Chapter 1

Factors Affecting Prognosis and Prediction of Outcome in Cystic Fibrosis Lung Disease

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Abstract

Cystic fibrosis (CF) is a multisystem disorder with a significantly shortened life expectancy with the major cause of mortality related to lung disease. Inflammation is seen in the CF airways from a very early age and contributes significantly to symptoms and disease progression. As the condition worsens over time, lung function declines, usually measured by Forced Expiratory Volume in 1 second (FEV1)% predicted, and extra-pulmonary complications often manifest. While the life expectancy in CF is still short, the median age of death and predicted survival age are continually increasing. Therapeutic interventions for CF have improved significantly in the last 20 years and now there are targeted therapies towards specific elements in CF that may impact upon exacerbation frequency, symptoms, and eventually mortality due to lung disease.

As life expectancy in CF increases, the need for predicting prognosis becomes more and more important. Numerous factors affect prognosis in CF and can be used to ultimately predict outcomes. These factors can be constant or dynamic variables ranging from genetic mutation and gender to clinical measurements including pulmonary function and weight. Further variables that affect prognosis in CF include Diabetes Mellitus, sex, and pancreatic insufficiency. Furthermore, genotype is becoming more and more important as novel targeted therapies are developed that may affect survival and improve prognosis.

While prognosis in CF has traditionally been associated with FEV1% predicted, decrements in lung function that are associated with recurrent pulmonary exacerbations are increasingly important, and these are increasingly common as CF lung disease progresses. What drives these pulmonary exacerbations is bacterial colonisation, particularly *Pseudomonas aeruginosa*, with early eradication shown to improve prognosis. Nutrition and weight are also very important in CF and low body mass index has been shown to predict poor outcomes. There are several clinical prediction tools in CF, both radiological and clinical and many are too complex to be used routinely in patient care. However, newer tools aimed at predicting outcomes based on readily available objective measure are now available, including the CF-ABLE score.

In this chapter we outline, firstly, how prognosis in CF has changed over the last decade as a result of changes in treatment, better diagnostics, and improved care. Secondly, we describe the effects that genotype, pancreatic status, gender, and diabetic status have upon outcome. Thirdly, this chapter highlights the usefulness and importance of clinical measurements, including lung function, radiology, bacteriology, and blood and sputum biomarkers of disease and inflammation in predicting outcomes and how changes in these parameters influence prognosis. Finally, we summarise the prediction tools that have been utilised in CF to predict survival and how these may be utilised in clinical practice.

In conclusion, the most sensitive way of predicating prognosis currently remains a multifaceted approach, including several markers of disease and the use of all factors and a composite clinical prediction tool is suggested to stratify patient risk.

Keywords: Prognosis, prediction, survival, outcome, cystic fibrosis

1. Introduction

Cystic fibrosis (CF) is a multisystem inflammatory condition that is associated with a significantly shortened life span, primarily as a result of the pulmonary manifestations of the disease [1]. For many years pulmonary function measurements have been utilised as the primary surrogate of disease severity, with forced expiratory volume in 1 second (FEV1) used to assess clinical status of both patients and to predict mortality [2, 3]. However, in the last two decades there has been a significant improvement in survival in CF and this subsequently has consequences on how to treat patients and predict prognosis in this complex condition. With longer life expectancy it is essential to better predict outcome and prognosticate in CF, thus the use of survival or death as an outcome measure has become almost negligible in clinical trials or indeed in studies to predict prognosis. Hence, the development of surrogate markers or disease severity is increasingly important in CF; these range from physiological measurements of lung function, biomarkers, radiological measures, and composite scoring systems and are becoming essential in CF care and development of new drugs. With groundbreaking therapeutic breakthroughs in CF over the last decade, particularly in the modulation of CFTR function [4], the use of surrogate outcomes has become more apparent. This has led to development of new imaging modalities such as flurodeoxyglucose positron emission tomography (FDG-PET) imaging [5-7] and hyperpolarised helium magnetic resonance imaging (He3-MRI) [8], as well as increased use of multiple breath washout (MBW) and lung clearance index (LCI) to assess disease severity [9]. Moreover, there has been huge progress in the research into and development of biomarkers of inflammation in CF [10–12], both systemic and pulmonary inflammation that correlates with clinical condition and can predict outcome, further highlighting the deeper understating of the pathophysiological changes in CF and the translational research ongoing in this area. Furthermore, the use of new composite scoring systems, taking into account many aspects of this multisystem condition have been developed to aid with the classification of disease severity and predict outcome over a defined period [13].

In this chapter we will outline, firstly, how prognosis in CF has changed over the last decade as a result of changes in treatment, better diagnostics, and improved care. Secondly, the chapter will describe the effects genotype, such as pancreatic status, gender, and diabetic status, have upon outcome. Thirdly, this chapter will highlight the usefulness and importance of clinical measurements, including lung function, radiology, bacteriology, and blood and sputum biomarkers of disease and inflammation in predicting outcomes and how changes in these parameters influence prognosis. Finally, the chapter will summarise the prediction tools that have been created in CF, both clinical and research tools, which utilise measurements of disease and radiological evidence of bronchiectasis to predict survival and how these may be utilised in clinical practice.

2. Prognosis in cystic fibrosis

Life expectancy in patients with cystic fibrosis is in a constant state of change. Whilst there are undoubtedly significant further gains to be made, the improvement in predicted survival in cystic fibrosis sufferers has been a relative success story since its original description as a clinical entity in 1938. Median life expectancy, the time period in which half of a given population will die, has increased from a few months in the 1940s to as high as 41 years old in the current era [14] at present in many countries. The predicted median survival of people born with CF today continues to rise.

Numerous factors have contributed to the changing statistics in CF prognosis. Earlier and more sensitive detection methods, centralised specialist multidisciplinary care and evidence-based research have provided patients, their families, and clinicians with an environment that facilitates the long-term management of this complex multisystem disorder. Identification of increasing numbers of CF genotypes (many of which are characterised by phenotypically milder variants) has also contributed to increasing the CF population and this consequently affects the overall statistics on outcome and prognosis.

What is relevant to a patient diagnosed in infancy with a severe form of CF may not be relevant to a patient diagnosed in middle adulthood. Equally, statistics on survival from one country may not relate accurately to another, not because of difference in treatment alone, but because of differences in the predominating demographics in the two cohorts and methodologies used in assessing outcomes. As such, a "one size fits all" approach to prognosticating is not appropriate. In this chapter, we review the evidence regarding prognosis based on key clinical and demographic parameters, and the biomarkers and prediction tools that may be used to predict outcome.

3. Influence of genotype on prognosis in cystic fibrosis

CF is the most common lethal genetic disease of Caucasian populations and is caused by genetic mutations of the cystic fibrosis transmembrane regulator (CFTR) gene. The CFTR gene encodes an ATP- and CAMP-dependent chloride channel expressed on the apical membrane of epithelial and certain non-epithelial cells throughout the body. To date, greater than 1,000 CFTR mutations have been discovered. In the lung, it also regulates the activity of the ENaC channel (an apical sodium transport channel) defects in which mediate the majority of pathogenic processes in the main target organ in CF sufferers.

Commonly, the multitude of various CFTR mutations are classified into 6 distinct groups based on their ultimate effects on a range of cellular mechanisms such as transcription, processing within the cell, localization of the channel, and quantity of correctly functioning protein. Class I includes mutations with complete lack of production of protein while Class VI involves unstable functional protein being produced that is then degraded at the cell surface (Table 1).

Class	Effect	Mutation Type	Example
I	No functional protein produced	Premature stop codons: nonsense; splicing; deletions	W128X; R553X; G542X
II	Defective processing and maturation	Missense; small deletions or insertions	F508del; N1303K
III	Defects in regulation of channel opening	Missense; small deletions or insertions	G551D; G551S; G1349D
IV	Defective Chloride transport	Missense; small deletions or insertions	R117H; R334W, R347P
V	Reduction of wild-type mRNA	Partial splicing	A455E
VI	Increased turnover of unstable protein at cell surface	Missense; nonsense	120del23; N287Y; 4279insA

Table 1. List of CFTR Mutations.

The most common CFTR mutation worldwide is delF508 that accounts for upwards of 70% of cases of CF and has long been associated with more severe disease and less favourable clinical outcomes [15-17]. Conversely, several mutations have been found to be associated with more favourable outcomes and milder clinical phenotypes. In a study based on the US CF Registry in 2003, it was found that significantly different mortality rates were observed when CFTR

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genotype was classified according to the effects on quantitative protein production. The authors proposed that groups with severely reduced levels of CFTR (I-III) had a more severe clinical phenotype and higher mortality than groups with some residual CFTR function (IV-VI) [18]. A follow up study found that 'high risk' patients (I-III) had a two-fold greater risk of death when compared to 'low risk' (IV-VI) patients [19] and this risk was not fully explained by lung function, pancreatic insufficiency, *Pseudomonas aeruginosa* (PA) colonisation, or nutritional factors. Hence, CFTR genotype may be useful as an initial measure of prognosis in early CF diagnosis when it is often the only available information about the disease. Knowledge of the genetic processes involved in CF is leading the way for new targeted therapies that ideally will improve mortality. One such therapy is ivacaftor, a potentiator drug that enhances gating at the cell surface in patients with the class III G551D mutation. This novel medication has been associated with sustained increases in FEV1 of up to 10%, reduced frequency of pulmonary exacerbation, weight gain, and subjective improvements in quality of life (CFQ-R) scores [4, 20, 21]. However, there is wide phenotypic variance observed frequently among patients with identical genotypes. This is observed in the clinical realms of lung function, pancreatic and diabetic status, nutritional status, and response to medications and this leads to reluctance to link genotype too closely with phenotype in terms of predicting clinical outcomes and prognosis.

4. Impact of gender on prognosis

It has long been recognized that there is a significant gender difference in terms of both morbidity and mortality in cystic fibrosis. Many studies, throughout early and current cystic fibrosis research, have focused on the poorer outcomes observed in female patients when compared with their male counterparts. This dichotomy endures across the areas of microbial colonization, lung function, frequency of exacerbations, and overall survival. However, an explanation for this vast difference remains to be found.

A notable early study conducted in Canada investigated the effects of numerous variables on mortality and found that on average, males had overall increased survival rates of greater than 5 years when compared with female cohorts from the same time period (1970-1989) [22]. These results were echoed across international cohorts for similar time frames and were postulated to relate to the lower bone mineral density observed in female populations. Over time, as survival in cystic fibrosis increased, this gender difference has persisted with Rosenfeld et al. in 1997 confirming a gender difference in CF survival (25.3 vs. 28.4 females vs. males) in a cohort of over 20,000 patients [23], and Harness-Brumley et al. in more recent 2014 study observed this difference in greater than 32,000 North American patients (36.0 years vs. 38.7 years, females vs. males) [24]. Despite accounting for variables known to influence CF-related mortality, it was demonstrated that female gender is an independent significant risk factor for death. Furthermore, women were found to be colonized at an earlier age with various pathogens and that their clinical course was much worse when colonized with common CF pathogens [24].

Though the relationship between gender and adverse outcomes has been described in a multitude of studies over a vast period of time, a full explanation of this dichotomy remains elusive. Much current research now centres on the role of estrogen in female CF patients. The primary female sex hormone is 17β-estradiol (E_2) and circulates in the body bound to sex hormone binding globulin, interacting with target tissues through a range of estrogen receptors (ERs) expressed on the cell surface. E_2 levels naturally vary over the course of the normal menstrual cycle and E_2 further dehydrates the already compromised airway surface liquid seen in CF and peak levels of E_2 lead to an increased risk of infection and subsequent exacerbation [25]. Furthermore, high levels of E_2 have been shown to promote TLR hyporesponsiveness to a range of bacteria driven by an inhibition of interleukin-8 (IL-8) release [26]. In a study targeted to investigate the effects of E_2 on *Pseudomonas Aeruginosa* (PA). it was found that high levels of E_2 promotes mucoid conversion, alginate synthesis, and genetic mutations in mucins lending increased infectivity and virulence to PA in those exposed to E_2 [15]. An interesting addendum to this study was the observation that the individuals studied had lower rates of exacerbation and required a lower number of antibiotic courses if they were using the combined oral contraceptive pill [15]. As exacerbation rate is commonly quoted as a predictor for mortality, there is scope here to assess the role of targeted estrogen therapies on mortality and the gender dichotomy in CF.

5. Relationship between exocrine disease and prognosis in cystic fibrosis

Pancreatic insufficiency is an extremely common complication of CF and affects over 85% of patients at some point during the course of their disease [27]. Loss of pancreatic exocrine function leads to malabsorption of fat, protein, and micronutrients, which in turn causes failure to thrive, steatorrhoea symptoms, and fat-soluble vitamin deficiencies. This arises as a consequence of obstruction of proximal intralobular ducts in the pancreas due to inspissated mucus plugs and tends to arise early in the disease. Chronic pancreatitis is another less common manifestation generally associated with milder (IV-VI) CF genotypes [28, 29], as residual pancreatic acinar tissue is a prerequisite for pancreatitis to develop. Pancreatitis affects over 10% of CF patients and tends to occur in a chronic relapsing and remitting fashion. It is thought to be due to a combination of obstructive tubulopathy and acidification of the acinar lumen due to reduced ductal bicarbonate secretion. Those with symptomatic pancreatitis can often become pancreatic insufficient as their disease progresses. A recent review of the European Cystic Fibrosis registry demonstrated that pancreatic insufficiency was associated with a statistically significant decreases in FEV1%, with pancreatic insufficient patients twice as likely as sufficient patients to experience severe lung disease, defined as FEV < 40% predicted [30]. This indicates that lack of pancreatic exocrine function is associated with worsening prognosis.

6. Cystic fibrosis-related diabetes is associated with poor prognosis

Cystic fibrosis-related diabetes (CFRD) is a common comorbidity with an estimated prevalence of 20% in adolescents and 40%–50% in adults [31]. As with other disease-related comorbidities, incidence of CFRD continues to increase as life expectancy improves. It encompasses a spectrum of disease from impaired glucose tolerance to CFRD with fasting hyperglycaemia. Impaired chloride channel function leads to thick pancreatic secretions that cause obstructive damage to the exocrine pancreas and subsequent architectural disturbance in islet cells with loss of endocrine function. Insulin deficiency is compounded by insulin resistance that occurs during pulmonary exacerbations as a consequence of increased levels of growth hormone, cortisol, catecholamines, and inflammatory cytokines [32]. Not all patients with CF go on to develop CFRD, and it has been demonstrated that multiple extrinsic factors contribute to disease pathogenesis such as malabsorption, immunosuppressant therapy following lung transplantation, use of glucocorticosteroids, and the presence of liver disease.

CFRD has a significant impact upon clinical parameters of disease and thus impacts upon prognosis. Insulin deficiency and hyperglycaemia negatively affects pulmonary function with the rate of decline in FEV1% over a 4 year period found to be related to the severity of insulin deficiency [33]. Moreover, insulin replacement therapy can improve both nutritional status and pulmonary function in patients with CFRD [34]. Hyperglycaemia also impacts clinically, with moderately elevated blood glucose levels leading to increased airway glucose concentrations, which in turn promotes the growth of various respiratory pathogens and can increase exacerbation rate [35]. CFRD also impacts, predictably, on nutritional status with both insulin deficiency and hyperglycaemia exerting effects. The classical complications of diabetes mellitus also contribute to morbidity in patients with CFRD. Macrovascular complications have not been documented, despite the increasing life expectancy of these patients. However, microvascular complications are common and include mild neuropathy as the most common manifestation with prevalence rates similar to those for non-CF diabetics [36]. Furthermore in one study, retinopathy occurred in 16% of CFRD patients and microalbuminaemia in 14% in a cohort of patients who had diabetes for more than 10 years [36].

In terms of direct mortality, CFRD has been shown to have a negative prognostic effect, with increased mortality seen in association with poorer nutritional status and greater severity of lung disease [37, 38]. In addition, CFRD mortality has been shown to be increased in female cohorts when compared to males [39]. However, over time there have been sustained improvements in CFRD-associated mortality with both female and male mortality decreasing in the period between 1992 and 2003 [31], this effect is presumably a reflection of increased awareness of the importance of CFRD and improvements in diagnosis and treatment strategies. CFRD is a common and complex co-morbidity in CF which negatively impacts on clinical outcomes and mortality. There is evidence to show that early treatment of CFRD can promote improved nutritional status, pulmonary function, and ultimately improve outcome.

7. Cystic fibrosis-related liver disease and prognosis

As the life expectancy of patients with CF continues to improve, cystic fibrosis-related liver disease (CFLD) is becoming increasingly more prevalent with an incidence estimated of up to 30%, according to multiple studies. Liver disease firstly manifests in its most simple form as biochemical derangements in liver enzymes. Structural disease develops next and manifests as fatty infiltration on ultrasound scan or increased bile content in liver parenchyma. Decompensated liver disease occurs last, which can involve portal hypertension, ascites, variceal disease, and impaired coagulation. These disease processes occur as a consequence of altered viscous bile due to abnormal CFTR-regulated ion transport across cholangiocytes. Consequently, biliary flow is reduced and there is obstruction of intrahepatic bile ducts. This causes damage to hepatocytes and cholangiocytes through inflammatory processes, bile duct proliferation, and portal tract fibrosis. The pathogenesis of fatty liver disease in CF is less well understood and has been loosely attributed to fatty acid deficiency, malnutrition, and insulin resistance [40].

Attempts have been made to link the development of CFLD with the presence of certain underlying CFTR mutations, the assumption being that CFLD would be seen with increasing frequency in patients with the classically severe or high-risk phenotypes as described above. However, this relationship has not been demonstrated to date. Non-CFTR modifier genes have been proposed to increase susceptibility to development of CFLD and it is thought that identifying these genetic modifiers may allow early identification of patients at risk. To date only polymorphisms in the SERPINA1 allele, which codes for an alpha-1 antitrypsin, has been demonstrated to be significantly related to CFLD and portal hypertension [41].

Liver disease is widely cited as the third most common cause of death in CF patients after respiratory failure and transplant complications, with a mortality rate estimated at 2.5% [30] and a higher mortality risk is observed in those with liver disease than in those without [40]. However, there continues to be massive variability in the severity of CFLD without adequate explanation as to why it affects only certain patients, thus it is a complex prognostic index.

8. Clinical measurements of disease severity and how they predict prognosis

Whilst recognising the importance of tailoring care of patients with CF to the individual genotypes and associated co-morbidities is essential, many of these factors are established and in many ways less dynamically modifiable than others in clinical practice.

The prognostic value of more dynamic markers of clinical condition offer more practical long-term targets around which to focus treatment and goals in the individual patient. On a day to day basis, these parameters guide practice and stratify patients in terms of expected outcomes.

9. Pulmonary function and how it predicts prognosis

Spirometric measurement of lung function, specifically FEV1, has been the pre-eminent surrogate marker of disease staging in CF for a long time. As it is reproducible, readily available, and cheap, it provides longitudinal measurement of airflow obstruction over years.

Seminal work by Kerem et al. in 1992 suggested that as an independent factor, FEV1 reliably predicts the relative risk of mortality, with a baseline FEV1 of less than 30% predicted giving a 50% two-year mortality [3, 42]. Following on from this work, further studies suggested that rate of decline of FEV1 could more accurately identify the most at risk patients [2, 43, 44]. Interestingly there is evidence that high baseline FEV1 is a risk factor for greater FEV1 decline and that this phenomenon may be explained by less aggressive prescribing patterns in patients with preserved lung function [45].

Few would argue that FEV1 is invaluable in clinical practice; however, it does fall short in identifying early lung disease where spirometry is often normal. This is especially the case in paediatric CF centres, where lung disease is often in its early stages or where technical limitations in performing reliable expiratory manoeuvres are more common. Recent interest has arisen in lung disease assessment using the Lung Clearance Index (LCI), a measurement derived from the multiple-breath inert gas washout. Whilst this technique is time consuming and less readily available, there is growing evidence that it may be more sensitive than FEV1 in diagnosing early lung disease [46, 47] and that abnormal LCI in the setting of normal FEV1 may predict future FEV1 decline [9]. Moreover, LCI correlates with high resolution computerised tomography (HRCT) findings [48] and predicts exacerbations and time to first exacerbation [49]. As such LCI may prove to be an appealing tool for more sensitively detecting improvements in lung health when assessing novel therapeutic options [50] and become a useful prognostic index.

10. Microbial colonisation in cystic fibrosis and its effect upon prognosis

Bacterial colonisation of the airways is the catalyst for cyclical infectious exacerbations of CF, leading to acute, subacute, and chronic inflammation. The identification of organism and subsequent in-vitro sensitivity testing helps in guiding treatment, antibiotic choices, and even infection control measures. The individual impact of specific organisms on prognosis and survival has been a focus of interest in clinical research for some time.

11. *Pseudomonas aeruginosa*

The most prominent pathogen with a specific affinity for the CF lung is *Pseudomonas Aeruginosa* (PA). Though its prevalence in CF populations varies with age [51], it is the most common airway pathogen in adult CF patients. PA colonisation predicts lower FEV1 at the time of culture [52, 53] and greater rate of decline in pulmonary function over time [54-56] when compared with Methicillin Sensitive *Staphylococcus Aureus* colonised (MSSA) and non-colonised patients. Moreover, evidence suggests that patients in whom PA colonisation is eradicated in a systematic manner have a significant reduction in treatment burden and days spent in hospital. This, in turn, can result in reduced expense on treatment of exacerbations [57].

12. *Staphylococcus aureus*

Amongst the earliest pathogens to become clinically prominent in the life of patients with CF is *Staphylococcus Aureus* (SA) [58]. Its prevalence globally is 44%–56% (2008) in its methicillin sensitive form (MSSA) and 8%–23% for methicillin resistant strains (MRSA). The difficulty in accurately establishing the relevance of SA as a pathogen in CF may lie in the complexity involved in characterising the specific virulence of the strains involved. MSSA, *Small colony variant MSSA* (SCV-MSSA) and MRSA (both community acquired-MRSA and healthcare associated MRSA) all differ in resistance patterns and apparent virulence. A study by Hoffman et al. in 2006 [59] suggested that co-colonisation with MSSA and PA favoured the formation of SCV-MSSA. Subsequent work by Besier et al. [60] associated colonisation with SCV-MSSA with worse lung function, more PA co-infection and more antibiotic resistance than those with MSSA. This is especially telling when colonisation with PA and SA is not uncommon. During a 1990s US-based clinical trial [61] an analysis of baseline sputum found 43% of participants to culture both PA and SA. Current evidence suggest that patients culturing MRSA have worse lung function and require more antibiotics than those with MSSA [62] and that PA/MRSA co-colonisation is associated with more pronounced decline in lung function than PA/MSSA co-colonisation [63]. Controversy still exists surrounding the long established practice of prescribing prophylactic antimicrobials with activity against MSSA. Although studies have suggested reduced cough and less culture positivity in the setting of prophylaxis, no clear benefits in terms of outcomes have been observed. Furthermore, several studies have pointed to increased and earlier incidence of PA culture in patients undergoing MSSA suppression therapy [64]. Whilst guidelines published by international bodies vary on their recommendation regarding chronic anti-staphylococcal use, a recent Cochrane review found no convincing evidence for treatment [65] and reiterated concerns around the increase in PA colonisation.

13. *Burkholderia cepacia* complex

Long mistaken for a *Pseudomonas*, *Burkholderia* species were identified more accurately in the 1980s and 1990s as diagnostic techniques improved. Now recognised as perhaps the most virulent pathogens in CF, they present a major treatment challenge. The *Burkholderia Cepacia Complex* (BCC) is comprised of at least 17 distinct species of gram-negative bacteria. Termed Genomovars, these species vary in prevalence and apparent virulence. The most common BCC strains identified are *B.Cenocepacia* and *B.Multivorans*. Evidence from 2002 revealed a four-fold mortality risk in patients colonised with epidemic *B.Cenocepacia*, associated with a more rapid rate of lung function decline versus others (FEV1 -1.9% vs. -0.3% per annum) [66]. Further data from 2004 showed *B.Cenocepacia* was associated with a statistically significant higher rate of lung function decline (-140 ml/year vs. -32 ml/year (p=0.01)) and reduction in BMI when compared to PA and *B.Multivorans* [67]. Whilst evidence is mounting that specific BCC genomovars have a hierarchy of virulence with *B.Cenocepacia* associated with the highest morbidity, it is worth noting that progressive disease can be caused by a multitude of strains. "*Cepacia Syndrome*", a constellation of sepsis, fevers, and leucocytosis and fulminant decline most often resulting in death, has been described with genomovars other than *B.Cenocepacia* [68]. The true determinant of virulence may best be assessed by identification of specific epidemic strains within distinct genomovars. Moreover, strains associated with poor outcomes in the native lungs of CF sufferers may not cause the worst outcomes in post-transplant patients. A 2008 study assessing mortality in CF patients on transplant waiting list and post-transplant revealed a higher waiting-list five year mortality in *B.Multivorans* and non-epidemic strain *B.Cenocepacia* carriers than those with epidemic strains of *B.Cenocepacia*. Furthermore, 5-year post-transplant mortality was highest in the non-epidemic *B.Cenocepacia* cohort and carriers of *Burkholderia Gladioli*, an organism not included in the *BCC* group, and generally considered less relevant as a CF pathogen [69]. Clearly a deeper understanding of the relevance and prognostic implications of specific BCC colonisation is needed. Despite the significant risk posed by *Burkholderia* species in the CF population, evidence for eradication protocols and recommended antibiotic regimens is lacking, which is concerning as it possibly has the most significant effect upon prognosis of all bacterial colonisers [70].

14. Non-tuberculous Mycobacteria (NTM)

A 2013 study by Bryant et al. [71] demonstrating patient to patient transmission of *Mycobacterium Abscessus* (*subspecies Massiliense*) in a CF centre re-focused attention on the clinical management and implications of NTM colonisation. Prevalence (6%-14%) of NTM organisms is variable and changing with time [72] and patient phenotype appears to dictate colonisation with younger, more malnourished patients with more severe genotypes culturing more *Mycobacterium Abscessus Complex* (MBASC) organisms than *Mycobacterium Avium Complex* (MAC) [73, 74]. Recurrent NTM culture positive status has been shown to be associated with progression of HRCT changes [75], however, despite these findings, statistical evidence indicating worse outcomes in pulmonary function or mortality is lacking. With the employment of prophylactic macrolide treatment for reduction of exacerbations, significant concerns were raised regarding the possibility of developing macrolide resistance in colonising NTM species; hence, NTM culture positivity is a contraindication to macrolide prophylaxis. Long-term macrolide use may, however, have a protective effect in reducing incidence of NTM culture positivity as highlighted by Coolen et al. in 2015 [76]. This finding could have a significant impact on prognosis and treatment options, as NTM colonisation is still considered a contraindication to transplant in some centres despite growing evidence that outcomes post-transplant in this cohort are acceptable [77].

15. Other microbial organisms in cystic fibrosis

Aspergillus Fumigatus (AspF) is a common airway fungus found in the CF lung. Previous treatment was aimed largely at patients meeting criteria for diagnosis of Allergic Broncho-pulmonary Aspergillosis (ABPA). More recent evidence, however, suggests that AspF carriage correlates with more severe changes on HRCT [78] and can predict greater rate of FEV1 decline in patients who are a) colonised but not sensitised, b) sensitised but do not meet ABPA diagnostic criteria, and c) those with a diagnosis of ABPA [79]. Suitable studies assessing the value of AspF eradication in patients with CF not meeting ABPA criteria are lacking.

*Stenotrophomonas Maltophilia (*SM*)* and its relevance has been a point of debate for some time. Previously regarded as a bystander in the CF microbiome there is growing belief that it represents a true pathogen with potentially significant impact of mortality [80]. Antibiotic options for the treatment of SM are limited and dedicated studies assessing treatment effectiveness are lacking [81].

Candida Species are highly prevalent in CF airway culture [82]. Difficulty arises in differentiating oropharyngeal contamination from bronchial colonisation without bronchoscopic sampling. Data from 2010 suggests that colonisation with *Candida Albicans* is associated with increased exacerbation rate and significant decline in FEV1 [83]. There is a paucity of data relating to the benefits of treating *Candida Species* routinely in CF.

16. Impact of respiratory failure on prognosis in cystic fibrosis

Despite being a predictable outcome of progressive lung disease, the management of respiratory failure in CF, both hypoxic (Type 1 Respiratory Failure) and hypercapnic (Type 2 Respiratory Failure), is lacking in terms of an evidence base [84]. Prescribing habits for oxygen (nocturnal, ambulatory, or resting) borrow largely from guidelines for other conditions. Hypoxia as a determinant of prognosis therefore has not been assessed, although there are suggestions that patients at higher mortality risk have an association with worsening six minute walk test results [85]. However, baseline hypercapnia has been shown to be an independent risk factor for death, even in patients with an FEV1 greater than 30% predicted [86]. There is a paucity of reliable data regarding the benefits of maintenance non-invasive bi-level positive airway pressure ventilation (BIPAP) in CF. One randomised placebo controlled trial from 2008 [87] did show significant benefits with nocturnal BIPAP in terms of symptoms (quality of life questionnaires scores, dyspnoea indices, and chest symptoms), improvements in modified shuttle walk test distances, and improved nocturnal (but not diurnal) arterial hypercapnia, but no significant improvements were shown in lung function. Data does suggest, however, that in the setting of acute respiratory failure requiring admission to intensive care units, non-invasive ventilation (NIV) was associated with significantly improved outcomes when compared to intubation and mechanical ventilation in patients with CF [88-90]. Hence, the importance of respiratory failure in predicting prognosis needs further study in CF.

17. Nutritional status and weight in determining outcome in cystic fibrosis

The impact of malnutrition in CF is of great interest; exocrine and endocrine dysfunction, coupled with high basal metabolic requirements in the setting of chronic disease, exposes patients to a high risk of malnourishment. Low BMI in CF is known to increase in incidence with age and be closely implicated in worsening lung function [91, 92] and predicts worse outcome over a 4-year period [93]. Furthermore, patients awaiting lung transplantation who require nutritional intervention have been shown to have a higher risk of death [86] and improving the nutritional status of malnourished patients may ultimately improve lung function, even in cohorts with relatively advanced lung disease [94-96].

18. Bone mineral density in cystic fibrosis

Low bone mineral density (BMD) and subsequently osteopenia and osteoporosis are common in CF. Thus far, no convincing association has been shown between lung function and BMD and predictors of low BMD include BMI, weight, and age [97, 98]. Despite much research focus in this area, recent evidence raises the possibility that, unlike lung function and life expectancy, there has not been a significant improvement inter-generationally in BMD [99]. The lack of clinical data proving concrete improvements in outcomes with bisphosphonate therapy, other than BMD change itself, has left a clinical conundrum regarding the management of low BMD in CF [100]. Further studies are needed to guide clinical decisions which are currently dictated by experience and judgement. However, there is no prognostic value in BMD scores in CF patients.

19. Biomarkers of disease severity and how they predict prognosis

19.1. Sputum and bronchoalveolar lavage fluid biomarkers

The need for useful and clinically relevant biomarkers is vital, and their use as predictors of prognosis as well as surrogates of clinical response to treatment is increasingly important. Numerous different sputum biomarkers have been investigated and used to correlate with clinical condition, including correlating with exacerbation frequency, pulmonary function, microbiological colonisation and overall prognosis. The use of sputum biomarkers is ideal in CF as patients produce significant amounts of sputum, hence samples are easy to obtain and samples are routinely collected to assess bacterial colonisation as part of best practice care.

Several studies have demonstrated how neutrophil elastase (NE) activity is significantly increased in the CF lung and a recent study by Sly et al. revealed how NE activity is an early biomarker for the development of bronchiectasis in CF [101]. The levels of NE in CF bronchoalveolar lavage fluid (BALF) correlate inversely with FEV1 [10] and furthermore the higher the level of NE detectable the more rapid the decline in lung function [12], neutrophil counts also correlate well with these measures. These results support the use of NE levels and activity as a useful biomarker available from BALF or sputum, and many other potential biomarkers are benchmarked against this measure as well as clinical correlation. Several inflammatory cytokines which are known to be elevated in the CF lung have potential to be useful biomarkers also, particularly interleukin-8 (IL-8) and tumour necrosis alpha (TNF-α). IL-8 is a neutrophil chemo-attractant and elevated levels are seen in CF BALF [102] and levels measured in sputum correlate inversely with FEV1 [10]. IL-8 and TNF- α levels are elevated at the time of an acute pulmonary exacerbation, and have been shown to significantly decrease in response to antibiotic treatment in an inverse pattern compared to lung function measurements [103]. Furthermore, the levels of IL-8 found in the lungs of CF patients correlates with microbial colonisation, with higher levels identifiable in patients colonised with *Pseudomonas Aeruginosa* (PA) and *Staphylococcus Aureus* (SA) compared to non-colonised CF patients and healthy controls [104]. Further support for the usefulness of these cytokines as markers is how they correlate with symptoms of deterioration as reported by patients [105], hence IL-8 and TNF-α are markers of degree of lung damage and bacterial colonisation. There are limitations to the use of sputum and BALF biomarkers such as these, as they do not always correlate with all clinical measurements of disease; in one study IL-8 did not correlate [106] with modified Bhalla scores [107], or other reversible changes on high resolution computed tomography (HRCT) that did correlate with lung function measurements.

Glycosaminoglycans (GAGs) are involved in the modulation of IL-8 activity in BALF and increased expression of GAGs is related to the sustained inflammation in the CF lung, hence the levels of GAGs may be a potential biomarker of disease progression in CF as their expression is related to the neutrophil chemotaxis in the lung [108]. Other cytokines including IL-10 and IL-4 are also significantly elevated in CF BALF compared to healthy controls [109]. However, fewer studies have been done on these cytokines.

Several other sputum and BALF biomarkers have been studied and some have more potential future utility than others. Some of the early sputum biomarkers investigated were nitrites, with sputum NO_2/NO_3 shown to be significantly higher in CF patients with acute exacerbations [110] and correlated with neutrophil counts and inversely with FEV1 [111]. However, the levels did not return to normal despite intensive antibiotic treatment, hence negating their potential use as a marker of response to treatment [110]. Biomarkers that correlate to PA colonisation also include club cell secretory protein (CCSP), which is inversely related to the NE concentration in CF sputum and patients with pseudomonas aeruginosa have significantly lower CCSP than non-colonised individuals [112]. Furthermore, levels of leukotriene B4 (LTB4) correlate with PA colonisation in CF compared to other organisms [104].

To date, the most accurate sputum and BALF biomarker in CF remains NE activity and levels, hence several other biomarkers have been compared to this to demonstrate their usefulness. Other proteases such as matrix metalloproteinases 2 (MMP-2) and MMP-9 correlate well with increased levels noted in BALF which possessed increased NE activity [109], while cathepsins do not correlate with PA colonisation or exacerbations [113]. Biomarkers specific to pulmonary exacerbations are ideal as defining the response to treatment is very difficult in CF,; these include mucins MUC5AB and MUC5AC which are degraded at the time of exacerbation and demonstrate increased sialylation compared to controls [114]. Granulocyte-macrophage colony-stimulating factor (GM-CSF) levels at the time of pulmonary exacerbation predicts a larger acute decline in FEV1[115], which is highly predictive of poor prognosis [13], hence this may be a useful marker of future disease progression. Finally, calprotectin, a neutrophil derived protein, may also be a useful biomarker, where levels both in sputum and serum have been demonstrated to decrease significantly following treatment of an acute exacerbation and predicted time to next exacerbation [116], this is extremely useful as both exacerbations and lung function decline are the most sensitive markers of disease progression in CF.

19.2. Serum biomarkers as markers of systemic inflammation

Similar to sputum biomarkers, the use of serum biomarkers is highly appealing to monitor disease progression and also predict outcomes. Several studies have investigated in CF an array of potentially useful peptides and cytokines measurable in serum that correlate with exacerbation severity, length and recurrence as well as lung function and microbiological colonisation. While there are many studies of biomarkers of inflammation in CF and it further strengthens our understanding of the disease, the use of biomarkers has not become routine clinical practice, hence the need for accurate measurements of both pulmonary and systemic inflammation, which makes serum levels a key factor in this process as they may also be useful in measuring the response to treatment and predicting prognosis especially as new therapeutic options emerge.

As discussed previously, markers of neutrophil activity and elastase levels and activity in the lung correlate excellently with clinical condition, hence the use of neutrophil markers from serum would be ideal as biomarkers. One such biomarker is calprotectin, a neutrophil derived protein that is released during neutrophil activation, which has been shown to correlate with the resolution of exacerbations [116], as well as correlating with radiological scores and pulmonary symptoms [117]. CD16b is a receptor expressed by human neutrophils which binds immunoglobulins and is involved in the inflammatory response in CF. Levels of alpha-1 antitrypsin (AAT) complexed to CD16b (AAT:CD16b complex) have been shown to be significantly higher in CF patients than healthy controls, and correlate to other pro-inflammatory cytokines including IL-8 and TNF-α [11]. Plasma concentrations of AAT:CD16b complex at the time of acute pulmonary exacerbation responded to antibiotic treatment and demonstrated a significant correlation to FEV1 improvement. These results suggest this may be a potentially useful biomarker of acute exacerbations and hence a useful prognostic tool.

The use of cytokines, similarly to sputum, is often viewed as an ideal surrogate of disease state, and many have been studied. Immunoglobulin G (IgG) and IL-6 have been shown previously to correlate with mortality, however, when adjusted for confounding factors, in particular FEV1, this correlation did not remain independent [118]. There is significant cross correlation between inflammatory markers such as TNF-α, IL-8 and cathepsins as well as IL-6 and IgG. However, none have shown any significant correlation with mortality. As survival becomes longer in this disease, the need increases for biomarkers that correlate together with other indices of disease such as pulmonary function, bacterial colonisation, exacerbation frequency, and radiological changes.

Leucocyte ribonucleic acid (RNA) measurements may be one such biomarker for potential future use. In identifying the presence of airway infection, whole blood levels of leucocyte RNA is an accurate measure and is more sensitive than FEV1 or c-reactive protein (CRP), and together with FEV1 is highly sensitive [119]. Other novel biomarkers include anti-neutrophil cytoplasmic antibodies specific for bactericidal/permeability-increasing protein (BPI-ANCA).

Bactericidal/permeability-increasing protein (BPI) is one of the most potent endogenously produced antibacterials secreted by neutrophils, and autoantibodies against this protein are present in up to 90% of CF patients [120]. Levels of BPI-ANCA correlate strongly with markers of lung disease and it may indicate a pathogenic role in CF [121] and a recent study has shown that the presence of BPI-ANCA correlated significantly with a poor outcome, being death or requiring a lung transplantation. Furthermore, in patients colonised with PA the outcome was significantly worse if associated with this biomarker [122].

While no single biomarker of disease severity exists from either sputum or serum, there are several potential biomarkers that need further study and more robust results to support their routine use in clinical practice.

One biomarker that has recently re-emerged as a useful index of disease severity is the measurement of CFTR function. This may be measured by nasal potential difference (NPD) and sweat chloride concentration. It is important as a biomarker as it has been shown that CFTR and sweat chloride concentration at diagnosis predicts long term prognosis [123]. NPD is now reproducible in a more robust manor than previously, as it was difficult to accurately to so in the past [124]. The use of this biomarker has been further established in the recent clinical trials of CFTR modulators and correctors such as ivacaftor, with a change in NPD and sweat chloride seen as marker of improvement and correlating with improvements in lung function and BMI, whether this will be a long-term prognostic indictor remains to be seen [4].

20. Radiological methods to predict prognosis

Due to the complexity of CF lung disease, multiple modalities are needed to fully assess the extent of disease severity, including radiological imaging. Several imaging techniques have been employed and studied in CF; with plain radiograph, CT, and MRI all having varying abilities to predict prognosis, as well as correlate with clinical condition, and a number of scoring systems exist to qualify the extent of pulmonary involvement. High-resolution CT imaging of the lungs is currently the most sensitive method of assessing the structural changes in CF. HRCT permits airway thickness measurements and the extent of bronchiectactic changes, and these changes closely correlate with FEV1 and often adult patients with CF show more acute changes in HRCT abnormalities than decline in spirometric results [125]. The progression of bronchiectasis also correlates with CFTR genotype and levels of neutrophilic inflammation [126], while also significantly predicting exercise capacity in CF patients [127].

Newer methods to image the lungs in CF include hyperpolarised helium magnetic resonance imaging (He3-MRI) [8] and flurodeoxyglucose positron emission tomography (FDG-PET) imaging [5-7]. Both modalities correlate closely with abnormalities seen on HRCT and improve with antibiotic treatment, making them both sensitive useful tools in the acute setting. He3-MRI may identify early ventilatory changes in paediatric disease before identifiable changes on HRCT [128] and may better correlate with spirometry in assessing response after exacerbation treatment [8]. These modalities are not currently in widespread use due to both cost and availability, however, He3-MRI may become more routine in the future as life expectancy increases and the risk associated with increased cumulative exposure to ionising radiation associated with CT and FDG-PET [129].

A number of different radiological scoring systems have been developed to assess disease burden in CF. Older scoring systems were based on chest radiograph changes, and these included the Brasfield [130], National Institutes of Health (NIH) chest radiograph [131], and the Royal Children's Hospital (RCH) chest radiograph score [132]. While these were somewhat useful, they correlated poorly with spirometry and with clinical condition [133]. With the continual improvement in CT imaging modalities, HRCT has become the gold standard for assessing structural abnormalities, and several robust validated scoring systems exist for CT abnormalities. These include the Brody II score [134] and the CF-CT score [135], while one of the older original scoring tools, the Bhalla score, for bronchiectasis is still widely used in modified versions [107]. The Bhalla scoring system is an objective measure incorporating all aspects of CF structural abnormalities and has been validated and correlates with spirometry[136], clinical condition [127, 137], and has some correlation with health related quality of life [138], however, there is little correlation between these scores and other biomarkers of inflammation [106].

Radiological scoring systems are useful in assessing the extent of structural changes in CF, and correlate with certain aspects of the disease, however, they alone are not sufficient to predict prognosis and are likely more beneficial when used as part of composite clinical prediction tools.

21. Usefulness of clinical prediction tools in cystic fibrosis

As previously outlined in this chapter, life expectancy continues to improve in patients with CF due to a combination of improvements in treatment, level of care, and diagnostic tools, as well as multidisciplinary input and the development of disease-specific centres. With continually improving clinical outcomes, the need arises to better predict the prognosis of CF at an individual and group level. This need was first identified in 1958 with the development of the Shwachman-Kulczycki (SK) score to assess the severity of CF [139]. This score formed part of a study which monitored 105 patients for 5 years, the first of its kind to assess the long term progress of young CF patients. It was seen that there was increased frequency of CF patients surviving to adolescence and young adulthood and demonstrated a need to assess disease severity in order to predict the likely course of the disease.

There are many criticisms of the SK score as it is largely a subjective measure that depends on the clinical estimation of the examiner. Another drawback is that it does not include evaluations of pulmonary function. It was also devised with reference to a paediatric population in a time when life expectancy was drastically decreased. However, there have been a range of studies since its conception that have validated this score against a host of parameters increasingly used to measure prognosis. For example, Brasfield et al. observed a significant correlation between the SK score and chest radiography in an evaluation of over 640 chest radiogrpahs of 118 CF patients [130]. A more recent evaluation of the usefulness of this score to assess disease severity was undertaken by Stollar et al. in 2011 where [140] significant correlations were demonstrated between FEV1, chest radiograph, HRCT, 6-minute walk test (6MWT), and SK score. It was felt that the SK score adequately reflects radiographic and functional impairments in patients with greater impairment of lung function, however, the score was less useful in patients with preserved lung function (FEV1 >70%). Regardless of its shortcomings, the SK score is regarded as a milestone in the history of CF and continues to serve as a somewhat tool in the determination of disease severity.

This score formed the basis for the development of a multitude of clinical prediction tools, the majority of which involve clinical parameters, radiological parameters, or a combination of both. One such early radiological scoring system is the Brasfield score [130], which is based on the chest radiograph findings of patients with CF and encompasses a maximum score of 25, with points scored according to the severity of air trapping, linear markings, nodular cystic lesions, large lesions, and an impression of the overall general severity of the radiograph. However, it similarly is a subjective scoring system and there can be inter-rater differences. The Brasfield score does correlate with pulmonary function tests and the SK score and is reproducible. A disadvantage of the Brasfield score is that it was developed to include radiographs assessed by a team of radiologists and clinicians, while the Northern score [141] is an advance on the Brasfield score which allows for a single examiner to determine the radiographic severity based on assessing chest radiographs divided into lung quadrants. The maximum score is 20, with higher scores reflecting poorer outcomes due to increased severity of disease. This score was validated against the Brasfield score and an earlier score, Chrispin-Norman [142], and was found to be equal in terms of consistency, reproducibility, and accuracy in reflecting overall clinical status as measured by the SK score.

The development of widespread use of computed tomography in clinical practice has led to the inclusion of HRCT in prognostic tools for CF. Nathanson et al. proposed the first such score which involved dividing the lung CT into 12 distinct zones in order to classify the severity of bronchiectasis on a 5-point scale in each zone [143]. This, once again, was validated against the SK and Brasfield scoring systems along with the results of pulmonary function tests carried out on the subjects. As discussed, Bhalla et al. [107] further developed the idea of CT scoring systems in order to aid selection for lung transplantation and put forward a score based on the severity of 9 different radiological parameters including peribronchial thickening, extent of bronchiectasis, and extent of mucus impaction. This score is very reproducible and correlates strongly with pulmonary function, hence is the gold standard for HRCT evaluation.

Clinically-based prognostic tools play a central role in the management of CF patients and serve to direct treatments, investigations, and multidisciplinary input. The National Institute of Health scale, developed in 1973, proposed a comprehensive scoring system which included multiple parameters including baseline demographics, various measures of lung function, and presence of common complications encountered in the disease [131]. A 100-point scale derived from these measurements correlated with severity of disease, the higher scores being associated with poorer outcomes. It is a complex and cumbersome scale that reduces the likelihood for its application across the broader clinical setting. However, it is a reliable and reproducible score which encompasses many aspects of the disease and this has led to its continued use in CF-related research.

With the advancement of CF survival and life expectancy a need to develop simple and reliable prognostic tools for use in the clinical setting became apparent. In 1997, Hayllar et al. developed a predictive index based on research from over 400 patients and studied and correlated the index result with a mortality curve [144]. In this way, a simple calculation could be made to estimate 6-month and 1-year survival rates for a given score. The score was based on height, presence of hepatomegaly, white blood cell count, FEV1, and forced vital capacity (FVC). This, and scores like it, revolutionised the approach to prognosis in previously unchartered territory and survival estimates became central to prognostic tools. Liou et al. advanced on the NIH and Hayllar scores to present a 5-year prognostic tool, the longest range survival model in the field at its time of development [145]. It is based on a composite score of 8 clinical factors, as well as measurement of FEV1 and is a comprehensive, reproducible, reliable prognostic tool. However, it remains a complicated score to perform clinically and so focus has shifted in recent times to the development of simplified prediction tools that can be used within the time constraints of the current clinical setting. The CF-ABLE score was devised with this in mind and it involves the measurement of 4 of the major clinical parameters encountered in day to day practice [93]. Age, BMI, FEV1, and frequency of pulmonary exacerbations have been evaluated on a 7-point scale for correlation with prognosis and it has been found that patients with higher scores have a 26% chance of a poor outcome (death or transplantation) within 4 years of measurement. This score has been validated on a national registry and highlights the applicability of simple prediction tools that can be employed in the clinical environment.

Clinical and radiological prediction tools have emerged as a vital resource in the treatment of CF. They allow us to stratify patients by disease severity and to a certain extent allow us to predict likely adverse outcomes in patients with poor prognostic indices. A multitude of prognostic tools have been developed since the original SK score as CF research has continued to expand, each reflecting the changing face of CF treatment and diagnostic tools. Clinical practice favours the use of simple reliable scoring systems which take into account easily measurable parameters, such as the Hayllar score and the more up to date CF-ABLE score. Future research will need to involve the development of further prognostic tools to reflect the changes occurring in the management of CF (Table 2).

Name of Score	Year Published	Number of patients in cohort	Parameters Used	Strengths	Limitations
Shwachman-Kulzcizy [139]	1958	105 CF patients followed for 5 years	- General activity - Physical exam - Nutrition - Chest radiograph	- Uncomplicated assessment - Reproducible - High correlation with pulmonary function	- Subjective - No inclusion of measurement of pulmonary function

Name of Score	Year Published	Number of patients in cohort	Parameters Used	Strengths	Limitations
				-High correlation with Brasfield score	- Developed in paediatric population
NIH Score [131]	1973	73 patients aged 3 to 30 years followed for a period between 3 and 6 years	100 point scale of severity of lung and general parameters as well as common complications: - Chest Radiograph - Pulmonary function - Pulmonary exacerbations - Pneumothorax - Haemoptysis - Pulmonary surgery - Cor Pulmonale - Lung auscultation - Cough and expectoration - Weight - Activity - General attitude - ABG - GI complications - Infertility - Salt depletion - Osteoarthropathy	- Comprehensive - Demonstrated to be useful in prognosis and assessment of disease evolution	- Complex scoring system - Overestimates rare clinical elements - Does not include patients younger than 5 years of age - High variability in pulmonary function evaluation
Brasfield [130]	1979	643 chest radiographs in 118 CF patients	Composite score of presence and severity of each of the following: - Air trapping - Linear markings - Nodular cystic lesions - Large lesions - Overall impression of severity	- Reproducible - Strong correlation with clinical severity - Uncomplicated assessment	- Somewhat subjective in measurement of overall severity - Inflexible - Designed for team of radiologists
Nathanson [143]	1991	28 HRCT of CF patients	Severity of bronchiectasis and mucous impaction on a 5 point scale as measured in 12 distinct lung zones	- Good correlation with existing radiographic scores and clinical outcomes	- No studies in reproducibility

Name of Score	Year Published	Number of patients in cohort	Parameters Used	Strengths	Limitations
Bhalla [107]	1991	HRCT scans of 14 patients studies by 3 radiologists	3-point severity score of the following parameters: - Bronchiectasis severity - Peribronchial thickening - Bronchiectasis extent - Extent of mucoid impaction - Abscesses - General impression - Number of blisters - Emphysema extent - Collapse/consolidation	- Excellent agreement between examiners - Reproducible - High correlation with pulmonary function tests	- Extensive number of parameters - Complex scoring system
Northern Score [141]	1994	45 chest radiographs read by 10 clinical physicians	Severity of radiographic alterations in each lung quadrant: - 0: normal - 1: minimally increased linear signs or nodular cystic lesions - 2: moderately diffuse nodular cystic lesions, more pronounced linear signs - 3: severe; profuse cystic lesions, extensive collapse/ consolidation - 4: very severe; small areas of visible lung with dense infiltrates throughout	- Allows for single-examiner approach - Better agreement seen among examiners - Reproducible - Uncomplicated	- May overly simplify picture and extent of lung disease - No strong correlation with clinical measures
Hayllar [144]	1997	Retrospective data analysed on 403 patients over 18 year period	Predictive index based on measurement of: - Height - Hepatomegaly - FVC (%) - FEV1 (%) - White blood cell count Mortality curve developed to relate predictive index to survival probability	- Directly relates clinical measures to an estimate of survival - Externally validated - Reproducible	- Excludes some known predictors of mortality - Developed based on data in 1970s and 1980s; does not reflect improved diagnostic techniques

Name of Score	Year Published	Number of patients in cohort	Parameters Used	Strengths	Limitations
Liou Predictive 5-year survivorship model of Cystic Fibrosis [145]	2001	Retrospective data collected 5820 patients in US registry between 1986 and 1993	Composite score of the presence or value of following parameters to predict 5-year survival: - Age - Gender (M=0, F=1) - FEV1 (%) - Weight-for-age z score - Pancreatic insufficiency - Diabetes mellitus - Staphylococcus aureus - Burkholderia cepacia - No. of acute exacerbations (0-5)	- Comprehensive - Widely applicable - Validated - User-friendly	- Does not account for radiological findings - Prediction rule is derived from the same cohort as the validation group
CF-ABLE Score [93]	2013	49 CF patients followed over a 7-year period. Validated in 370 patients collected from national registry over 5 years	7-point scale based on evaluation of: - Age <24 = 1 point - BMI <20.1 kg/m^2 = 1 - FEV1 (%) < 52% = 3.5 - Number of exacerbations in past 3 months > 1 = 3.5 points Score of >5 indicates 26% chance of poor outcome in the next 4 years	- Common clinical measurements used - Easy to caluclate - Validated	- Difficult to define pulmonary exacerbation - Adult only score

Table 2. Summary of Clinical Prediction Tools in Cystic Fibrosis.

22. Conclusion

Over the last two decades, prognosis has improved significantly in CF and this has led to the need to better predict outcomes. Subsequently, many studies have looked at all aspects of the disease and identified modifiable risks, as well as identified biomarkers to follow disease progression. This increased knowledge of the condition has allowed improved treatment and more phenotypically specific therapy to be developed. Many different clinical features and markers predict outcome and this is a complex area, and a multifaceted approach to risk stratifying patients is needed. However, what must be not overlooked as the survival increases in CF are the extrapulmonary manifestations and the significant psychosocial issues associated with chronic illness. It is important to note that up to 22% of CF patients demonstrate symptoms of depression, 10% report anxiety symptoms, and up to 5% report suicidal thoughts [146]. The incidence of depression and anxiety is 2–3 times higher than age matched community control individuals [147]. This is highly important and there is an association between depression and lower FEV1 [146]. Also, patients with well-preserved spirometry who have depression demonstrate more significant decline in lung function than those with no depressive symptoms [148]. Depression is associated with negative medication beliefs leading to lower medication adherence, which ultimately may lead to poorer prognosis, hence it is important to evaluate patients holistically beyond the medical complications of CF when assessing prognosis [149]. Other important factors that are easily overlooked are socio-economic issues that impact upon survival, including lower household income and socio-economic status [150-152], larger family size with more than one person with CF [153], and exposure to cigarette smoke [154] all predicting a poor outcome. These risk factors are sometimes more difficult to quantify and hence are often overlooked. They are also difficult to measure as part of composite prediction tools, but they must be taken into account when assessing the prognostic indices of each individual with CF.

As survival continues to improve, the use of composite scoring systems and multi-disciplinary approach to improving care is essential in CF. Many clinical prediction tools exist for CF and some are more useful in clinical practice than others, however, these are underutilised in general and should be employed in more clinical trials, as well as routine care.

In summary, the prognosis of CF has improved significantly over the last two decades and may improve further as newer medications are developed. The need to accurately predict prognosis is essential as the decision for lung transplantation or to aggressively treat certain aspects of disease may be more tailored and appropriate per individual, this improving survival further. The most sensitive way of predicating prognosis currently remains a multi-faceted approach, including several markers of disease and the use of all factors and a composite clinical prediction tool is suggested to stratify patient risk.

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