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Validation of the French 3-year prognostic score using the Canadian Cystic Fibrosis registry

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ABSTRACT

Studies of large CF populations using registry data are important to identify people at high risk for death. Nkam et al. published a prognostic score developed on French CF registry data to predict death or lung transplantation (LT) over a 3-year period in the adult CF population. The goal of our study was to validate the proposed tool using the Canadian CF registry. Using data between 2011 and 2014, a total of 2043 adult CF patients were included. We found that the French prognostic score was a good predictor of death or LT in the Canadian CF population (OR for each unit increase: 3.12, 95% CI: 2.74–3.55; p value < 0.001). The proposed prognostic score accurately categorizes patients when applied to an external dataset. This score provides an important tool for early identification of patients at high risk for death or LT, in whom specific therapeutic intervention can be proposed.

1. Introduction

Epidemiological studies using registry data have been instrumental to show improvements in the health status of CF patients over the last 40 years and have been used to develop prognostic survival models, both pre- and post-lung transplant in various countries [1–5]. France recently published a prognostic score for adult CF patients which predicts the 3-year risk of lung transplantation (LT) or death [6]. To do so, they identified 8 risk factors associated with death or LT that would be combined to produce a prognostic score. However, before prognostic models become widely used, it is important to evaluate how such models function outside of the population that was used to construct the score. Our objective was to validate the 3-year prognostic survival score developed in France using the Canadian CF Registry (CCFR).

2. Methods

The CCFR provides a comprehensive, national picture of the CF population longitudinally dating back to the 1970s and captures >95% of the Canadian CF population with a low rate of lost-to-follow-up (~5%) [7]. The CCFR contains annual records from 42 accredited Canadian CF clinics. Demographic, longitudinal clinical, hospitalization and treatment information are recorded in the registry. All patients included in the CCFR have consented to the collection and use of their medical information for research purposes. The research ethics board at St. Michael's Hospital approved the study.

2.1. Patient selection

Patients included in the analysis had the following criteria: aged ≥18 years and alive as of December 31st 2011 with an annual record in 2011 and were not lost to follow-up (LTFU) by the end of 2014. Patients who received a LT prior to 2011 were excluded.

2.2. Model validation

Patient outcome was defined as those patients who received a lung transplant or who died before December 31st, 2014. Variables were

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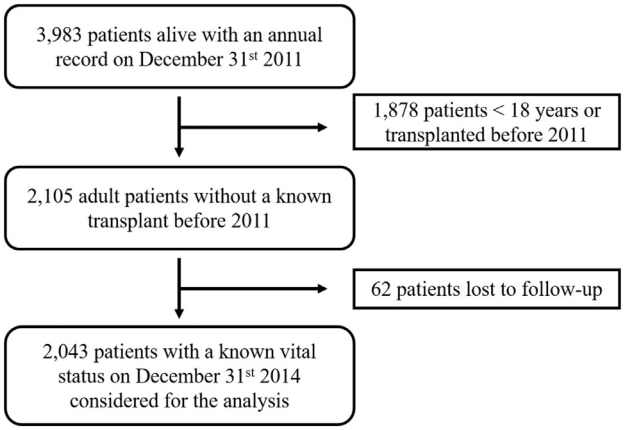

Fig. 1. Patient selection in the Canadian registry.

defined such that they mirrored the French definitions as closely as possible. Forced expiratory volume in 1 s (FEV_1) was expressed as a percentage of the predicted values using the Knudsen reference equations [8]. BMI was calculated as weight (kg)/height $(m)^2$. Patient characteristics between those who died or received a LT in 3 years and those who were alive without a LT at the study end were compared using the Mann-Whitney test for continuous variables and the Fisher's exact test for categorical variables. The calculation of the prognostic score and its categorization were defined as outlined in Nkam et al. [6]. The association between death or LT and the prognostic score was assessed using logistic regression. The c-statistic was used to measure model discrimination and model calibration was assessed by graphical means. All statistical analysis was done using the R software (version 3.4.3) [9].

3. Results

A total of 2043 patients were selected for the validation of the prognostic score. Based on the study criteria, 1940 patients were excluded ($N = 1878$ LT or <18 years of age prior to 2011, $N = 62$ LTFU) (Fig. 1). Patients were then subdivided according to their outcome status in 2014 (Table 1).

Table 2A presents all parameters included in the prognostic score with their respective values, as previously described [6]. We found that the prognostic score accurately predicted death or LT in the Canadian population with each one unit increase in the score corresponding to an increased odd of death or LT at 3 years of 3.12 (95% CI: 2.74–3.55, p value < 0.001). We then categorized the groups based on the previously described classes of prognostic score: low (≤1.5), intermediate (2–3.5) and high (≥4) (Table 2). A higher proportion of death or LT individuals had a score ≥4 (54.5%) compared to the alive without LT group (45.5%) (p value < 0.001). When comparing the risk of death or LT between score categories, we observed that the highest score classification had a higher odds ratio (OR) than the intermediate class, using the low class as the reference group, with ORs of 96.53 (95% CI: 59.70–156.05) and 15.37 (95% CI: 9.94–23.75), respectively.

The prognostic score indicated a good discriminative ability with a c-statistic of 0.904. Additional analysis showed that the discriminant ability of the prognostic score was significantly higher than that for FEV_1 < 30% alone (c-statistic of 0.643). In addition, no significant difference in c-statistic was found using an alternative reference equation to calculate FEV_1% predicted such as the Global Lung Function Initiative (GLI) equation (c-statistic of 0.906). Calibration of the French prognostic score in Canadian CF patients graphically showed no significant difference between the predicted probability and the observed probability (Supplementary Fig. 1).

4. Discussion

The purpose of the present study was to validate a 3-year prognostic score for the risk of death or LT developed using the France CF registry in the adult Canadian CF population. We found that the French prognostic score performed well to predict death or LT in the Canadian CF population. Furthermore, the tool was able to accurately identify low, medium and high-risk patients for death or LT in this external dataset.

When comparing to the study by Nkam et al., we found no major difference in the demographic, clinical and therapeutic characteristics between the French and the Canadian CF population when comparing outcome groups (alive versus death or LT) [6]. One reason that the prognostic score was easily applied in the CCFR could be the striking resemblance in patient characteristics to the French registry. Also, it might be because France and Canada share comparable healthcare systems and similar access to transplantation. It would be important to validate this prognostic score in a CF population that does not utilize the same type of healthcare system or have the same clinical and demographic profiles in order to confirm it functions as well in a different environment.

The strength of this study includes the fact that all variables required for the score were included in the CCFR, which captures data on the majority of the Canadian CF population, providing a comprehensive picture of the CF population in the country. This study is potentially limited by patients that were excluded because they were LTFU or were missing

Table 1
Characteristics of 2043 adult CF patients in 2011 according to vital status on December 31st 2014.

Patient characteristics	Missing data (%)	Total	Alive without LT	Death or LT	*P* values
		$n = 2043$ (%)	$n = 1850$ (%)	$n = 193$ (%)	
Gender, male	0	1113 (54.5)	1017 (55.0)	96 (49.7)	0.172
Age (years)	0	28.2 (22.8–37.1)	28.2 (22.7–36.9)	29.4 (23.8–40.3)	0.04
BMI (kg/m^2)	78 (3.8)	22.3 (20.3–24.7)	22.5 (20.5–24.8)	20.6 (19.0–22.5)	<0.001
delF508 genotype	18 (0.9)				0.062
Homozygote		986 (48.3)	879 (47.9)	107 (56.6)	
Heterozygote		825 (40.4)	762 (41.5)	63 (33.3)	
Other		214 (10.5)	195 (10.6)	19 (10.1)	
Airway colonization					
Burkholderia cepacia	0	324 (15.9)	279 (15.1)	45 (23.3)	0.005
FEV_1, % predicted	106 (5.2)	70.2 (51.5–88.0)	72.4 (55.6–89.8)	37.3 (28.8–56.0)	<0.001
Number IV Ab courses/year	0	0 (0–1.0)	0 (0–1.0)	2.0 (0–4.0)	<0.001
Number days hospitalization/year	0	7.0 (0–20.0)	4.0 (0–14.3)	25.0 (8.0–59.0)	<0.001
Non-invasive ventilation	0	9 (0.4)	3 (0.2)	6 (3.1)	<0.001
Long-term oxygen therapy	0	101 (4.9)	28 (1.5)	73 (37.8)	<0.001
Oral corticosteroids	0	272 (13.3)	173 (9.4)	99 (51.3)	<0.001

FEV_1: forced expiratory volume in 1 s, BMI: body mass index, IV Ab: intravenous antibiotic, LT: lung transplantation. Continuous variables: median (interquartile range). *p value* was assessed using Fisher's exact test for categorical variables. For continuous variables, *p value* was assessed using the Mann-Whitney test.

Table 2
A) Parameters used to calculate the prognostic score with their respective values, and B) Proportion of "Alive without LT" or "Death or LT" CF patients when classified into prognostic score categories.

A)

	Score
FEV_1, % predicted	
≥60	0
[30–60] x2	1.5
<30	3
BMI (kg/m^2)	
≥18.5	0
[16–18.5] x2	0.5
<16	1
Burkholderia cepacia colonization	
Test negative	0
Test positive	1
No test	0
Number of intravenous antibiotics courses/year	
0	0
[1, 2]	0.5
>2	1
Hospitalization (yes vs no)	0.5
Oral corticosteroids (yes vs no)	1
Long-term oxygen therapy (yes vs no)	1
Non-invasive ventilation (yes vs no)	1

B)

Prognostic score categories	Total	Alive without LT	Death or LT	P value
	$n = 2043$ (%)	n = 1850 (%)	n = 193 (%)	
Low (≤1.5)	1303 (63.8)	1287 (98.8)	16 (1.2)	<0.001
Intermediate (2–3.5)	480 (23.5)	403 (84.0)	77 (16.0)	
High (≥4.0)	154 (7.5)	70 (45.5)	84 (54.5)	
Missing	106 (5.2)	90 (84.9)	16 (15.1)	

LT: lung transplantation, FEV_1: forced expiratory volume in 1 s, BMI: body mass index. P value was assessed using chi-square test.

data for 2011. However, these exclusions represent approximately 10% of the study population and therefore bias due to these exclusions will be minimal. It should be noted that some of the variables in the CCFR used to validate the prognostic score could not be defined exactly as the original French study. The French registry captured oral steroid use as >3 months, while the CCFR defines steroid use after 10 consecutive days. Also, the CCFR may be double counting a small number of intravenous (IV) courses for patients who continued IV antibiotics upon hospital discharge. However, despite these differences, it is important to note that the score still validated well in our cohort, establishing the robustness of the original model. Finally, our study did not impute missing data; however, we wanted to test the French prognostic score to mimic the real-life setting where registries would normally have a certain amount of missing information.

The prognostic score developed in France has been shown to efficiently predict the health outcome (alive versus death or LT) in the Canadian CF population. In addition, the prognostic score is also valuable in identifying patients who are at low risk of death or LT, allowing CF clinicians to reassure these patients about their future clinical evolution. Validation of existing prediction models will provide clinicians with robust and valid tools with which to predict survival and council patients about more aggressive therapies before LT.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcf.2018.10.014.

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Declaration of interest

None.

References

[1] Jackson AD, Goss CH. Epidemiology of CF: how registries can be used to advance our understanding of the CF population. J Cystic Fibrosis 2018;17(3):297–305. https://doi.org/10.1016/j.jcf.2017.11.013.
[2] Canada CF. Canadian Cystic Fibrosis Registry. 2015 Annual Report. Toronto, Ontario, Canada; 2015.
[3] Aaron SD, Stephenson AL, Cameron DW, Whitmore GA. A statistical model to predict one-year risk of death in patients with cystic fibrosis. J Clin Epidemiol 2015;68(11):1336–45. https://doi.org/10.1016/j.jclinepi.2014.12.010.
[4] Stephenson AL, Sykes J, Berthiaume Y, Singer LG, Chaparro C, Aaron SD, et al. A clinical tool to calculate post-transplant survival using pre-transplant clinical characteristics in adults with cystic fibrosis. Clin Transplant 2017;31(6). https://doi.org/10.1111/ctr.12950.
[5] Liou TG, Adler FR, Huang D. Use of lung transplantation survival models to refine patient selection in cystic fibrosis. Am J Respir Crit Care Med 2005;171(9):1053–9. https://doi.org/10.1164/rccm.200407-900OC.
[6] Nkam L, Lambert J, Latouche A, Bellis G, Burgel PR, Hocine MN. A 3-year prognostic score for adults with cystic fibrosis. J Cystic Fibrosis 2017;16(6):702–8. https://doi.org/10.1016/j.jcf.2017.03.004.
[7] Sykes J, Stanojevic S, Goss CH, Quon BS, Marshall BC, Petren K, et al. A standardized approach to estimating survival statistics for population-based cystic fibrosis registry cohorts. J Clin Epidemiol 2016;70:206–13. https://doi.org/10.1016/j.jclinepi.2015.08.026.
[8] Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. Am Rev Respir Dis 1983;127(6):725–34. https://doi.org/10.1164/arrd.1983.127.6.725.
[9] Team RC. R: A language and environment for statistical computing. 3.4.3 edn R Foundation for Statistical Computing; 2014.