% and specificity of 96%. The area under the receiver operating curve (AUC) for the 2-year mortality model was significantly greater than the AUC for a model that predicted survival based on FEV_1 below 30% predicted (AUC 0.95 vs. 0.68 respectively, $P<0.001$). The Canadian-derived model validated well with the UK data and correctly identified 79% of deaths and 95% of survivors in a single year in the UK.

Conclusions: The prediction models provide an accurate risk of death over a one and two-year time horizon. The models performed equally well when validated in an independent UK CF population.

INTRODUCTION

Survival in patients with Cystic Fibrosis (CF) has improved steadily over the past three decades, with the median age of survival in many countries now exceeding 45 years.(1, 2) Despite these improvements, CF remains a life-shortening illness with half of all deaths occurring before the age of 35 years.(3) There have been many studies that have developed predictive models for CF mortality (4-10); however, forced expiratory volume in 1 second (FEV_1) below 30% predicted remains the most commonly used indicator of 2-year survival, and CF clinicians generally use the 30% FEV_1 threshold to guide patient referrals for lung transplantation assessment. There are also several methodological limitations to existing prediction models, including age-related bias, the lag time between risk factor measurement and death, and the introduction of confounding by indication when transplant recipients are included in the study population. There is still a great need to develop an accurate prediction model for mortality in order to identify patients who would benefit from expedited referral to a lung transplant program.

We previously published a clinical scoring tool to predict the 1-year risk of death for CF patients living in Canada.(6) This tool predicted the risk of death in Canadian patients with CF by modelling two components of a patient's disease course, namely, a chronic health index that measured baseline disease severity and a shock index that measured the potential for acute deterioration in health, such as deterioration that occurs at the time of a pulmonary exacerbation. The 1-year model had good internal validity and goodness-of-fit but had not been externally validated. Further, given the wait time required to complete a transplant evaluation and receive a lung transplant, a 2-year predictive risk model would also be clinically useful as this would give adequate lead time to successfully initiate a transplant.

Here we aim to 1) develop a clinical predictive scoring tool for 1- and 2-year risk of death using updated Canadian CF Registry data, and 2) externally validate the tool using United Kingdom (UK) CF Registry data.

METHODS

Data Source

Canadian CF Registry (CCFR) data from 1982 to 2015, for patients ages 6 and older were used to develop the one and two-year models **(see Supplement for details).** A detailed description of the clinical variables that were considered in the development of the risk model is included in the online supplement.

Risk Models

The predictive risk models for death as the outcome were developed using threshold regression which assumes that the decline in lung function over time is a stochastic process explained by two components: 1) a declining chronic health status (health index), and 2) intermittent shocks typically due to pulmonary exacerbations (shock index). The health index and shock index represent separate but complementary influences on mortality risk. The interpretation of the model is based on a joint association between the chronic health index and shock index. A single pool of variables is considered that may be important in none, one or both domains. Patient survival times were time until death censored by date of first transplant or date of next annual visit. The model and methodology have been described in detail in prior publications.(6, 11) Clinical data from the preceding year were used to calculate a patient's chronic health and shock indices for the *1-year risk of death*. Backward step-wise elimination was utilized for variable retention until all p-values were less than 0.05.

A *2-year risk of death* prediction was calculated by multiplying (1) the estimated survival probability for the first year and (2) the estimated conditional probability of surviving the second year given survival for the first year. For this second probability, we constructed a separate risk

model for the second year using the same predictors from the 1-year model that are lagged by one annual visit (i.e. predictors that are two years out-of-date). The construction follows the same statistical procedure used for the one-year risk, with the final model including only risk factors that are significant at the $p<0.05$ level.

Over-Sampling

Since each patient contributes multiple years of observation to the model, the outcome of death in any given year is extremely rare (<1%), thus heavily weighting the model's fitted regression function towards the survivors. To address this issue, we applied a Synthetic Minority Oversampling Technique (SMOTE) to re-weight the model coefficients. In our application of the technique, we oversampled under-represented or minority events in the sample, which in our context are death events, and under-sampled survivor records.(12) On average, this resulted in approximately 1300 deaths (6% of the sample) and 21 000 survivor records in each of the sampled populations, compared with 893 deaths (1.6 % of the total population) and 55 942 survivor records if no over-sampling was done. Deaths were over-sampled by creating synthetic records using a 5-nearest neighbor approach. For each death, two synthetic records were created by randomly selecting two neighbors from the nearest 5 neighbors. Survivor records were randomly under-sampled such that 10 survivor records were selected for every death. We subsequently used bootstrap sampling to create 1000 samples where deaths were over-sampled and re-estimated the coefficients for the 1- and 2-year risk models. The final models represent the average coefficients from the 1000 models.

Sensitivity Analyses

In order to evaluate the robustness of our primary results, we carried out several sensitivity analyses which involved re-estimating the predictive model (1) excluding pancreatic status as a covariate; (2) excluding patients on CFTR-modulator treatments; (3) using pulmonary death as the outcome rather than death from any cause; (4) using death or transplant as the outcome; (5) excluding patients born before 1970; and (6) using clinical data from only 1 year prior rather than up to 3 years prior to predict risk.

External Validation of Risk Models

UK CF Registry data from 2007 to 2013 were used to externally validate the models. Exclusion criteria and variable definitions used for the Canadian dataset were matched with the UK dataset whenever possible. The two main exceptions encountered were: (1) Hospitalization data in the UK were not available until 2007. Thus, patients whose only clinic visit year was in 2007 were excluded because they did not have 'look-back' data available. (2) The number of hospital days per year was available in the UK Registry rather than the number of hospitalizations. In order to harmonize the data, hospital days from the UK Registry were scaled by dividing by 14 days, assuming an average patient spends two weeks in hospital for each stay.

The probability of survival at 1- and 2-years was calculated for each patient and each year by directly applying the weighted Canadian model coefficients (i.e., the model derived from the over-sampled data).

Goodness of Fit

Model validation was assessed by looking at both model calibration and discrimination. Discrimination was evaluated using areas under ROC curves (AUC measures). Calibration was assessed by graphical investigation of cumulative Martingale residual plots. Martingale residuals are calculated as differences between actual death outcomes (represented as binary outcomes) and estimated probabilities of death.(6)

RESULTS

1- and 2-year Predictive Models

The Canadian dataset used to build the predictive models contained 56, 839 annual records for 4,993 patients (**Figure 1a**); there were 893 deaths recorded. The demographic and clinical characteristics of the study population are listed in **Table 1**.

The 1-and 2-year risk factors for death are summarized in **Figure 2 and Figure 3** and in **Table S1.** Positive coefficients in the model were associated with a favorable outcome (i.e. lower risk of death), whereas negative coefficients were associated with a greater risk of death. The joint modelling of the chronic health index and shock index allow for some covariates to contribute to both domains. For example, lung function contributes to both overall health status and shock events, such that the combined contribution of low lung function to mortality risk in the shock index is greater in individuals with low overall health status. When deaths were over-sampled, the same risk factors were found to be statistically significant; but the magnitudes of the regression coefficients changed (**Figure 2, Figure 3)**.

The nature of the model is such that a shock event has a lower risk of causing death for a patient with a good chronic health index than a sicker patient as demonstrated in **Figure 4**. For example, a patient with a 1-year chronic health index of 4.2, and a shock index of 0.24, has a 1% 1-year risk of death **(see Supplement for calculations)**. The chronic health and shock indices combine in a similar way to give the probability of two-year survival conditional on surviving the first year. For example, if the 1-year probability of survival is 99.0% (1.0% risk of death), and the calculated conditional probability of survival for the second year is97.4 % (2.6% risk of death),

then the computed conditional 2-year probability of survival is 100(0.990)(0.974)=96.4 % (3.6 % risk of death).

To examine the tradeoff between sensitivity and specificity implied by our prediction model, we selected a single calendar year of Canadian experience (2012) and used a cut-off where the estimated probability of death in the next year was 20% or greater **(Table 2)**. In that year, we identified 110 patients at 'high-risk' of death (i.e. having a *20% or greater* risk of death), of whom 14 died. Conversely, only 5 of the 2434 patients identified as 'low risk' died. Overall, this cut-point had a sensitivity of 74% and specificity of 96%.

We also compared the threshold model results with the traditional model which uses FEV_1 < 30%, which is still commonly used as a general indicator for transplant referral, to identify those with more than a 50% risk for death in the next 2 years. The 2-year threshold model was superior (AUC 0.95) to the traditional model (AUC = 0.68) (**Figure 5**).

The results of the model were consistent across all sensitivity analyses (**Figure S1**), with notably wider confidence intervals when the look-back window for clinical data was limited to 1 year. Several of the coefficients, including FEV_1 and the change in FEV_1 increased in magnitude when death or transplant was used as the outcome, rather than censoring survival at time of transplant.

External Validation using UK data

The threshold model was externally validated using data from 2007-2013 which included 7,450 patients with 27,014 annual records from the UK patient Registry (**Figure 1b**). The UK and

Canadian populations were similar with respect to most clinical and demographic characteristics (**Table 1**). Canada had more patients infected with *B. cepacia* complex while the UK had more cases of CFRD. In 2012, the model identified 409 UK patients as 'high-risk' of death (i.e. those with a 20% or greater risk of death) of whom 73 died **(Table 3)**. Only 336 of the 6029 UK patients identified as 'low-risk' died. The Canadian-derived survival model exhibited similar sensitivity and specificity when applied to UK patients compared to when it was applied to Canadian patients (Canadian sensitivity 74%, UK sensitivity 79 %; Canadian specificity 96%, UK specificity 95 %).

Goodness of Fit

The overall 1-year model discrimination was good; the area under the curve (AUC) was 0.92 using the un-weighted threshold regression coefficients and increased to 0.95 using the over-sampled coefficients for the 1-year model. These values imply that if we select two patients at random, one that survives 1 year and one that dies in the coming year, there is a 95% probability that the model will assign a higher risk of death to the patient that dies compared to the one that survives. The AUC for the 2-year model similarly improved from 0.86 to 0.90 after over-sampling. Martingale residuals were used to plot cumulative actual deaths and cumulative estimated probabilities of death for the unweighted model. The plots indicate good calibration and predictive power of the model (see Figure S2). The same 1- and 2-year over-sampled adjusted models derived from the Canadian data performed well when validated using the UK dataset with AUCs of 0.95 and 0.91, respectively **(Figure S3)**.

DISCUSSION

We have developed an updated clinical tool that predicts 1- and 2-year mortality in Canadian CF patients, and demonstrated that the tool is applicable to the UK CF population. The tool is novel in that it uses two distinct components (chronic health index and shock index) to determine the risk of death using accessible clinical parameters. As a result clinicians will be better able to identify those individuals at high risk for death thus allowing time for consideration of transplant referral or listing, or more aggressive therapy and follow-up.

This analysis is based on comprehensive longitudinal Registry data and the final model validated well with external data on multiple levels. Our validation using UK data confirmed that the Canadian model could be applied to the UK data to identify patients at greater risk of death without the need for adjustments to the model or its coefficients. Another advantage of our model is that we used predictor variables readily available in most CF registries so that the model may be applied to other countries. Nonetheless we have not validated our model outside of Canada and the UK and use of this model in other countries may require adjustments in predictor variables or regression coefficients to account for structural differences in health care systems and CF patient populations.

Like all clinical prediction tools there is a trade-off between correctly predicting death, while minimizing the number of patients who are identified as high risk. We used a conservative cut-off of 20% risk of mortality in Tables 2 and 3 to as identify those patients who were at a relatively high-risk for death in order to ensure that the opportunity for transplant discussions or more aggressive therapy is not missed. Finally, the model can easily be incorporated into a web-

based or electronic health record platform to provide clinicians with a calculated survival probability score to facilitate discussions with patients.

As the rate of death in the CF population is relatively low, we purposefully oversampled deaths, and re-estimated the model coefficients to ensure that the model correctly estimated the probability of death. In both the original and over-sampled analysis the model AUC was higher than reported for similar prediction models, especially the commonly used 30% FEV_1 predicted cut-off.(9, 10, 13) After applying the over-sampling technique the coefficients were all found to be in the same direction and of similar magnitude as the original model results, indicating that the original model is robust. Overall, patients at the extremes of the risk scale remain at the extremes regardless of whether the over-sampling technique is used, whereas there is a down-weighting of the probability of death for patients in the middle of the scale. The distinct advantage of the over-sampling technique is that the coefficients are weighted toward deaths, and therefore more accurately calculate a probability of death.

Our updated risk models include both a 1-year, and a conditional 2-year risk of death. The regression coefficients for variables change in magnitude and even direction between the 1-year and conditional 2-year models highlighting that more distant clinical measures have less of an impact on survival prospects. For example, a drop in FEV_1 during the immediate previous year portends a greater one-year risk of death; however if a patient survives the immediate first year after an FEV_1 decline, their conditional survival during the second year is no longer adversely affected by their remote FEV_1 decline.

In our models, pancreatic status produced the counter-intuitive result that patients who were pancreatic sufficient had a higher risk of death. This effect might be caused by our treatment of pancreatic status as a time-dependent variable in the model, with each annual review being an independent observation. Furthermore, pancreatic insufficiency was derived from reported pancreatic enzyme use which is only a proxy variable and may have been misclassified for some patients in both directions. In the sensitivity analysis which excluded coefficients for other covariates were very similar whether pancreatic status was excluded or not.

The risk factors identified in our analysis are similar to the Nkam et al. model which used a simpler logistic regression model for predicting 3-year risk of death using French registry data.(13) In addition to patient characteristics, the French model included treatments. Treatment data were not available in the Canadian Registry until 2015, and therefore not used in our analysis. The other main difference between our analysis and the French prognostic score was their use of death and/or transplant as the outcome, rather than death alone. The predictors associated with either death or transplant, especially lung function, may differ depending on the outcome may differ depending on the outcome. We chose to only include deaths prior to transplant as the outcome, as the clinical features, and risk factors for death post-transplant are quite distinct. As indicated in the sensitivity analyses this approach may introduce bias due to informative censoring; patients who are referred and ultimately go on to receive a transplant may be different from those that do not.

Our prediction model does have some limitations. Although the majority of predictor variables were obtained in the previous 12 months (for the 1-year model), or in the 12-month interval one

year back (for the conditional 2-year model), the annual measurements recorded in the Canadian registry do not reflect acute deterioration in health status.. In future, it would be useful to utilize encounter-based records and re-calibrate our model. The study population includes observations spanning more than 30 years, during which time the prognosis and treatment of CF have changed considerably. In particular this has implications for the inclusion of *B. cepacia* complex in the model; there are multiple known strains of *B. cepacia* complex and not all are associated with increased mortality. The majority of patients in both Canada and the UK would have been infected with *B. cenocepacia*, which may not represent the strains of *B. cepacia* complex common in patients living with CF today. In cases where the specific strain of *B. cepacia* complex is not known, the model may over-estimate mortality risk. Despite these limitations the model is clinically plausible, robust and closely mimics historical experience with CF mortality.

In conclusion, the mortality prediction models provide accurate risks of death over 1- and 2-year time horizons. The calculated probability of death may provide physicians and patients with important information with which to access key clinical decisions, such as transplant discussion and referral when the risk of death in the next 2-years is considered high. The model can be easily integrated into electronic health records or patient registries to automatically calculate the risk of death, which would facilitate use.

Figure Legend

Figure 1a. Consort Diagram of Canadian CF Population used to Derive Prediction Models (1982-2015)

Figure 1b: Consort Diagram of UK Population used to Validate Prediction Models (2008-2013)

Figure 2: Forest plot of original and Synthetic Minority Oversampling Technique (SMOTE) estimates for the chronic health index and shock index in the Canadian 1-year predictive model.

Abbreviations: Age at Dx, age at diagnosis of CF; *B. cepacia* complex, *Burkholderia cepacia* complex; CFRD, CF-related diabetes; PI, pancreatic insufficiency; FEV_1 % predicted, forced expiratory volume in 1 second percent predicted; FVC, forced vital capacity; yr, year.

Figure 3: Forest plot of original and Synthetic Minority Oversampling Technique (SMOTE) estimates for the chronic health index and shock index in the Canadian 2-year predictive model (conditional on 1^{st} year survival).

Abbreviations: Age at Dx, age at diagnosis of CF; *B. cepacia* complex, *Burkholderia cepacia* complex; CFRD, CF-related diabetes; PI, pancreatic insufficiency; FEV_1 % predicted, forced expiratory volume in 1 second percent predicted; FVC, forced vital capacity; yr, year.

Figure 4. Heat map of 1-year survival probability for the Canadian CF population, showing how the probability varies with the chronic health index and exacerbation shock index. Larger values of both indices generally represent improved survival prospects.

Figure 5: Comparison of the threshold regression 2-year risk model and the traditional $FEV_1 <$ 30% risk model

Table 1 Clinical and Demographic Characteristics of the Canadian and UK CF Populations

	Canada 1982-2015		UK 2008-2013		Canada 2008-2013[a]	
	N/Median	**%/Range**	**N/Median**	**%/Range**	**N/Median**	**%/Range**
Number of Patients	4,993		7,450		3,342	
Number of Annual Records	56,839		27,014		15,226	
Gender						
Female	2,365	47.4	3,472	46.6	1,569	46.9
Male	2,628	52.6	3,978	53.4	1,773	53.1
Age at diagnosis (yrs)						
Median (range)	0.7	0-73.7	0.422	0 – 79.2	0.7	0-73.7
<2 yrs	3,186	63.8	5,222	70.1	2,131	63.8
≥2 yrs	1,807	36.2	2,228	29.9	1,211	36.2
Birth Cohort						
<1970	989	19.8	580	7.8	400	12.0
1970-1979	1,059	21.2	887	11.9	484	14.5
1980-1989	1,260	25.2	1,966	26.4	930	27.8
1990-1999	1,124	22.5	2,535	34.0	1,063	31.8
≥2000	561	11.2	1,482	19.9	465	13.9
Pancreatic Status (ever/never)						
Sufficient	814	16.3	941	12.6	437	13.1
Insufficient	4,179	83.7	6,509	87.4	2,905	86.9
CF-Related Diabetes (ever/never)						
No	3,647	73.0	4,176	56.1	2,464	73.7
Yes	1,346	27.0	3,274	43.9	878	26.3
FEV_1 % Predicted	55.8	8.7-138.3	69.5	9.2 - 138.9	70.0	10.6-136.7
<40%	1,786	35.8%	1,361	18.3%	621	18.6%
40-69%	1,307	26.2%	2,412	32.4%	1,048	31.4%
70-89%	991	19.8%	2,111	28.3%	871	26.1%
≥90%	909	18.2%	1,566	21.0%	802	24.0%
FVC % Predicted	76.4	13.7-147.4	83.8	12.1 - 146.7	86.9	16.7-149.7

Hospitalizations in prior year[b]	0	0-14	0	0 – 19.3	0	0-14
0	2,942	58.9%	4,161	55.9%	2,324	69.5%
1-2	1,338	26.8%	2,282	30.6%	759	22.7%
3+	713	14.3%	1,007	13.5%	259	7.7%
Nutritional Status						
Underweight	1,114	22.3	1,002	13.4	438	13.1
Normal	3,184	63.8	5,134	68.9	2,348	70.3
Overweight	695	13.9	1,314	17.6	556	16.6
Microbiology						
Neither Pa nor BCC	1,901	38.1	3,373	45.3	1,364	40.8
Pa, no BCC	2,168	43.4	3,684	49.4	1,563	46.8
BCC	924	18.5	393	5.3	415	12.4
Transplant						
Yes	589	11.8	220	3.0	197	5.9
Vital Status						
Dead	893	17.9	355	4.8	142	4.2

[a]The threshold regression model was developed using the full Canadian dataset from 1982-2015. The UK validation dataset had data from 2008-2013 so a subset of the Canadian data for the same time period was used for comparison.

[b]UK hospitalizations are derived by dividing total days in hospital by 14 (two weeks).

Abbreviations: Age at Dx, age at diagnosis of CF; BCC, *Burkholderia cepacia* complex; BMI, body mass index; CFRD, CF-related diabetes; FEV_1 % predicted, forced expiratory volume in 1 second percent predicted; FVC, forced vital capacity; Pa, *Pseudomonas aeruginosa*; yrs, years. Observations on clinical variables for the last clinic visit unless otherwise stated.

Table 2. Summary of the sensitivity and specificity for the 1-year risk of death for a randomly selected year (2012) for the Canadian CF population.

	Died in one year	Alive at one year	
Risk of death 20 -99 %	14	96	PPV 13 %
Risk of death 0 – 19.9 %	5	2,429	NPV 100%
	Sensitivity 74 %	Specificity 96 %	

Table 3. Summary of the sensitivity and specificity for the 1-year risk of death for a randomly selected year (2012) for the UK CF population.

	Died in one year	Alive at one year	
Risk of death 20 -99 %	73	336	PPV 18 %
Risk of death 0 – 19.9 %	19	5,693	NPV 100%
	Sensitivity 79 %	Specificity 95 %	

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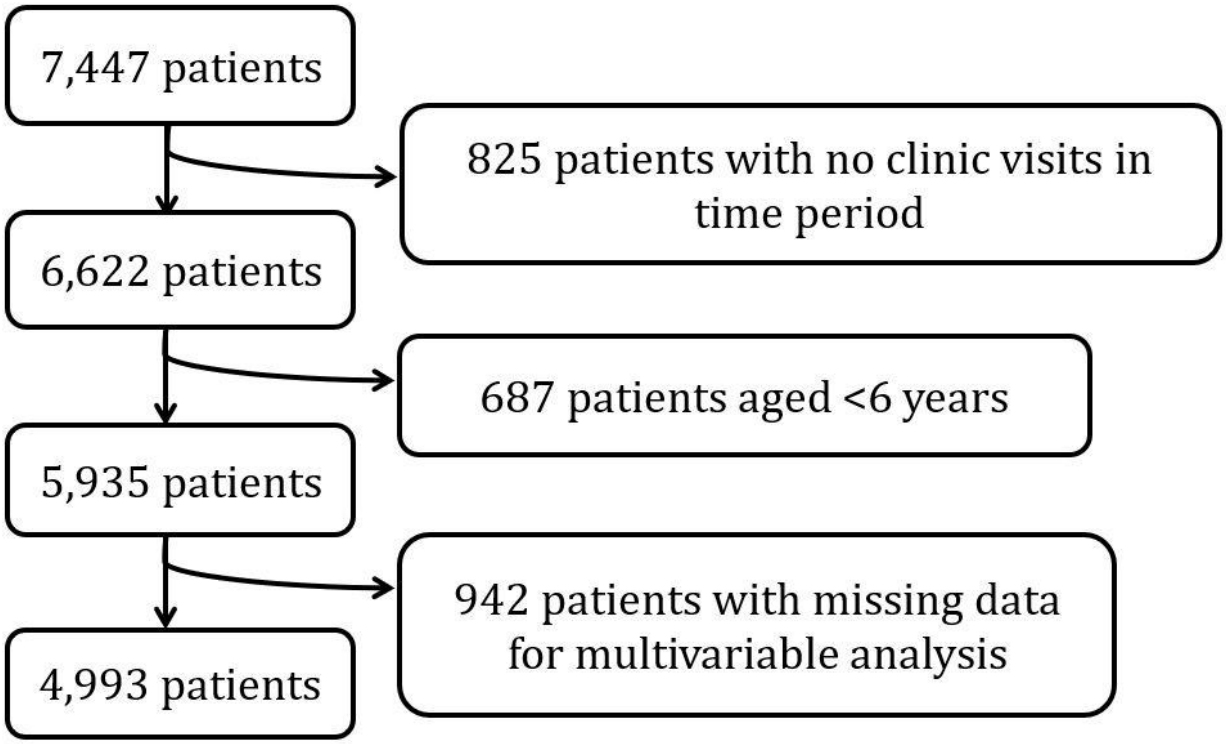
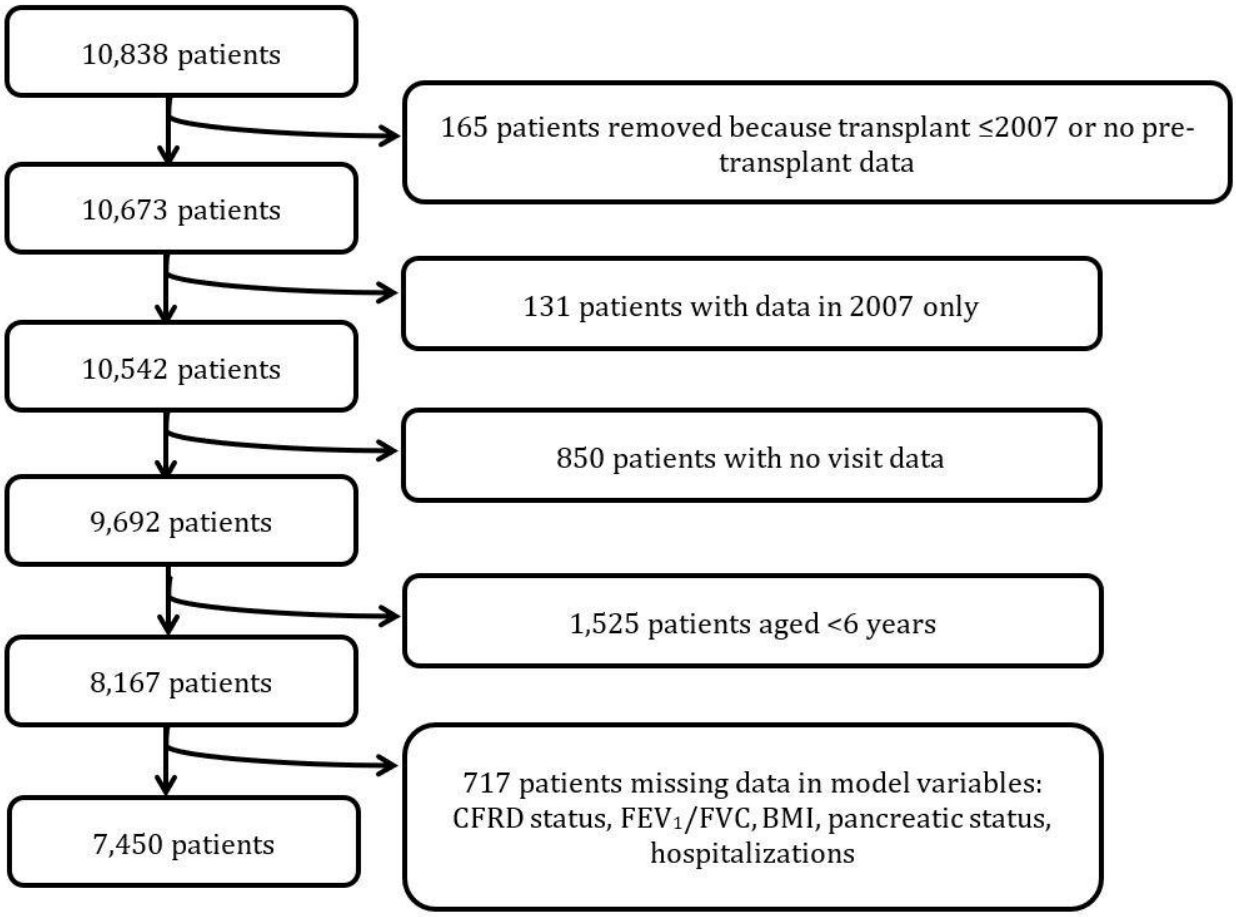
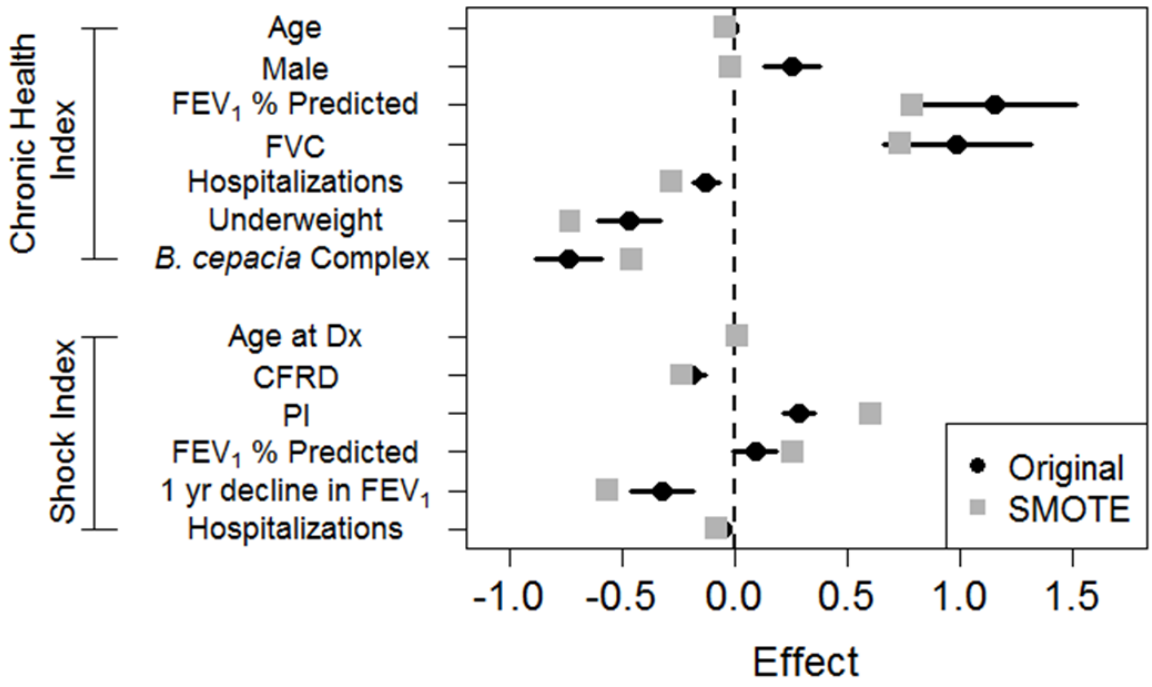


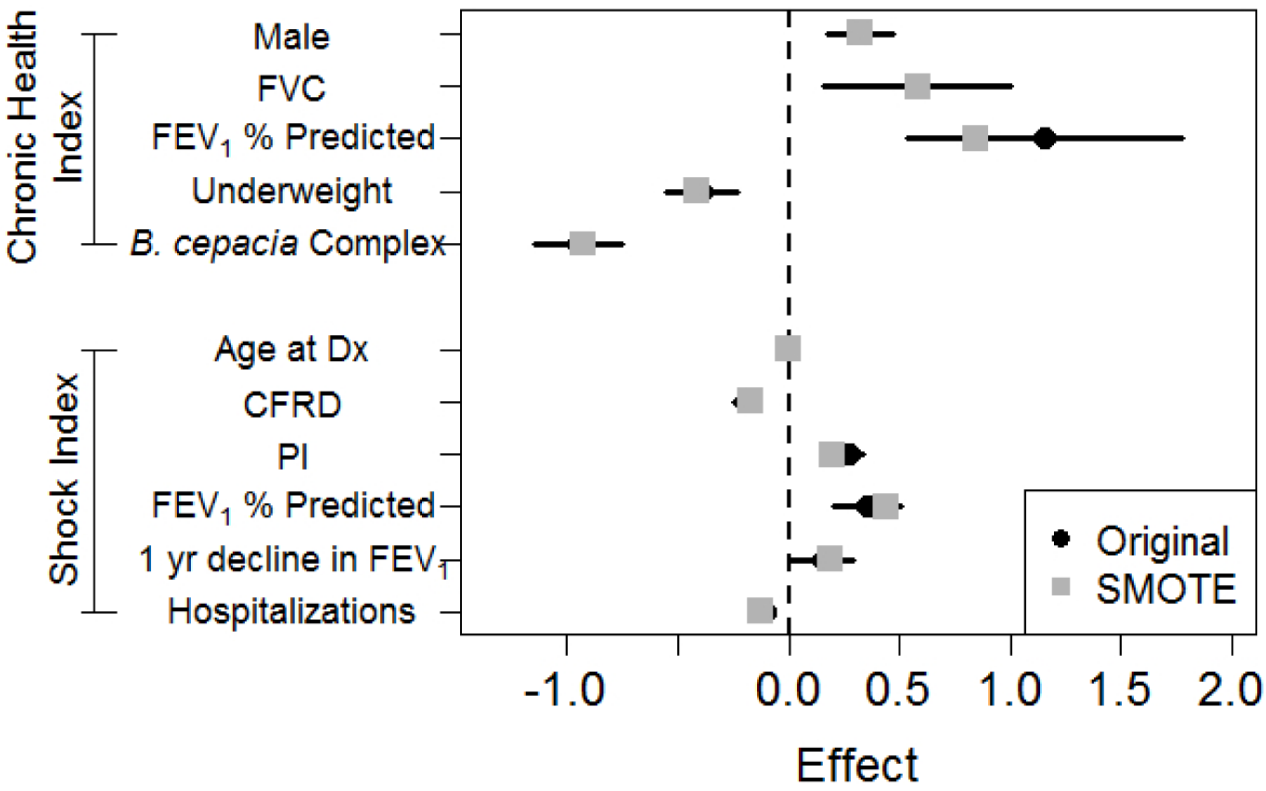
Consort Diagram of Canadian CF Population used to Derive Prediction Models (1982-2015)



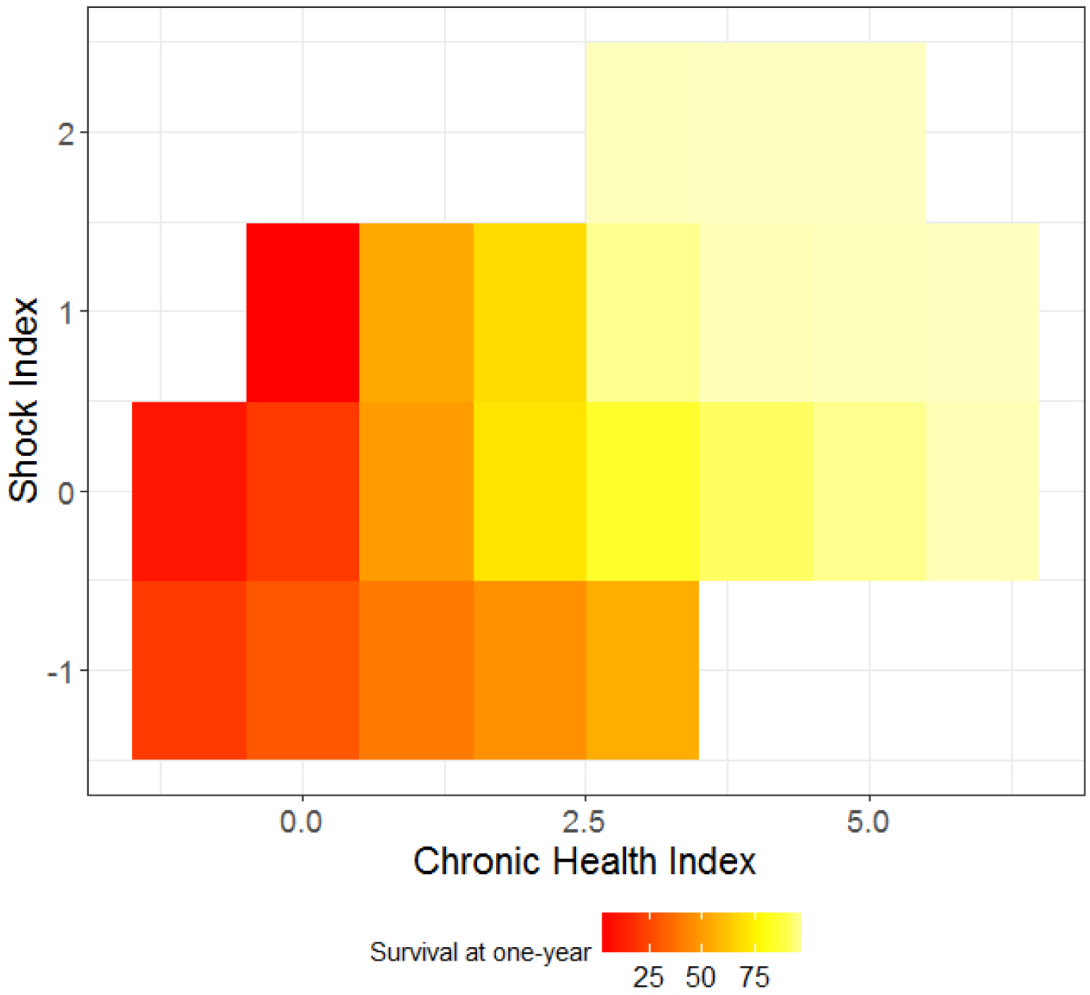
Consort Diagram of UK Population used to Validate Prediction Models (2008-2013)



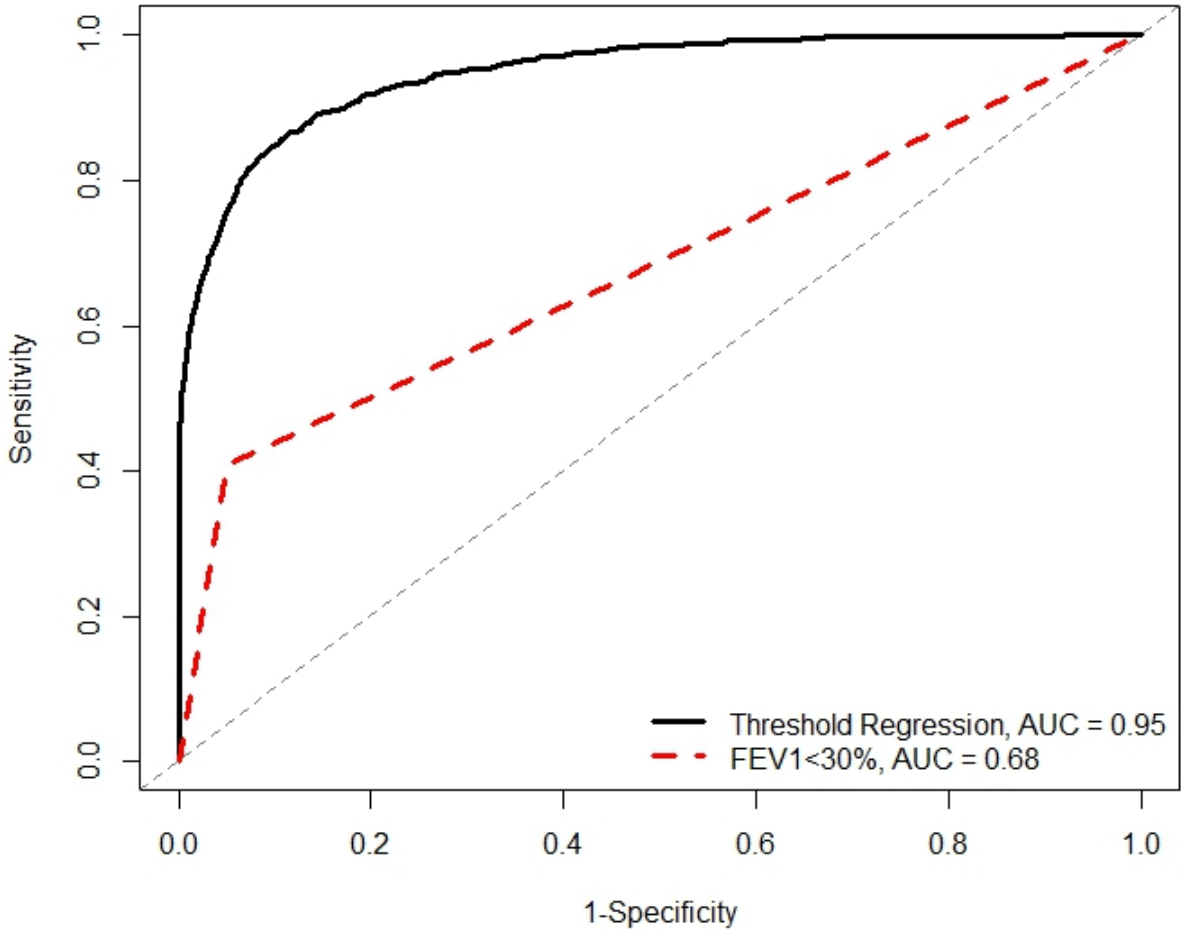
Forest plot of original and SMOTE estimates for the chronic health index and shock index in the Canadian 1-year predictive model. Abbreviations: Age at Dx, age at diagnosis of CF; B. cepacia complex, Burkholderia cepacia complex; CFRD, CF-related diabetes; PI, pancreatic insufficiency; FEV1 % predicted, forced expiratory volume in 1 second percent predicted; FVC, forced vital capacity; yr, year.



Forest plot of original and SMOTE estimates for the chronic health index and shock index in the Canadian 2-year predictive model (conditional on 1st year survival).Abbreviations: Age at Dx, age at diagnosis of CF; B. cepacia complex, Burkholderia cepacia complex; CFRD, CF-related diabetes; PI, pancreatic insufficiency; FEV1 % predicted, forced expiratory volume in 1 second percent predicted; FVC, forced vital capacity; yr, year.



Heat map of 1-year survival probability for the Canadian CF population, showing how the probability varies with the chronic health index and exacerbation shock index. Larger values of both indices generally represent improved survival prospects.



Comparison of the threshold regression 2-year risk model and the traditional FEV1 < 30% risk model

Development and External Validation of 1- and 2- year Mortality Prediction Models in Cystic Fibrosis

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SUPPLEMENT

Study Population

Patient data are entered into the CCFR once a diagnosis of CF has been confirmed based on diagnostic guidelines (1) and after patient consent has been obtained. All 42 Canadian CF clinics submit data annually to the Registry and each CF clinic receives financial support from Cystic Fibrosis Canada dependent on data submission to the Registry. It is estimated that less than 1% of the Canadian CF population has declined consent to have their data captured in the Registry (personal communication with CF Canada). The frequency of CF in Canada as captured by national statistics was virtually the same as found in the Registry suggesting that the Registry captured most CF patients in the country. (12)

Description of Clinical Variables

Date of CF diagnosis, if missing, was imputed by assuming the date of diagnosis occurred 30 days after the date of birth.(2) Pancreatic status was defined by whether the patient had ever used pancreatic enzymes and was used as a proxy for functional impairment of the CFTR protein since many older patients were missing genotype classification. Lung function measurements FEV_1 and forced vital capacity (FVC) were converted to percent predicted values using the Global Lung Function Initiative (GLI) reference equations.(3) Extreme values of FEV_1 or FVC percent predicted that were clinically implausible (<8% or >150% predicted) were set to missing. The change in lung function was calculated as the log-relative decline in lung function since the preceding year if a decline has occurred and 0 otherwise. The log-relative decline is the natural log of the ratio of the current FEV_1 percent predicted to the previous measurement. If the preceding year's lung function was missing, the most recent lung function (up to a maximum of three years earlier) was used. Nutritional status was categorized as underweight (Body Mass

Index (BMI) < 18 kg/m^2), overweight (BMI ≥ 25 kg/m^2) and normal weight (BMI ≥ 18 and BMI < 25 kg/m^2) according to World Health Organization (WHO) cut-offs for adults (4). For children, Centers for Disease Control and Prevention growth charts were used, as follows: underweight (BMI centile <12), overweight (BMI centile ≥85), normal weight (BMI centile ≥12 & BMI centile <85).(5) CF-related diabetes (CFRD) was defined by each clinic based on published consensus guidelines.(6) History of microbiological infections was categorized using a hierarchical approach: patients with a history of (1) *Burkholderia cepacia* complex, (2) *Pseudomonas aeruginosa*, and (3) neither *B. cepacia* complex *nor P. aeruginosa* infection. Once a patient was infected with *B. cepacia* complex the patient was assumed to be positive from that point forward, whereas infection with *P. aeruginosa* was categorized as positive/negative based on the culture results from the report year. Hospitalizations treated with intravenous (IV) antibiotics and home IV antibiotic courses were treated as separate variables. **The vast majority of IV courses were administered in hospital, and it is likely that courses administered at home represent 'milder' events. Due to the retrospective nature of the analysis it was not possible to clearly distinguish these events. There also may be some overlap of these variables.** The number of outpatient clinic visits per patient was recorded annually.

Table S1. Model Coefficients for the 1-year and 2-year models.

Model	Variable	One-year Coefficients	Two-year Coefficients
Chronic Health Index	Intercept	5.702963	4.55962
	Male	-0.0162938	.3189947
	Log_e(FVC % Predicted/100)	0.7360137	.5809873
	Log_e(FEV_1 % Predicted/100)	0.7899955	.8404154
	Underweight	-0.7302478	-.4187824
	B. cepacia complex	-0.4588687	-.9285728
	Age (in years)	-0.0398486	N/A
	# Hospitalizations in preceding	-0.2818584	N/A

	year		
Shock Index	Intercept	0.1146547	.1863934
	# Hospitalizations in preceding year	-0.0792965	-.1263516
	1 year decline in lung function	-0.5616525	.1858131
	$Log_e(FEV_1$ % Predicted/100)	0.2554754	.4353779
	Pancreatic Insufficient	0.6058589	.1927758
	CFRD	0.2340407	-.172767
	Age at CF diagnosis (in years)	0.0079757	.0012487

How to calculate the probability of survival at 1-year and 2-years.

Step 1: Sum the intercept and the products of the coefficients and values of the variables for each patient for the chronic health index. This sum is denoted by lnY.

Step 2: Sum the intercept and the products of the coefficients and values of the variables for each patient for the shock index. This sum is denoted by $ln\beta$.

Step 3: Exponentiate both lnY and $ln\beta$, i.e. Y = exp(lnY) and β=exp($ln\beta$).

Step 4: $lnS = \frac{1}{(-1)*\beta}\left(\frac{1}{Y}\right)^{\beta}[\exp(\beta) - 1]$

Step 5: Calculate S_1 = exp(lnS). This is the probability of survival at one year.

Step 6: To calculate the probability of survival at two years, we repeat Steps 1-5 to calculate S_2 using the two-year coefficients. Then, the overall probability of survival at two years is S_1*S_2.

Example Calculations:

Table S2. Baseline values for two patients – one at low risk of death in one year, and one at high risk of death in one year.

Model	Variable	Low Risk Patient	High Risk Patient
Chronic Health Index	Age (years)	16	40.4
	Gender	Female	Male
	FEV1 % Predicted	47.4%	19.2%
	FVC % Predicted	66.7%	25.7%
	# Hospitalizations in preceding year	0	6
	Underweight	No	Yes
	B. cepacia Complex	No	Yes
Shock Index	Age at CF Diagnosis	0.9 yrs	27.2 yrs
	CFRD	No	No
	Pancreatic Status	Insufficient	Sufficient
	FEV1 % Predicted	47.4%	19.2%
	FEV1 % Predicted in preceding year	80.5%	20.0%
	1-year decline in FEV1	33.1%	0.8%
	# Hospitalizations in preceding year	0	6
Outcome	Status in one year	Alive	Deceased
	Status at two years	Alive	N/A
One-year survival	ln Y	4.18	-1.11
	Y	65.37	0.33
	ln β	0.24	-0.59
	β	1.27	0.55
	ln S	-0.01	-2.45
	S	0.990	0.086

Two-year survival	ln Y	3.70	N/A
	Y	40.45	
	ln β	0.15	
	β	1.16	
	ln S	-0.026	
	S	0.975	
	Overall 2-year survival	0.965	

To determine the probability of survival at one-year for the low-risk patient:

Step 1:

$$lnY = 5.702963 - 0.0162938 * (Male) + 0.7360137 * ln(FVC\ \%\ Predicted/100) + 0.7899955 * ln(FEV1\ \%\ Predicted/100) - 0.7302478 * (B.cepacia\ Complex) - 0.4588687 * (Underweight) - 0.0398486 * (Age\ in\ years) - 0.2818584 * (\#\ Hospitalizations\ in\ preceding\ year)$$

$$lnY = 5.702963 - 0.0162938 * (0) + 0.7360137 * ln(66.7/100) + 0.7899955 * ln(47.4/100) - 0.7302478 * (0) - 0.4588687 * (0) - 0.0398486 * (16) - 0.2818584 * (0)$$

$$lnY = 4.18$$

Step 2:

$$ln\beta = 0.1146547 - 0.0792965 * (\#\ Hospitalizations\ in\ preceding\ year) - 0.5616525[ln(FEV1\ \%\ Predicted\ in\ Preceding\ Year/100) - ln(FEV1\ \%\ Predicted\ in\ current\ year/100)] + 0.2554754 * (ln(FEV1\ \%\ Predicted\ in\ current\ year/100)) + 0.6058589 * (Pancreatic\ Insufficient) + 0.2340407 * (CFRD) + 0.0079757 * (Age\ at\ CF\ diagnosis\ in\ years)$$

$$ln\beta = 0.1146547 - 0.0792965 * (0) - 0.5616525 * [ln(80.5/100) - ln(47.4/100)] + 0.2554754 * (ln(47.4/100)) + 0.6058589 * (1) + 0.2340407 * (0) + 0.0079757 * (0.9)$$

$$ln\beta = 0.24$$

Step 3:

$$Y = exp(lnY) = exp(4.18) = 65.4$$
$$\beta = exp(ln\beta) = exp(0.23) = 1.27$$

Step 4:

$$lnS = \frac{1}{(-1) * \beta}\left(\frac{1}{Y}\right)^{\beta}[exp(\beta) - 1]$$
$$lnS = \frac{1}{(-1.27)}\left(\frac{1}{65.4}\right)^{1.27}[exp(1.27) - 1]$$
$$lnS = -0.00997$$

Step 5:
$$S = exp(lnS)$$
$$S = exp(-0.00997)$$
$$S = 99.0\%$$

Therefore, the probability of survival at one-year is 99.0%.

Step 6:

Repeat Steps 1-5 to calculate S_2:

Step 6_1:

$$lnY = 4.55962 + .3189947 * (Male) + .5809873 * (ln(FVC\ \%\ Predicted/100)) + .8404154 * (ln(FEV1\ \%\ Predicted/100)) - 0.4187824 * (Underweight) - 0.9285728 * (B.\ cepacia\ Complex)$$
$$lnY = 4.55962 + .3189947 * (0) + .5809873 * (ln(66.7/100)) + .8404154 * (ln(47.4/100)) - 0.4187824 * (0) - 0.9285728 * (0)$$
$$lnY = 3.70$$

Step 6_2 :

$$ln\beta = .1863934 - .1263516 * (\#\ Hospitalizations\ in\ preceding\ year) + .1858131 * [ln(FEV1\ \%\ Predicted\ in\ Preceding\ Year/100) - ln(FEV1\ \%\ Predicted\ in\ current\ year/100)] + .4353779 * (ln(FEV1\ \%\ Predicted/100) + .1927758 * (Pancreatic\ Insufficient) - 0.172767 * (CFRD) + .0012487 * (Age\ at\ CF\ Diagnosis)$$
$$ln\beta = .1863934 - .1263516 * (0) + .1858131 * [ln(80.5/100) - ln(47.4/100)] + .4353779 * (ln(47.4/100) + .1927758 * (1) - 0.172767 * (0) + .0012487 * (0.9)$$
$$ln\beta = 0.15$$

Step 6_3:
$$Y = exp(lnY)$$
$$Y = exp(3.70)$$
$$Y = 40.45$$

$$\beta = exp(ln\beta)$$
$$\beta = exp(0.15)$$
$$\beta = 1.16$$

Step 6_4:

$$lnS = \frac{1}{(-1) * \beta}\left(\frac{1}{Y}\right)^{\beta}[exp(\beta) - 1]$$

$$lnS = \frac{1}{(-1.16)}\left(\frac{1}{40.45}\right)^{1.16}[exp(1.16) - 1]$$

$$lnS = -0.0258$$

Step 6_5:

$$S_2 = exp(lnS)$$

$$S_2 = exp(-0.0258)$$

$$S_2 = 97.4\%$$

Step 6:

$S_2 * S_1 = 0.974 * 0.990 = 0.964$

Therefore, the overall probability of survival at 2 years is 96.4%.

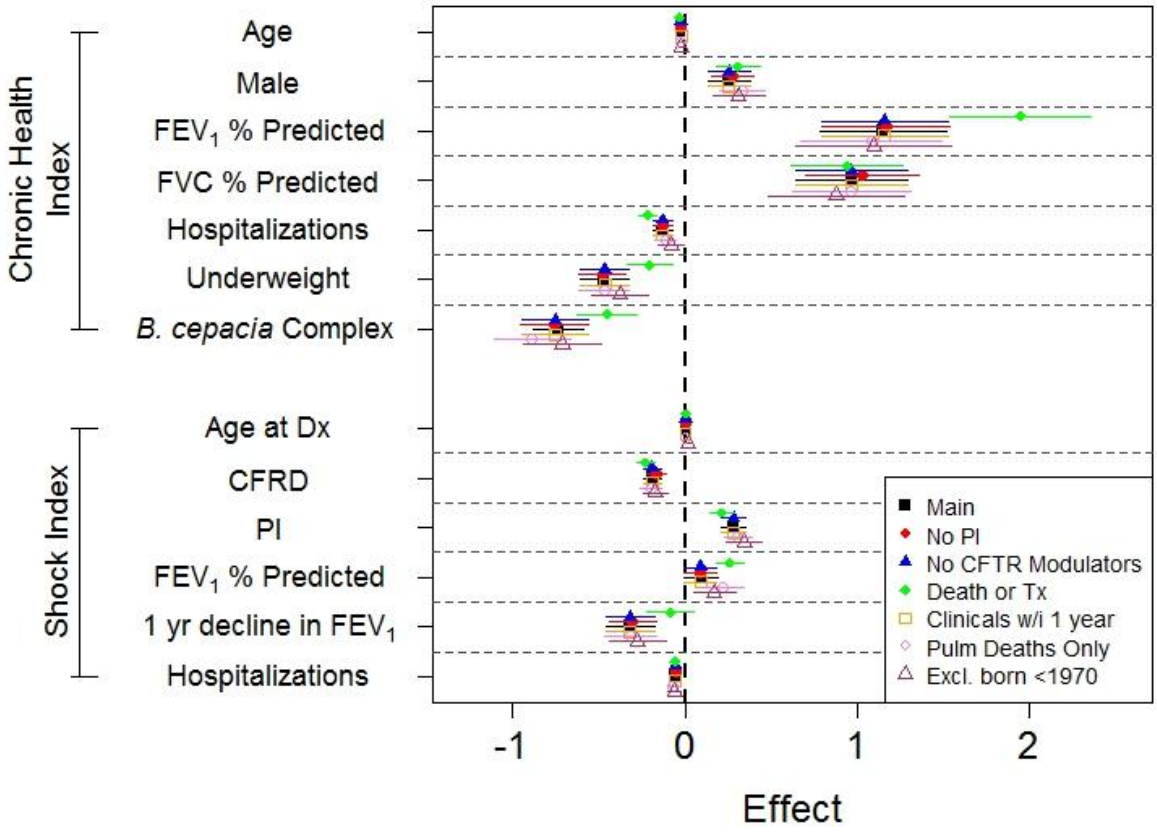
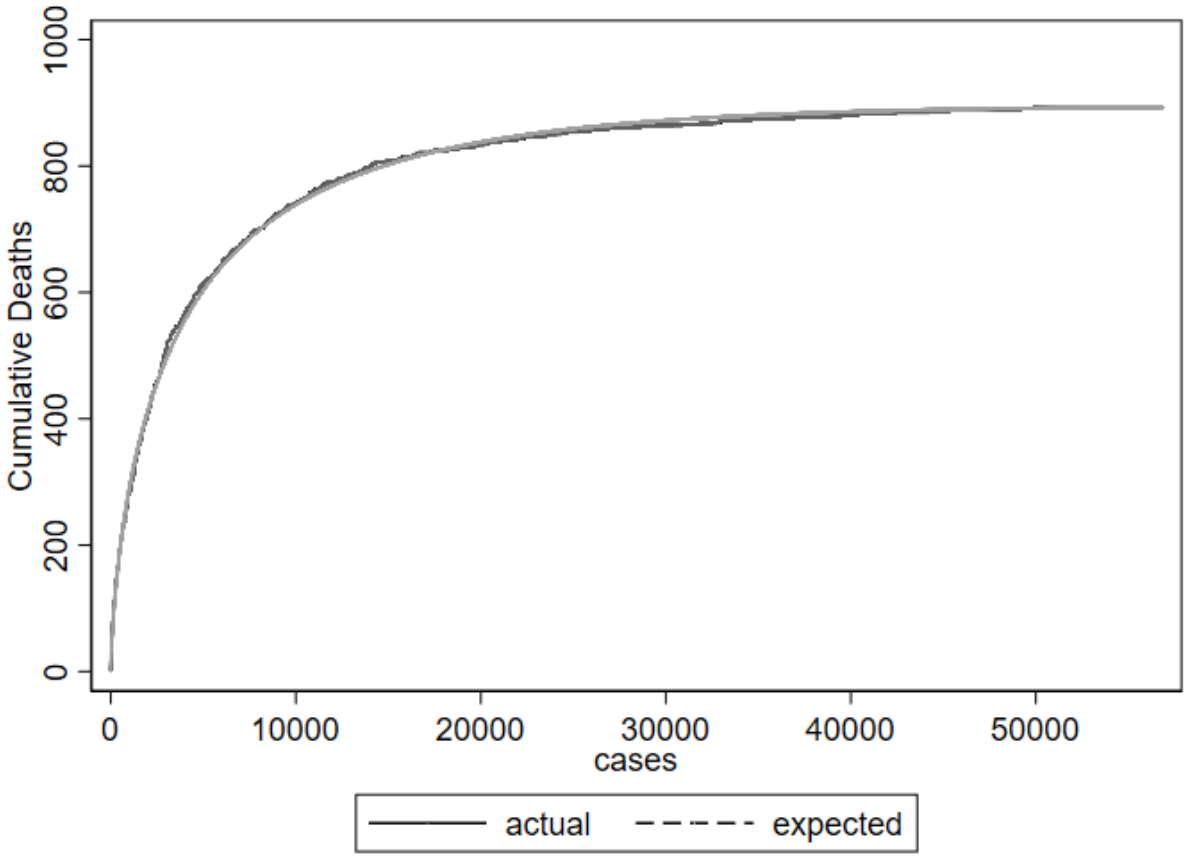


Figure S1: Summary of Sensitivity Analyses

a)


Cumulative Deaths
0
200
400
600
800
1000
0
10000
20000
30000
40000
50000
cases
actual
expected

b)

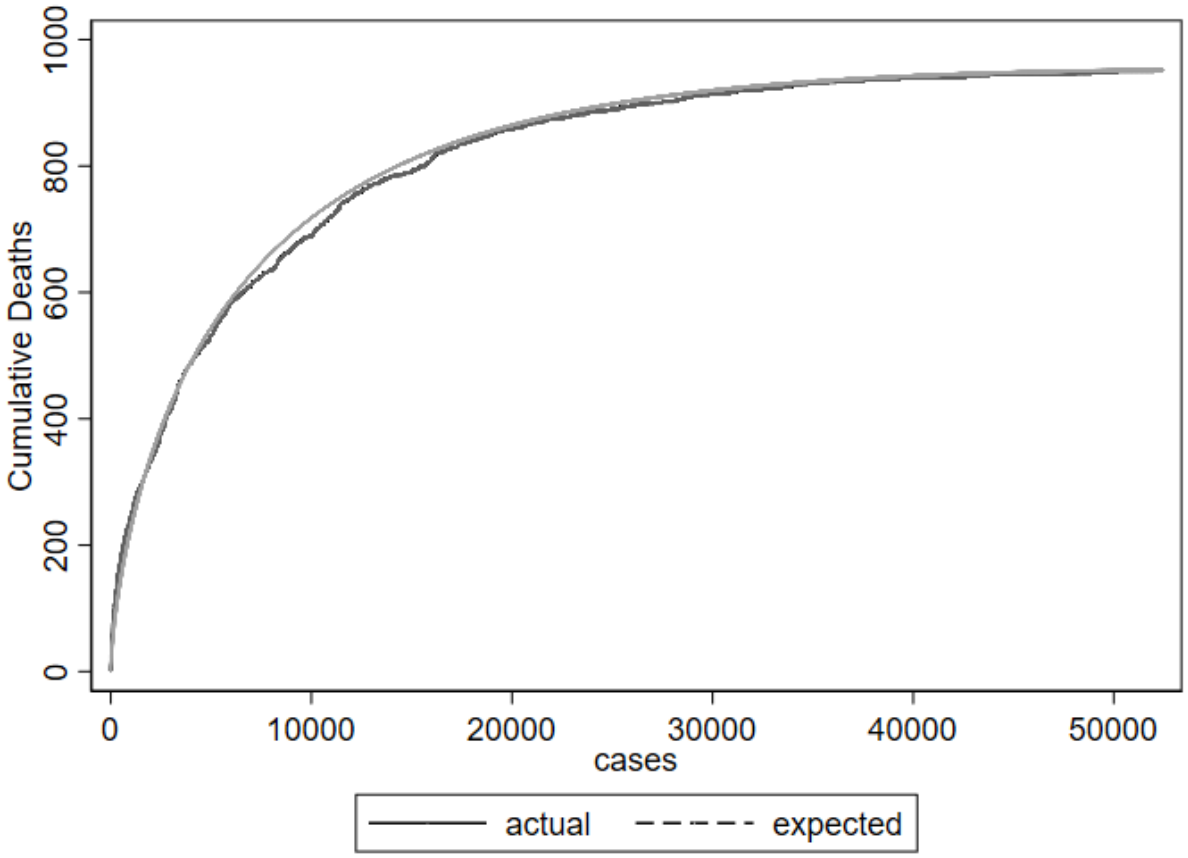
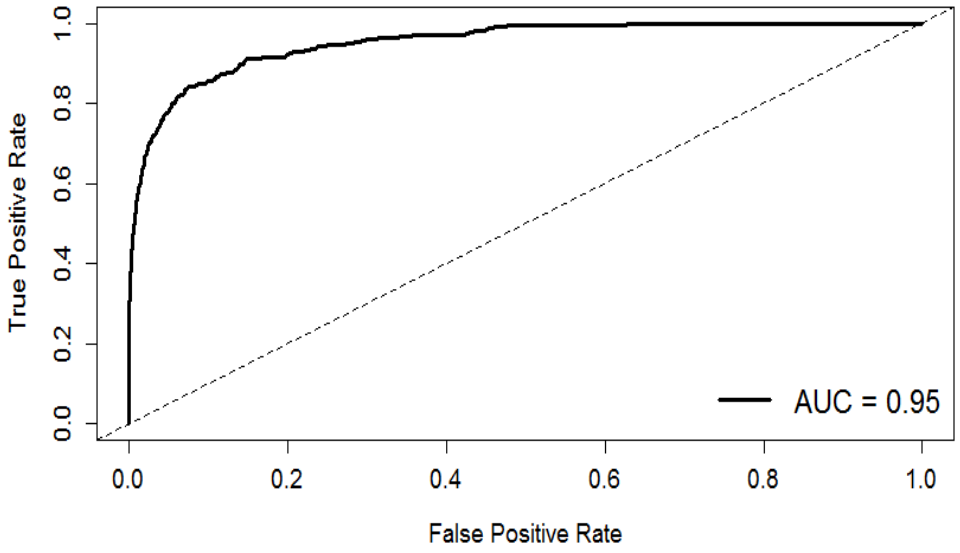


Figure S2: Goodness of fit for the un-weighted a) 1-year model and b) 2-year model for the combined health index and shock index. Both figures indicate good model fit as judged by comparison of the estimated probability of death and the actual deaths that were observed. The tracking of the two lines (actual and expected deaths) indicate good calibration; whereas the shape of the curve, the degree the curves bend towards the upper-left corner, indicates good predictive power.



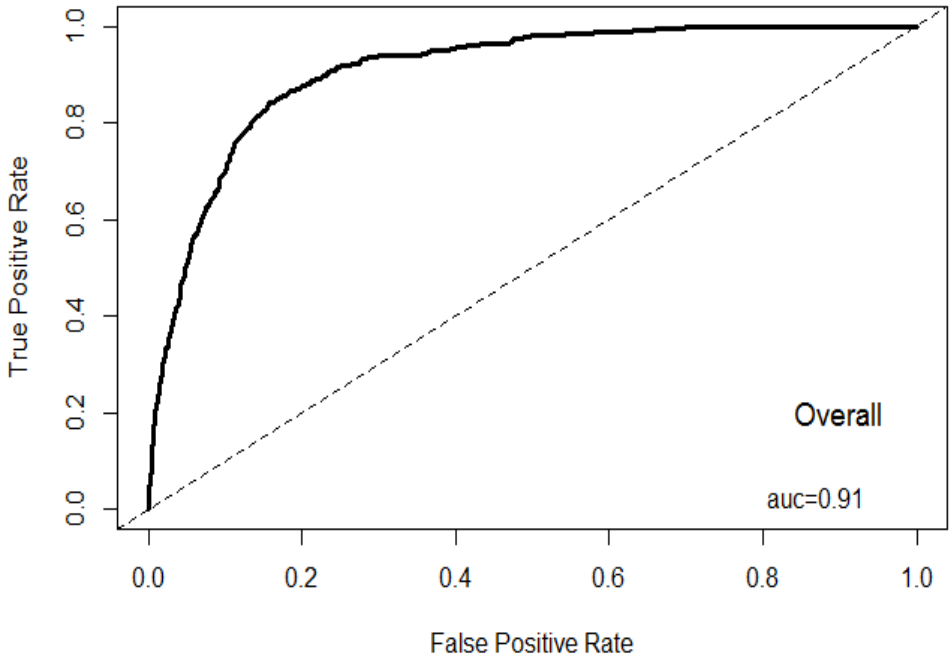


Figure S3: Goodness of fit for UK dataset validation for the a) 1-year model and b) 2-year model.

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