9-1-2021

Risk factors leading to pulmonary exacerbation in patients with cystic fibrosis: A systematic review

Danish Abdul Aziz

Syeda Khadija Fatima

Hasan Nawaz Tahir

Risk factors leading to pulmonary exacerbation in patients with cystic fibrosis: A systematic review

Danish Abdul Aziz,[1] Syeda Khadija Fatima,[2] Hasan Nawaz Tahir[3]

Abstract

Objective: To ascertain major risk factors associated with pulmonary exacerbation and pulmonary function decline in cystic fibrosis.

Method: The systematic review was conducted at Aga Khan University, Karachi, in September 2018, and comprised electronic search of PubMed, Ovid, Science Direct and Cumulative Index of Nursing and Allied Health Literature databases of studies conducted from January 1990 to September 2018 which were categorised into 3 sets; 1990-98, 1999-2007 and 2008-18. Studies included for review focussed on articles with pulmonary exacerbation as the health outcome indicator, and had diagnosis of cystic fibrosis as the inclusion criteria, while risk factors were the exposure terms used in the search process. References in bibliographies of the included studies were also systematically searched for relevant documents.

Results: Of the 60 studies obtained, 31(51.7%) were selected; 2(6.45%) from 1990-98, 7(22.58%) from 1999-2007 and 22(70.96%) from 2008-18. Overall, 17(54.83%) were cohort studies, 7(22.5%) were cross-sectional studies, 3(9.6%) were case-control studies, 3(9.6%) were randomised controlled trials and 1(3.2%) was systematic review and meta-analysis. In terms of major risk factors, genetic mutations were cited by 4(12.9%) studies, infections and inflammatory biomarkers by 15(48.4%), nutritional deficiencies by 9(29%) and geographical and socioeconomic status by 3(9.6%) studies.

Conclusion: Early identification and recognition of risk factors associated with pulmonary exacerbation can have an explicit impact on its management, leading to decreased morbidity and mortality burden in cystic fibrosis cases.

Keywords: Pulmonary exacerbation, Cystic fibrosis, Risk factors, Systematic review.

DOI: https://doi.org/10.47391/JPMA.04-515

[1]Department of Paediatrics and Child Health, [2,3]Department of Community Medicine, Aga Khan University Hospital, Karachi, Pakistan.

Correspondence: Danish Abdul Aziz. Email: drdanishaziz@gmail.com

Introduction

Cystic fibrosis (CF) is an inherited disorder affecting multiple organ systems. Autosomal recessive mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) gene on chromosome 7 plays a pivotal role in pathogenesis. Major morbidity and mortality are attributed to pulmonary manifestations of CF. Infections comprise the major lung disease burden. Structural and functional decline in pulmonary parenchyma occurs with recurrent pulmonary exacerbations. In the United States, 1 out of every 3,200 Caucasian births have CF. Current medical advancements and research developments have increased median survival to the 4th decade. However, patients still experience shortened life expectancy secondary to devastating pulmonary manifestations and progressive lung function decline.[1]

Pulmonary exacerbation is as an escalation of the pulmonary decline with deterioration in forced expiratory volume in 1 second (FEV1), nutritional decline, regression in daily functioning and quality of life (QOL). Progressive lung descent is the central determinant of disease outcome in CF.[2] Pulmonary exacerbation serves as a key indicator for disease severity and is a crucial variable in studies assessing overall survival (OS) related to CF. Moreover, lung disease remains the primary target for pivotal treatments decreasing morbidity and mortality in CF. Multiple risk factors associated with pulmonary manifestations contributing to exacerbations have been identified. These include nutritional deficiencies, infections, medications, biochemical markers indicating acute episodes and the effect of socioeconomic status (SES).[3]

Identification of risk factors has a vital role in treatment and can improve management outcomes in CF population which in turn can affect life-expectancy and rate of exacerbations.

The current study was planned to systematically review literature to recognise risk factors correlated with pulmonary exacerbations in CF.

Methods

The systematic review was conducted at Aga Khan University, Karachi, and comprised electronic search of PubMed, Ovid, Science Direct and Cumulative Index of

Nursing and Allied Health Literature (CINAHL) databases of studies conducted from January 1990 to September 2018 which were categorised into 3 sets; 1990-98, 1999-2007 and 2008-18. The year 1990 was set as the starting point for literature search to maintain relevance.

The initial database search was done in September 2018 followed by screening of articles. The review of relevant full text completed in the last quarter of 2018, and the manuscript was finalised in the first quarter of 2019.

The search covered all reports in indexed and non-indexed local and international English-language journals which described primary epidemiological research concerning risk factors for pulmonary exacerbation in CF in Asian populations. Studies included for review focussed on articles with pulmonary exacerbation as the health outcome indicator, and had diagnosis of cystic fibrosis as the inclusion criteria, while risk factors were the exposure terms used in the search process. References in bibliographies of the included studies were also systematically searched for relevant documents.

Full-text copies of all the studies found were scrutinised. Those that met the inclusion criteria were then abstracted and summarised using a standardised form. Following the initial electronic search carried out independently by all the authors, decisions and abstracted summaries were compared and disparities were settled through discussion. For the development of protocol, manuscript and reporting of study findings, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used.[4] Quality assessment of the studies was done using the Newcastle-Ottawa scale (NOS) for cross-sectional and cohort studies,[5] interpreted as per the given criteria; Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain". Cochrane risk of bias tool was used for interventional studies.[6]

In assessing publications apposite for review, findings were assembled by health outcomes, and conclusions were measured that could be drawn given the strengths and limitations of each study.

Results

Of the 60 studies obtained, 31(51.7%) were selected

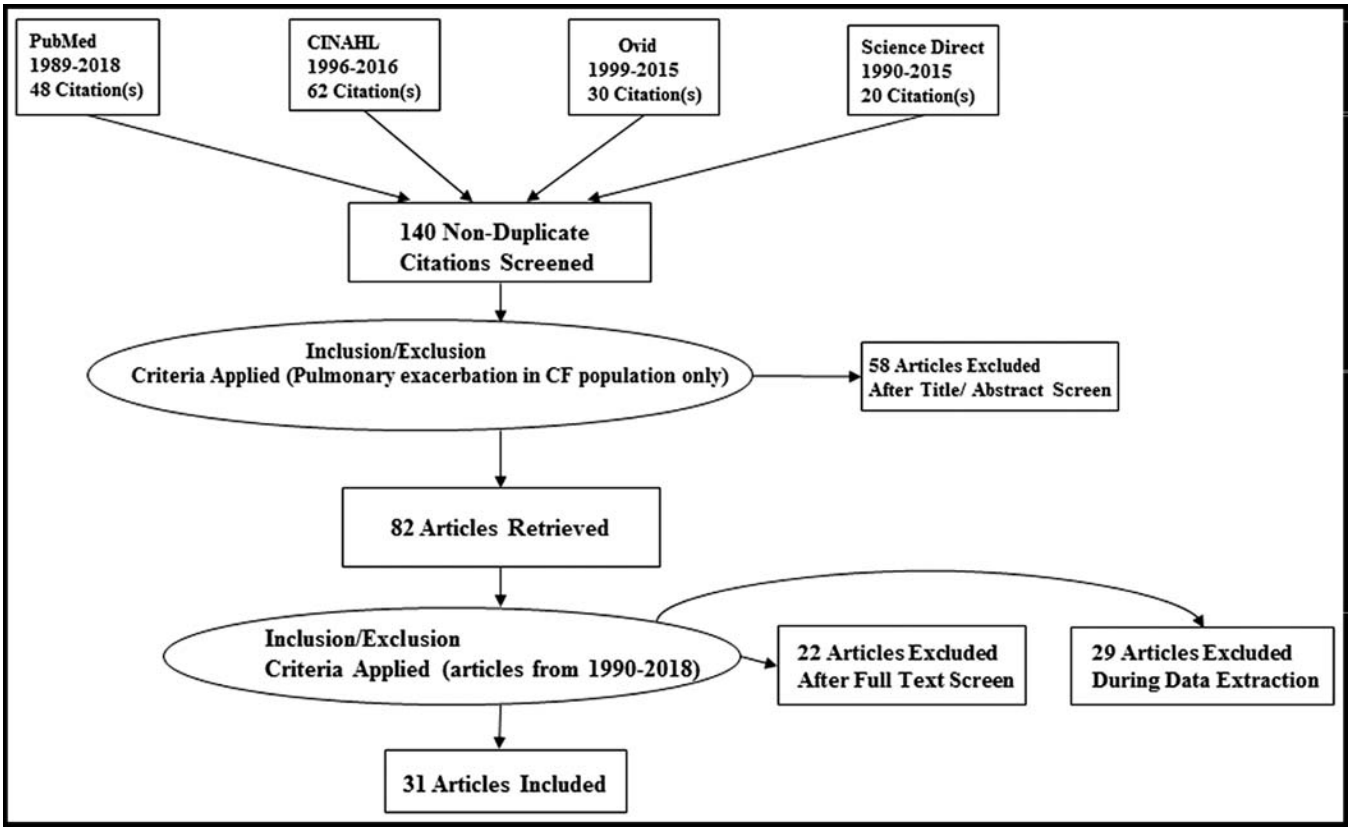

Figure: Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow-chart.

Table-1: Duration and type of studies.

Total of n=31 studies included, from 1990-2018. The timeline was divided into three stages:
- 1990-1998= 2 studies
- 1999-2007=7 studies
- 2008-2018=22 studies
- Cohort studies=54.83% (17)
- Cross-sectional studies=22.5 % (7)
- Case-control studies= 9.6 % (3)
- Randomized controlled trials= 9.6 % (3)
- Systematic Reviews/Meta-analysis= 3.2 % (1)

Table-2: Themes for analysis.

Risk factors associated with Pulmonary exacerbation in Cystic Fibrosis: (n=31)
- Genetic mutations (n=4)
- Infections and Inflammatory biomarkers (n=15)
- Nutritional deficiencies (n=9)
- Geographic and socioeconomic status (n=3)

(Figure). Of them, 2(6.45%) were from the 1990-98 period, 7(22.58%) from 1999-2007 and 22(70.96%) from 2008-18. Overall, 17(54.83%) were cohort studies, 7(22.5%) were cross-sectional studies, 3(9.6%) were case-control studies, 3(9.6%) were randomised controlled trials (RCTs) and 1(3.2%) was systematic review and meta-analysis (Table-1). Of the 17(54.83%) cohort studies, 13(76%) were of good quality and the remaining 4(24%) had fair quality. All the 7(22.5%) cross-sectional studies had good quality.

In terms of major risk factors, genetic mutations were cited by 4(12.9%) studies, infections and inflammatory biomarkers by 15(48.4%), nutritional deficiencies by 9(29%) and geographical location and SES by 3(9.6%) studies (Table-2).

In terms of genetic mutations, a 2011 study analyzed correlation between CFTR class I and class II mutations in CF patients, and determined that two class I mutations were linked with grave pulmonary functional decline in contrast to two class II mutations or combination of classes I and II.[7] A 2002 study proposed that pulmonary disease showed an association with severity of CFTR mutations. Precarious disease with earlier onset (1.7 years vs 7.9 years, p=0.0001) was seen in patients with two severe mutations, and they displayed critical respiratory impairment, mean FEV1 decline (29% of predictive value vs 58% of predictive value, p<0.001); high pseudomonas (P.) colonisation (97% vs 57%, p<0.01); prominent occurrence of end-stage respiratory disease, having FEV1 <30% (73% vs 29%, p<0.05); and with pronounced regression of FEV1 (3% vs 1.4%, p<0.001) annually. Multivariate logistic regression analysis, containing two extreme mutations, was self-governing indicator of an existence constraining respiratory deficiency (relative hazard, 6.75; 95% confidence interval [CI] 1.79-26.50, p=0.003).[8]

A retrospective observational study in 2015 demonstrated that mean yearly deterioration in FEV1% predicted was 1.01%. Homozygous F508del mutations showed a large decrease in FEV1. Moreover, pulmonary regression was associated with female gender, low body mass index (BMI), recurrent/productive cough, one or more pulmonary exacerbation, high FEV1 (>/=115% predicted), methicillin-sensitive staphylococcus aureus (MSSA), methicillin-resistant staphylococcus aureus (MRSA) or stenotrophomonas (S.) maltophilia-positive cultures.[9] A 1997 study, with a large cohort from CF database, showed that the patients deceased prior to age 15 had a considerably reduced lung function compared to their first test and had a fleeting drop in pulmonary function. Lung deterioration was pronounced in delta F508 mutation homozygotes compared to delta F508 mutation heterozygotes. Females had a noteworthy precipitous waning than males, and those with pancreatic insufficiency had exorbitant regression than those with good pancreatic function.[10]

Infections and inflammatory biomarkers were identified by 15(48.4%) studies. A prospective 2004 study established that a new pulmonary exacerbation in majority of patients was not secondary to the attainment of new P. aeruginosa strain. Further, 40(48%) patients required intravenous (IV) antibiotics for exacerbation, while 36(43%) patients had genetically typeable P. aeruginosa isolates, amd in 34(96%) of these 36 patients, strains recovered during exacerbation and clinical stability were of the same genotype. Only 2(6%) patients (95% CI 0-18%) had clone P. aeruginosa strain cultured during exacerbation.[11] A multicentre study in 2014 found a correlation between P. aeruginosa phenotypes during infection stages and their prognostic value in pulmonary exacerbation prediction. It concluded that two in vitro phenotypes differentiated early and late stages of infection: pyoverdine production (31% of new cultures, 48% of intermittent, 69% of chronic) and low protease production (31%, 39%, 65% respectively). Mucoidy (odds ratio [OR] 1.75, 95% CI 1.19-2.57) and reduced twitching motility (OR 1.43; 95% CI 1.11-1.84) were strong predictors for succeeding exacerbations in the following 2 years.[12] A review in 2012 set out to assess the effectiveness of antibiotics in patients with chronic Burkholderia cepacia complex infection, determining it as a distinguishing infection in CF population, and found a deficiency of trial evidence to establish definite results.[13]

A cross-sectional and retrospective cohort in 2011

recognised stenotrophomonas (S.) maltophilia as an autonomous risk factor for pulmonary decline. Patients infected chronically with S. maltophilia were found to have mean antibody titers to bacterial flagellin (p<0.0001) and antibody titers to whole bacterial cell (p=0.0004) substantially high compared to patients with no or intermittent infections. Pulmonary exacerbation risk demanding hospitalisation and antibiotics was noticeable in patients infected with S. maltophilia compared to uninfected patients (relative risk [RR] 1.63, p=0.0002).[14] A prospective study in 2013 recognised a marked risk of pulmonary exacerbation with viral infections (OR 2.19, 95% CI 1.56-3.08, p<0.001) and antibiotic need in CF patients (OR 2.26, 95% CI 1.63-3.13, p<0.001).[15]

The remaining 10(66.6%) studies in the category were related to biomarkers. A cohort study in 2015, conducted to find blood-based biomarkers to foresee impending CF pulmonary exacerbations using specific proteomics, established the likelihood of imminent exacerbations prediction with the use of multiple reaction monitoring mass spectrometry (MRM-MS) in which protein panel (area under the curve [AUC] 0.74) had the AUC in contrast to FEV1% predicted (AUC 0.55), C-reactive protein (CRP) (AUC 0.61) and interleukin-6 (IL-6) (AUC 0.60) which were the chief biomarkers correlated in exacerbation prediction.[16] A case-control study in 2007 found a rise in OS and sputum levels of bioactive lipid mediators during an exacerbation. The sputum 8-iso-prostaglandin F2α (8-iso-PGF2α) levels were high in acutely ill CF patients (p<0.001) along with high cysteinyl leukotrienes (cys-LT) and prostaglandin E2 (PGE2) levels. Sputum total cell count (p=0.03) regressed with antibiotic treatment, but 8-iso-PGF2α, cys-LT or PGE2 levels remained unaffected, indicating the need of also addressing this respective aspect of CF management.[17] A cohort in 2014 concluded that 37(70%) of 53 patients suffered pulmonary exacerbations during the study period. At baseline, reduced pulmonary function, lower clinical scoring and QOL values were related with increased risk of exacerbation events. Pulmonary exacerbations were associated with increased inflammatory markers at baseline on the first day, and treatment led to improvements in the levels of biomarkers. CRP and IL-8 were the main biomarkers identified and they correlated with an early re-exacerbation.[18]

A double-blinded RCT concluded that subjects treated with liposomal prostaglandin E1 (TLC C-53) had a less rapid pulmonary functional decline compared to controls (FEV mean difference 4.3%, 95% CI -6.8-15.4%) and had more time till next exacerbation (26 weeks against 11.9 weeks). The biomarkers used as primary outcome determinants were IL-6, IL-8 and sputum neutrophil elastase.[19] A study in 1999 concluded that OS, activity of free radicals and subsequent damage and their response to treatment parameters were high during pulmonary exacerbations and showed improvements with treatment.[20]

A cohort study measured levels of desmosine in the sputum of CF patients during pulmonary exacerbation treatment, and established significant decrease in desmosine during the first week of hospitalisation (p=0.04). A definite association was found in desmosine levels, plasma CRP (p=0.59; p=0.03), sputum IL-8 (p=0.86; p<0.01), and sputum neutrophil elastase (p=0.78, p<0.01).[21] A prospective study in 2011 aimed at establishing the role of baseline procalcitonin levels in CF paediatric population and relation of the values with onset of pulmonary exacerbation. It established that baseline procalcitonin (n=92) was 0.05±0.07ng/ml, and at admission for in-patient management of exacerbation (m=22) it was 0.07±0.06ng/ml; not distinct from levels reported in healthy children.[22] A cross-sectional study in 2014 established the role of soluble cluster of differentiation 14 (sCD14) as a biomarker in recognising patients at risk of experiencing a CF exacerbation. It found sCD14 levels high during exacerbations (p=0.03) and in patients with IV antibiotics due to exacerbation within 4 months of a steady clinical course (p=0.001).[23]

An observational study in 2010 established a reduction in sputum calprotectin after treatment of an exacerbation (p<0.05). A substantial decrease was found in serum levels of calprotectin (p=0.002), CRP (p=0.002) and vascular endothelial growth factor (VEGF) (p=0.013). Moreover, serum calprotectin showed predictive value for interval towards next exacerbation (p=0.032) post-treatment.[24] One study in 2000 studied an elevation in mean VEGF levels in pulmonary disease patient groups, including CF and other lung diseases, and compared reference values, finding higher VEGF in CF (p=0.02). The study showed an inverse relation between VEGF and FEV1 in CF, (r-0.51, p=0.007). Following antibiotics, VEGF levels regressed in CF exacerbation (p=0.001).[25]

With respect to nutritional sdeficiencies, a 2014 study using the CF database established that low BMI, pancreatic insufficiency, CF-related diabetes and P. aeruginosa infection had significant (p<0.001) impact on FEV1. Patients with low BMI had higher OR (95% CI 5.0-7.3) of experiencing a debilitating pulmonary decline, pancreatic insufficiency had more risk (95% CI 1.6-2.5) and two-fold increase in OR of severe lung disease, and CF-related diabetes patients had 1.8 times increased OR (95% CI 1.6-2.2) in contrast to unaffected patients.[26] A cohort

study in 2008 indicated a gradual rate of pulmonary deterioration in patients with good nutritional state, slower BMI decline, lack of P. aeruginosa infection and Dornase alfa (Pulmozyme) therapy introduction at an early age.[27]

A prospective, observational study in 2013 established a positive association between stronger pulmonary system at 6-18 years of age and weight-for-age percentile (WAP) >10% at age 4. Patients aged 18 years with WAP >50% at age 4 had less acute exacerbations, limited hospital stay and lower rate of diabetes. Good weight during childhood correlated with greater height, better pulmonary function, reduction in CF complications and improved survival through age 18.[28]

With respect to vitamin D, a 2016 RCT indicated that high-dose vitamin D3 had anti-catabolic effects in pulmonary exacerbations of CF.[1] Another RCT done in 2012 showed a decrease in inflammatory markers, like tumour necrosis factor-alpha (TNF-α) ($p<0.001$, 50.4% decrease) and IL-6 ($p=0.09$, 64.5% decrease) in subjects given high-dose vitamin D during an exacerbation, supporting the role of vitamin D in inflammation regulation.[29] An ongoing RCT is assessing the impact of vitamin D in CF-related pulmonary exacerbation, but is yet to publish its findings[1] A cohort study in 2013 indicated that vitamin D-deficient patients had a substantially higher rate of exacerbations (13.1/10) patient-year compared to patients with vitamin D insufficiency (4.3/10) patient-year.[30] One case-control study in 2012 showed pronounced bacterial colonisation in vitamin D-deficient patients ($p<0.001$) along with increased airway inflammation with increased markers myeloperoxidase (MPO) ($p=0.007$), IL-8 ($p<0.001$), TNF-α ($p=0.03$) and FEV1 decline.[31]

A cross-sectional study in 2016 evaluated folate and vitamin D deficiency, and found an enhanced degree of atopy in patients with folate deficiency and a 2.2 times odd of acquiring at least one asthma exacerbation (95% CI 1.1-4.6). Patients with both folate and vitamin D insufficiencies had eight-fold amplified OR of one or more severe asthma exacerbation (95% CI 2.7-21.6).[32]

A cohort study in 1996 assessed vitamin A status and suggested plasma retinol concentrations regressed in acute pulmonary exacerbation. Overall, 8 of 35 subjects had plasma retinol levels in the deficient range (<0.07micromol/L), mean concentrations of plasma retinol-binding protein (RBP) increased during hospitalisation (1.46 to 2.24 micromol/L), and CRP declined.[33] Another study in 2004 indicated a very large cohort of CF being deficient in antioxidants. Deficiencies of carotenoids and vitamin E occurred in early disease, and antioxidant levels decreased with subsequent lung infections.[34]

Finally, with respect to geographical status and SES, a study in 2016 showed regional variability in hospital stay duration and risks for subsequent hospitalisations for CF patients in the US; with the western region having longer length of inpatient stay. Northeast had decreased risk of hospitalisation ($p=0.038$), and the Caucasians in the south had lower risk compared to African Americans ($p=0.0009$, hazard ratio 0.79)[35] A study in 2011 investigated the impact of SES and found that it had little impact on the treatment of exacerbations, but IV antibiotics were frequently prescribed for patients with low SES.[36] A cohort study in 2017 assessed the association of outcomes, including lower SES and tobacco smoke exposure, and found that these variables had significant correlation with decreased FEV1% predicted, poorer lung function and nutritional decline.[2]

Discussion

Progressive lung disease and functional decline are chief roots of morbidity and mortality in CF. The critical genetic factors noted through literature review were delta F508 mutations and CFTR mutations.[9,10] Homozygous mutations showed a swift regression in pulmonary function compared to heterozygous mutations. High-risk genotype population for CFTR mutations showed pronounced risk for respiratory decline.[8] Severity of mutations was addressed in two studies, showing patients with two severe mutations manifested earlier disease onset and severe respiratory impairment.[7]

Infectious agents highlighted in the studies reported significant P. aeruginosa association with pulmonary exacerbation and respiratory symptoms.[11,12] S. maltophilia[14] and burkholderia (B.) cepacian[13] were among the other infections implicated in causing pulmonary decline. Viral respiratory infection was associated with exacerbations in one of the studies.[15] Inflammatory biomarkers were reported as indicators of acute exacerbations, like CRP, Leukotriene B4 (LTB4) and IL-6.[24] Calprotectin, CRP and VEGF showed a decline in serum and sputum levels following exacerbation treatment, implicating their role in acute episodes and a negative correlation with FEV1.[24] Sputum desmosine levels in a study showed a positive association with inflammation and declined following treatment.[21] Also, sCD14 levels were found to be substantially pronounced in patients who suffered an exacerbation and exhibited a role in predicting subsequent exacerbations.[23] Overall, biomarkers can be used to predict, measure severity and responsiveness of treatment and tailor management.

Studies showed that patients with lower BMI and

pancreatic insufficiency presented with severe lung decline than pancreatic-sufficient patients. Better weight and height were associated with less complications and improved lung function.[27] Vitamin deficiencies were highlighted, showing a positive correlation with pulmonary function and bouts of exacerbations. Vitamin D was also underscored, and it was found to have an anti-catabolic effect and inflammation reduction.[1] In another study, higher incidence of exacerbations and airway inflammation was linked to vitamin D deficiency.[30] Deficiencies of vitamin A, vitamin E, carotenoids and antioxidants showed positive associations with disease progression.[33,34]

Geographic and regional variability was reported in the US, with the western region showing increased risks and subsequent hospitalisations compared to the northeast.[35] Caucasians in the south showed lower risk relative to African Americans. SES was emphasised in two studies, showing that low SES and tobacco exposure had a role in lung function decline, and antibiotics were frequently prescribed to patients belonging to low SES.[2,36]

A systematic review in 2016 defined the rate of pulmonary regression in CF and identified influencing risk factors, while also summarising some findings about potential risk factors similar to the current review.[37]

The current review, along with the mentioned factors, analysed data describing other potential indicators, like S. maltophilia, viral infections and certain biomarkers showing correlations with both progression and management of respiratory disease, stressing their role in aiding diagnosis. We took a step forward and included studies describing low BMI, vitamin deficiencies, pancreatic insufficiency, and keeping pulmonary exacerbation as the main emphasis.

The current review had certain limitations as it could not find any study from South Asia representing the risk factors prevalent in this region. Non-indexed journals and grey literature were not reviewed. Despite the limitations, however, the review calculated risk of bias for studies using standardized tools, such as NOS and the Cochrane risk of bias tools.[5,6] Also, to our knowledge, the current review is the first to highlight major risk factors associated with pulmonary exacerbation that can be used as a guide for future research. On the basis of findings, we strongly stress the need for research in the domains of causes, identification of risk factors, and their roles in overall management of pulmonary exacerbations in CF cases.

Conclusion

Early detection of risk factors can result in prompt diagnosis and abate grave outcomes, reducing overall disease burden and mortality related to pulmonary exacerbations. This can lead to an overall reduced strain on healthcare, ensuring collective cost-effective and efficient management of CF.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

References

1. Tangpricha V, Smith EM, Binongo J, Judd SE, Ziegler TR, Walker S, et al. The Vitamin D for Enhancing the Immune System in Cystic Fibrosis (DISC) trial: Rationale and design of a multi-center, double-blind, placebo-controlled trial of high dose bolus administration of vitamin D3 during acute pulmonary exacerbation of cystic fibrosis. Contemp Clin Trials Commun. 2017; 6:39-45.
2. Ong T, Schechter M, Yang J, Peng L, Emerson J, Gibson RL, et al. EPIC Study Group. Socioeconomic Status, Smoke Exposure, and Health Outcomes in Young Children With Cystic Fibrosis. Pediatrics. 2017; 139:e20162730.
3. Goss CH. Acute Pulmonary Exacerbations in Cystic Fibrosis. Semin Respir Crit Care Med. 2019; 40:792-803.
4. Liberati A, Altman D, Tetzlaff J, Mulrow C, Gotzsche P, Ioannidis J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009; 339:b2700.
5. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyse 2008.[Online] [Cited 2020 May 12]. Available from: URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
6. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011; 10:343:d5928.
7. Geborek A, Hjelte L. Association between genotype and pulmonary phenotype in cystic fibrosis patients with severe mutations. J Cyst Fibros. 2011; 10:187-92.
8. Loubières Y, Grenet D, Simon-Bouy B, Medioni J, Landais P, Férec C, et al. Association between genetically determined pancreatic status and lung disease in adult cystic fibrosis patients. Chest. 2002; 121:73-80.
9. Cogen J, Emerson J, Sanders DB, Ren C, Schechter MS, Gibson RL, et al. Risk factors for lung function decline in a large cohort of young cystic fibrosis patients: Lung Function Decline Risk Factors in Pediatric CF. Pediatr Pulmonol. 2015; 50:763-70.
10. Corey M, Edwards L, Levison H, Knowles M. Longitudinal analysis of pulmonary function decline in patients with cystic fibrosis. J Pediatr. 1997; 131:809-14.
11. Aaron SD, Ramotar K, Ferris W, Vandemheen K, Saginur R, Tullis E, et al. Adult cystic fibrosis exacerbations and new strains of Pseudomonas aeruginosa. Am J Respir Crit Care Med. 2004; 169:811-5.
12. Mayer-Hamblett N, Rosenfeld M, Gibson RL, Ramsey BW, Kulasekara HD, Retsch-Bogart GZ, et al. Pseudomonas aeruginosa in vitro phenotypes distinguish cystic fibrosis infection stages and outcomes. Am J Respir Crit Care Med. 2014; 190:289-97.
13. Horsley A, Jones AM. Antibiotic treatment for Burkholderia cepacia complex in people with cystic fibrosis experiencing a

pulmonary exacerbation. Cochrane Database Syst Rev. 2012; 10:CD009529.
14. Waters V, Yau Y, Prasad S, Lu A, Atenafu E, Crandall I, et al. Stenotrophomonas maltophilia in cystic fibrosis: serologic response and effect on lung disease: Serologic response and effect on lung disease. Am J Respir Crit Care Med. 2011; 183:635-40.
15. Flight WG, Bright-Thomas RJ, Tilston P, Mutton KJ, Guiver M, Morris J, et al. Incidence and clinical impact of respiratory viruses in adults with cystic fibrosis. Thorax. 2014; 69:247-53.
16. Quon BS, Dai DLY, Hollander Z, Ng RT, Tebbutt SJ, Man SFP, et al. Discovery of novel plasma protein biomarkers to predict imminent cystic fibrosis pulmonary exacerbations using multiple reaction monitoring mass spectrometry. Thorax. 2016; 71:216-22.
17. Reid DW, Misso N, Aggarwal S, Thompson PJ, Walters EH. Oxidative stress and lipid-derived inflammatory mediators during acute exacerbations of cystic fibrosis. Respirology. 2007; 12:63-9.
18. Wojewodka G, De Sanctis JB, Bernier J, Bérubé J, Ahlgren HG, Gruber J, et al. Candidate markers associated with the probability of future pulmonary exacerbations in cystic fibrosis patients. PLoS One. 2014; 9:e88567.
19. Taylor CJ, McGaw J, Rigby AS, Threlfall D, Karmel J. Pilot safety study of liposomal prostaglandin (PGE1) in respiratory exacerbations in cystic fibrosis. J Cyst Fibros. 2002; 1:90-3.
20. McGrath LT, Mallon P, Dowey L, Silke B, McClean E, McDonnell M, et al. Oxidative stress during acute respiratory exacerbations in cystic fibrosis. Thorax. 1999; 54:518-23.
21. Laguna TA, Wagner BD, Luckey HK, Mann SA, Sagel SD, Regelmann W, et al. Sputum desmosine during hospital admission for pulmonary exacerbation in cystic fibrosis. Chest. 2009; 136:1561-8.
22. Louw JJ, Toelen J, Proesmans M, Vermeulen F, Billen J, de Boeck K. Serum procalcitonin is not an early marker of pulmonary exacerbation in children with cystic fibrosis. Eur J Pediatr. 2012; 171:139-42.
23. Quon BS, Ngan DA, Wilcox PG, Man SFP, Sin DD. Plasma sCD14 as a biomarker to predict pulmonary exacerbations in cystic fibrosis. PLoS One. 2014; 9:e89341.
24. Gray RD, Imrie M, Boyd AC, Porteous D, Innes JA, Greening AP. Sputum and serum calprotectin are useful biomarkers during CF exacerbation. J Cyst Fibros. 2010; 9:193-8.
25. McColley SA, Stellmach V, Boas SR, Jain M, Crawford SE. Serum vascular endothelial growth factor is elevated in cystic fibrosis and decreases with treatment of acute pulmonary exacerbation. Am J Respir Crit Care Med. 2000; 161:1877-80.
26. Kerem E, Viviani L, Zolin A, MacNeill S, Hatziagorou E, Ellemunter H, et al. Factors associated with FEV1 decline in cystic fibrosis: analysis of the ECFS patient registry. Eur Respir J. 2014; 43:125-33.
27. McPhail GL, Acton JD, Fenchel MC, Amin RS, Seid M. Improvements in lung function outcomes in children with cystic fibrosis are associated with better nutrition, fewer chronic pseudomonas aeruginosa infections, and dornase alfa use. J Pediatr. 2008; 153:752-7.
28. Yen EH, Quinton H, Borowitz D. Better nutritional status in early childhood is associated with improved clinical outcomes and survival in patients with cystic fibrosis. J Pediatr. 2013; 162:530-5.
29. Grossmann RE, Zughaier SM, Liu S, Lyles RH, Tangpricha V. Impact of vitamin D supplementation on markers of inflammation in adults with cystic fibrosis hospitalized for a pulmonary exacerbation. Eur J Clin Nutr. 2012; 66:1072-4.
30. McCauley LA, Thomas W, Laguna TA, Regelmann WE, Moran A, Polgreen LE. Vitamin D deficiency is associated with pulmonary exacerbations in children with cystic fibrosis. Ann Am Thorac Soc. 2014; 11:198-204.
31. Chalmers JD, McHugh BJ, Docherty C, Govan JRW, Hill AT. Vitamin-D deficiency is associated with chronic bacterial colonisation and disease severity in bronchiectasis. Thorax. 2013; 68:39-47.
32. Blatter J, Brehm JM, Sordillo J, Forno E, Boutaoui N, Acosta-Pérez E, et al. Folate deficiency, atopy, and severe asthma exacerbations in Puerto rican children. Ann Am Thorac Soc. 2016; 13:223-30.
33. Duggan C, Colin AA, Agil A, Higgins L, Rifai N. Vitamin A status in acute exacerbations of cystic fibrosis. Am J Clin Nutr. 1996; 64:635-9.
34. Lagrange-Puget M, Durieu I, Ecochard R, Abbas-Chorfa F, Drai J, Steghens J-P, et al. Longitudinal study of oxidative status in 312 cystic fibrosis patients in stable state and during bronchial exacerbation. Pediatr Pulmonol. 2004; 38:43-9.
35. Kopp BT, Nicholson L, Paul G, Tobias J, Ramanathan C, Hayes D Jr. The geographic impact on hospitalization in patients with cystic fibrosis. J Pediatr. 2016; 170:246-52.
36. Schechter MS, McColley SA, Regelmann W, Millar SJ, Pasta DJ, Wagener JS, et al. Socioeconomic status and the likelihood of antibiotic treatment for signs and symptoms of pulmonary exacerbation in children with cystic fibrosis. J Pediatr. 2011; 159:819-24.
37. Harun SN, Wainwright C, Klein K, Hennig S. A systematic review of studies examining the rate of lung function decline in patients with cystic fibrosis. Paediatr Respir Rev. 2016; 20:55-66.