International Validation of the "DECAF score" to predict disease severity and hospital mortality in acute exacerbations of COPD in the United Arab Emirates

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Abstract

Background:

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide. Acute exacerbation of COPD (AECOPD) is a concern due to its high mortality rate and negative outcomes in patient care. Therefore, tools that can predict the severity of the disease and inpatient mortality have gained much attention. In this regard, the Dyspnoea, Eosinopenia, Consolidation, Acidaemia, and Atrial Fibrillation (DECAF) score was adopted in many hospital settings for AECOPD patients in the United Kingdom because of its ease of use and effectiveness. However, less is known about its accuracy and association with patient clinical outcomes in worldwide healthcare systems, with no information available in the Middle East.

Objectives:

To validate the DECAF score for predicting inpatient death due to AECOPD and investigate whether the DECAF score can predict disease severity, hospital readmission, and length of hospital stay in a Middle Eastern healthcare setting. Furthermore, this study aimed to assess factors associated with inpatient death due to AECOPD.

Methods:

This was a retrospective observational study conducted between 2019 and 2021 in 19 hospitals in the United Arab Emirates. Data were retrieved from the electronic records of patients admitted for acute exacerbation of chronic obstructive pulmonary disease (AECOPD) in 17 hospitals across six Emirates. Patients who were diagnosed with AECOPD, aged over 35 years, were included in the study. There were three major primary outcomes for this thesis: 1) the validation of the DECAF Score for inpatient death, 30-day death, and 90-day readmission, 2) length of stay across DECAF scores, and 3) differences in the means of blood pH, eosinophils, C-reactive protein (CRP), and urea across patients with different DECAF scores. In addition to descriptive statistics, the validation of the DECAF score using the area under the receiver operator curve (AUROC) for inpatient death, 30-days death, and 90-day readmission was performed. The Hosmer-Lemeshow statistic and Nagelkerke statistic were used to assess the model fitness. The mean length of stay and laboratory markers (pH, eosinophil, CRP, and urea) across patients with different DECAF scores were compared using the ANOVA test, and p-values less than 0.05 were considered significant results. Error bar tests with 95% confidence intervals (CI) were used to measure differences in the

proportions of patients with atrial fibrillation and activity tolerance across the DECAF score. The Statistical Package for the Social Sciences (SPSS) version 26 was used for data analysis.

Results:

Of the 512 patients included in the study, 169 (33.0%) were females, and 64 (12.5%) were smokers. The mean (SD) age and length of stay in the hospital were 73.3 (11.9) years and 14.3 (32.5) days, respectively. The incidence of inpatient death and 90-day readmission was 24.4% and 35.9%, respectively. The median DECAF score was 3 [IQR: 1-6]. The top three comorbidities were hypertension (48.3%), diabetes (45.4%), and atrial fibrillation (45.2%). The AUROC DECAF curves for inpatient death, 30-days death, and 90-day readmission were 0.8 (95% CI: 0.8-0.9), 0.8 (95% CI: 0.7-0.8), and 0.8 (95% CI: 0.8-0.8), respectively. The model was a satisfactory fit to the data (Hosmer-Lemeshow statistic = 0.195, Nagelkerke R2 = 31.7%). There were significant differences in means of the length of stay across patients with different DECAF scores ($p = 0.008$). The highest mean (SD) length of stay in days was seen in patients with a DECAF score of 6, 29.8 (31.4), and the lowest value was reported in patients with a 0 DECAF score of 3.6 (2.0). There was no significant difference in serum albumin levels across patient death statuses. Additionally, BMI categories were not associated with inpatient death.

Conclusion:

The DECAF score shows strong predictive performance for the high levels of inpatient mortality, 30-day mortality, and 90-day readmission in the UAE setting. Additionally, the DECAF score can predict clinical parameters that can be helpful in clinical decision making.

Keywords

AECOPD, DECAF score, UAE, COPD

Dedication

I dedicate my dissertation work to my family and many friends. Special gratitude to my loving husband, Khalfan Alabdouli, whose words of encouragement and push for perseverance keep ringing in my ears. My parents, Ahmed and Maryam, have never left me and always pray for me.

I dedicate this work and give special thanks to my lovely family, and my siblings for supporting me throughout the entire doctorate program. All of you have been my best cheerleaders. I dedicate this work and give special thanks to my friend, Amal Alseriedi and Sheikha AlKhatri, for agreeing to be there for any help.

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Abbreviation

AECOPD	Acute Exacerbation of Chronic Obstructive Pulmonary Diseases
ATS	American Thoracic Society
COPD	Chronic Obstructive Pulmonary Diseases
NIV	Non-Invasive Ventilation
UAE	United Arab Emirates
UK	United Kingdom
US	United States
DECAF	The Dyspnoea, Eosinopenia, Consolidation, Academia, and Atrial Fibrillation
CURB-65	The Confusion, respiratory rate, and Blood pressure score
MENA	Middle East and North Africa
CVD	Cardiovascular disease
BOLD	The burden of obstructive lung disease
FEV1	Forced expiratory volume
GOLD	Global Initiative for Chronic Obstructive Lung Disease
WHO	World Health Organization (WHO)
BTS	British Thoracic Society
ETS	European Thoracic Society
GCL	Glutamate cysteine ligase
SPSS	SPSS
CRP	C-reactive protein
SN	optimal sensitivity

PEF	peak expiratory flow
eMRCD	extended Medical Research Council Dyspnoea score
NSVT	non-sustained ventricular tachycardia
MAT	multifocal atrial tachycardia
AFL	atrial flutter
GSTM1	glutathione S-transferase M1
CAT	COPD assessment test
BMI	Body mass index
GERD	Gastroesophageal reflux disease
MDI	Metered dose inhaler
AF	Atrial fibrillation
IL	Interleukin

Chapter 1. Introduction

Background and Research Context

Chronic obstructive pulmonary disease (COPD) is a major condition affecting the lungs and characterised by irreversible airflow obstruction. It is a forward progressive, chronic respiratory condition and is one of the most common global respiratory diseases (Terzikhan *et al.*, 2016; Woldeamanuel, Mingude and Geta, 2019) with a considerable burden of morbidity and mortality. The disease is not correctable, yet it is possible to live with, despite its severity. COPD is mainly caused by tobacco smoking, second-hand smoking, biomass fuels, noxious substance inhalation, and ageing (Terzikhan *et al.*, 2016). The severity of the disease is characterized by one or more airway disorders. The most predominant clinical features of the disease are the structural changes caused by the inflammation and the mucociliary dysfunction (Ruvuna and Sood, 2020). Exacerbations of chronic obstructive pulmonary disease (ECOPD) are a well-known complication of COPD all over the World. It affects the individual's quality of life negatively, and the symptoms may continue for several weeks (MacNee, 2005; Zhou *et al.*, 2012; Ruvuna and Sood, 2020). Acute exacerbation of COPD (AECOPD) are a major risk factor for hospitalisation and are linked with severe respiratory problems and even complete lung failure. Furthermore, AECOPD can deteriorate patients' quality of life and cause death in 4.4% to 7.7% of the AECOPD cases (MacNee, 2005). AECOPD has received much attention over the last decades and appropriate management is a challenging area in the field of disease burden. That is because the global number of COPD patients is increasing, and the World Health Organization (WHO) anticipated that COPD will rank as the third disease that causes death after ischemic heart disease and cerebrovascular disease in 2020 (Woldeamanuel, Mingude and Geta, 2019). Hospital admission due to hypercapnia exacerbation will have an in-hospital mortality of up to roughly 10%. If patients are ventilated during the admission, the mortality approaches about 40% one year after discharge. (Mannino and Buist, 2007). As a result of its severity and trends worldwide, COPD therefore has a huge burden in healthcare utilization with hospital-admission recurrences and intensive therapy required (Mannino and Buist, 2007). The complex disease burden of COPD needs to be tackled by a thorough strategy that includes prevention, immediate diagnosis, and exacerbations. COPD exacerbation can be triggered by respiratory infection, air pollution, congestive heart failure, pulmonary embolism and interruption of maintenance therapy (Calverley *et al.*, 2003). And about one-third of exacerbation are not recognized. When exacerbations occur once or twice yearly, the COPD patients are recognised as a "frequent exacerbation". Acute exacerbations impact the course

of the disease treatment. These exacerbated cases have a healthcare and economic burden in societies. Previous studies in Spain indicated that 10 out of 100 admissions are due to COPD crises, and 2% of emergency visits are due to exacerbations (García-Sanz *et al.*, 2012). Healthcare professionals therefore face a serious challenge regarding an accurate and reliable prediction instrument of the AECOPD prognosis in hospitalised patients (Gunen *et al.*, 2005). This potential instrument may help in appropriate allocations of resources, reducing risks of mortality, adopting new diagnostic measures, advancing information management, and improving quality of life for patients with AECOPD. The Diagnosis of AECOPD is based on the development of the disease symptoms such as dyspnoea, cough, and/ or sputum production. It is important to determine the vital biomarkers for management and prevention of COPD disease worsening (Burkhardt and Pankow, 2014; Pascual-Guardia *et al.*, 2017). Such Biomarkers have the potential to mitigate the frequencies of the exacerbations and finally have a beneficial impact on the outcomes (Burkhardt and Pankow, 2014), through guiding personalised treatment. Currently available data prior to the use of DECAF, have not indicated the hospital length of stay of AECOPD patients. Multiple prognostic indices related to higher death rates in COPD include; Patient age, initial FEV1 (5), comorbidities (6), body mass index, serum albumin/sodium levels, PaCO2 levels (8), and Hypoxemia (9). Studies assessing prognostic factors in AECOPD hospitalized patients have been performed infrequently (Dijk *et al.*, 2011) and reliable scores have not yet been created to assist in AECOPD management. The BODE score is a robust tool in predicting mortality of stable chronic obstructive pulmonary disease COPD. The conventional scores available have mainly been developed and performed in stable-COPD cases to forecast mortality risk for admitted patients.

In 2012, J Steer and his colleagues (Steer, Gibson and Bourke, 2012) created a new, prognostic score to predict the severity and in-patient mortality of acute COPD exacerbation that was well received and supported in the scientific literature. In this regard, The Dyspnoea, Eosinopenia, Consolidation, Acidaemia, and atrial Fibrillation (DECAF) score was adopted in many hospital settings for AECOPD patients because of its ease of use and effectiveness (Steer, Gibson and Bourke, 2012), predominantly in the UK clinical setting within the National Health Service (NHS). The main aim of the DECAF score is to predict inpatient death using readily available markers and findings available in the electronic patient records. This also involves the use of the extended Medical Research Council Dyspnoea score (eMRCD) (Sangwan, Chaudhry and Malik, 2017). This

tool includes five predictors. Namely: Dyspnoea (eMRCD), Eosinopenia, Consolidation, Acidaemia and Atrial Fibrillation.

The DECAF score helps healthcare providers stratify the patient into risk categories- DECAF 0-1 (low risk); DECAF 2 (moderate risk); and DECAF 3–6 (high risk) - with the aim of thereby reducing mortality and morbidity, through appropriate treatment and patient stratification (Echevarria *et al.*, 2016). The DECAF score is a robust tool for predicting in-hospital mortality from AECOPD. DECAF assimilates typically available indicators at admission, and it assists in deciding the level of care, augmenting the care with ventilator support (Echevarria et al., 2018). Thus, it will direct healthcare professionals to the most rational use of resources, reducing mortality and morbidity. Although DECAF score was recommended by health authorities in the UK and has been used in many countries, it needs validation to ensure its predictive effectiveness and accuracy, before being formally adopted in the Middle Eastern healthcare setting. Therefore, this multicentre PhD study attempts to validate the DECAF score and re-assess its predictive effectiveness for short, medium, and long-term inpatient deaths of AECOPD patients in the UAE.

Statement of Research Problem

Mortality cases caused by AECOPD are preventable if accurate prediction and interventions are adopted. In addition, the quality of life for patients admitted to hospitals due to AECOPOD can be improved. However, the performance of the tools required to predict these cases cannot be guaranteed without validation. The main goal of validation is to ensure that the DECAF tool is assessing what it is supposed to assess (Lai, 2013). In terms of the DECAF score, although it has been tested for validation in other countries, such as the United Kingdom (Echevarria *et al.*, 2015, 2016), their findings may not be generalizable to other settings and countries without performing prediction model studies in these settings and countries.

Research Questions

The first research question in this thesis was "*can DECAF score predict inpatient mortality in general and 30-day inpatient mortality?*" This question will be addressed by validating the DECAF score. The findings will offer insight into the accuracy and predictive performance of the DECAF score in the UAE. Eventually, we will know whether this tool has the potential to prevent

inpatient mortality due to AECOPD. The second question was, "*Can DECAF score predict 90-day readmission?*" This question is important given that hospital readmission is associated with deterioration of patients' quality of life and increased burden on healthcare facilities and practitioners. Additionally, some studies found that hospital readmission is associated with increased risk of inpatient death (Upadhyay, Stephenson and Smith, 2019). The third research question in this thesis was, "*Can DECAF score predict the duration of hospital stay?"* While duration of hospital stay is multifactorial, DECAF score may be helpful in predict the longer duration cases and thus provide them with prioritised special care and improve their clinical features. Although other factors cannot be ruled out, addressing this question will help in providing a better understanding of DECAF score predictive performance. The fourth question was, "*Can DECAF score predict the status of patients in terms of needing assistance on daily activities*?" Addressing this question will shed light on the personal needs of AECOPD patients. If the answer to this question is yes, then the hospital administration and patients' relatives will be notified to take measures and provide patients with proper care. Finally, "*What are the individual and possibly factors that can affect mortality rate?*" Although this study did not address causality, addressing this question will offer insight into probable factors that may influence the inpatient death. These factors include sex, age, body mass index (BMI), duration of hospital stay, and pulse rate at admission.

Thesis Design

This thesis was structured to include seven chapters. The first chapter describes the research context, problem, questions, objectives, and significance. The second chapter summarises the theoretical framework of the research programme. The third chapter presents a comprehensive review of the published literature on validation of DECAF score and diagnostic tools used for the benefit of AECOPD patients. The fourth chapter describes the methods developed and adopted to fulfil the research purposes. This includes the study design and setting, research instrument, participants' criteria and data collection, study outcomes, and data analysis. The fifth chapter is chiefly concerned with the presentation of the study findings. The sixth chapter discusses the study findings and its implications in the context of the literature and plausible explanations. Also need a chapter, which can be few pages or many which details how the PhD was affected by the pandemic.

The final chapter presents the study conclusion, recommendation, and limitations.

Chapter 2. Theoretical Framework of the Research Programme

2.1. Chronic Obstructive Pulmonary Disease History

The Greek verb “aazein” means ‘hard breath’. Aristaeus of Cappadocia, the Greek practitioner who worked in Rome circa 200 CE, is credited as the first to describe this symptom in humans (May and Li, 2015). Aristaeus was therefore a breakthrough clinician who worked with the observational studies and incorporated a lot in allowing clinical medication to advance. After that, a Persian physician Ibn Sinai clarified disease epidemiology, aetiology and disease categorization. Furthermore, he mentioned the other cardinal factors incorporated into the condition: food, drink, air, residence, occupation, habits, age, and sex (Lange *et al.*, 2012).At the commencement of the 16th century, a group of elite scientists showed great enthusiasm in what they could detect from autopsies. In 1679, the initial scientist Théophile Bonet linked dyspnoea to the lung bloated by air (Mannino and Buist, 2007). In the connection between the disease findings and the manifestations, Bonet created the disease mechanisms -a comprehensive approach- involving signs, symptoms, and aetiology over time (Franchi M., 2010). Throughout the 19th century, the evaluation of pulmonary function progressed considerably and in 1816, René-Théophile-Hyacinthe Laennec invented the stethoscope (May and Li, 2015); as a doctors′ ears cannot detect the symptoms clearly alone. Although stethoscopes are considered good for detecting rales and wheeze, there was still no convenient tools to assess lung function. The first clinical recognition of the COPD types can be referred to Badham in 1814, who invented the word “catarrh”, including severe cough and secretion of mucous, which are the main manifestations of the disease. In the 19th century John Hutchinson created a machine dedicated for evaluating lung function called the “the spirometer”. These apparatuses delivered a new concept to pulmonary function testing by unifying the functional test for standardized observation and intervention in patients.

2.1.1. COPD Definitions

In the last century, there were several international debates and discussions on the definition and management of COPD. As a result, several guidelines such as the American Thoracic Society (ATS), the European Respiratory Society’s (ERS), and the British Thoracic Society’s (BTS) were produced. In the early beginning of this century, an international cooperation between the US heart, Lung, and Blood institute and the World Health Organization (WHO) resulted in creating a global guideline for COPD, which was the Global Initiative for Chronic Obstructive Lung Disease (GOLD). **Table** 1 summarises the most common definitions of COPD. According to these

guidelines, COPD can be regarded as an umbrella term that includes several different pathologies which importantly includes emphysema and chronic bronchitis. In Emphysema, the pulmonary air sacs are damaged and lose elasticity with impaired air exchanging and the waste product of breathing trapped inside the alveoli. Chronic bronchitis is defined by mucus hypersecretion due to increased number of secretory goblet cells as a result of chronic airway irritation and remodelling. Damaged cilia means that the movement of mucus is impaired. This can lead to airflow limitation due to decreased radius of the airways involved and can lead to airway occlusion with mucus plugs. The prevalence of chronic bronchitis ranges from 3% to 7% among healthy individuals. Nonetheless, among COPD patients, the prevalence of chronic bronchitis approaches 74% (Ferré *et al.*, 2012).

Table 1. A Summary of COPD Definitions according to current international guidelines.

Organization	Definition	Elements included	Elements absent
ATS	"COPD is a disease characterised by the presence of airflow obstruction due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway hyper reactivity, and may be partially reversible". Further," COPD may include a significant reversible component and some patients with asthma may go on to develop irreversible airflow obstruction indistinguishable from COPD" (Celli et al., 2015)	1- Presence of airflow obstruction 2- Caused by chronic bronchitis or emphysema 3- Progressive in nature 4- May be accompanied by airway hyperreactivity 5- May be partially reversible 6- Can have a significant reversible component	1- Specific causes or risk factors of COPD 2- Severity or stages of COPD 3- Outcomes or complications of COPD 4- Diagnostic criteria or methods for identifying COPD
ERS	"COPD is a disorder characterised by reduced maximum expiratory flow, and slow forced emptying of the lungs; features which do not change markedly over several months. Most of the airflow limitation is slowly progressive and irreversible. The airflow limitation is due to varying combinations of	1- Reduced maximum expiratory flow 2- Slow forced emptying of the lungs 3- Features that do not change markedly over several months 4- Airflow limitation that is slowly progressive and irreversible 5- Airflow limitation due to varying combinations of	1- The comment that asthma may overlap with COPD 2- The mention of COPD as a common, preventable, and incurable disease

Organization	Definition	Elements included	Elements absent
	airway disease and emphysema; the relative contribution of the two processes are difficult to define in vivo" Emphysema is defined anatomically chronic bronchitis's defined clinically. Further, the guidelines states that "the most difficult problem is distinguishing COPD from chronic airflow limitation of chronic asthma in older subjects" Also, "the distinction may sometimes be impossible" (Celli et al., 2015)	airway disease and emphysema 6- Difficulty in defining the relative contribution of airway disease and emphysema in vi	
BTS	"COPD is a general term which covers many previously used clinical labels that are now recognised as being different aspects of the same problem. Diagnostic labels encompassed by COPD include: chronic bronchitis, emphysema, chronic obstructive airway disease, chronic airflow limitation and some cases of chronic asthma" (BTS, 2019)	1- General term 2- Encompasses many previously used clinical labels 3- Some cases of chronic asthma 4- Diagnostic labels	1- Details about the specific symptoms or features that are characteristic of COPD. 3- Information on the causes or risk factors that may contribute to the development of COPD.

Organization	Definition	Elements included	Elements absent
GOLD	"COPD is a disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases". There is a comment that asthma may overlap with COPD. The guideline also states that "COPD is a common, preventable, and incurable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. The chronic airflow limitation that characterizes COPD is caused by a mixture of small airways disease (e.g., obstructive bronchiolitis) and parenchymal destruction	1- Disease state characterized by airflow limitation 2- Airflow limitation is usually both progressive and associated with abnormal inflammatory response of lungs to noxious particles or gases 3- Chronic respiratory symptoms 4- Airflow limitation due to airway and/or alveolar abnormalities 5- Small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema) contribute to chronic airflow limitation 6- Chronic inflammation causes structural changes, small airways narrowing, and destruction of lung parenchyma 7- Loss of small airways may contribute to airflow limitation and mucociliary dysfunction	Not applicable

Organization	Definition	Elements included	Elements absent
	(emphysema), the relative contributions of which vary from person to person. Chronic inflammation causes structural changes, small airways narrowing, and destruction of lung parenchyma. A loss of small airways may contribute to airflow limitation and mucociliary dysfunction, a characteristic feature of the disease" (Global Initiative for Chronic Obstructive Lung Disease, 2020)	8- Asthma may overlap with COPD	

GOLD (Global Initiative for Chronic Obstructive Lung Disease) is a collaborative project established to improve lives worldwide for people affected by chronic obstructive pulmonary disease (COPD). GOLD provides evidence-based guidelines for its diagnosis, management and prevention as well as working toward raising understanding among healthcare providers, policy makers and members of the general public alike. The British Thoracic Society (BTS), located in England and Wales, is an influential professional society of respiratory specialists such as doctors, nurses and other healthcare workers who focus on respiratory conditions. They develop and promote best practice within respiratory medicine while producing guidelines on diagnosis, treatment and management of respiratory disease. ERS stands for European Respiratory Society and is a not-for-profit medical organization dedicated to improving lung health and patient care within respiratory medicine. Through research, education, advocacy activities and networking events the society brings together physicians from over 140 countries as they share knowledge and best practices related to respiratory medicine - organizing conferences, publishing research findings, offering education programs for healthcare providers as well as advocating policies which support respiratory health globally. The American Thoracic Society (ATS) is an international professional organization focused on respiratory and critical care medicine with a mission of improving global health through advanced research, clinical care and public health initiatives in respiratory disease, critical illness and sleep disorders. To support its goals the Society offers education, advocacy and funding support as well as guidelines and recommendations that outline best practice in respiratory critical care medicine practice.

2.2. Pathophysiology of COPD

COPD is a severe condition of the inflamed airway, lung parenchyma, and pulmonary vasculature (MacNee, 2006). This has been hypothesised to happen as a result of a defect in the equilibrium between oxidative stress and protease-antiprotease defences (Cukic *et al.*, 2012). This defect plays a vital role in the destruction of the air sacs and eventually leads to pulmonary airway failure especially during exhalation. Hogg et al (Hogg *et al.*, 2004), investigated the nature of small airways in COPD and found potential destruction with up to 30% loss of small airways. They also found that this destruction might have been caused by accumulated mucous triggered by the immune response. COPD can result in a decrease in the forced expiratory volume (FEV1) and severe tissue damage, which lead to airway blockage and gas exchange deterioration. The inflammatory response and obstruction of the airways causes a decrease in the forced expiratory volume (FEV1), and tissue destruction leads to airflow limitation and impaired gas exchange. Hyperinflation is generally seen in x-ray images and is strongly related to abnormal retention of air in the lungs where it is difficult to exhale efficiently (Hogg, 2004). The incompetent complete exhalation can cause a high level of carbon dioxide (CO_2). Overall, airways inflammation is present in almost all cigarette smokers. Nevertheless, COPD patients' response to smoking is amplified and usually leads to hypersecretion of mucous, tissue damage, and impairing the physical mechanisms for defence in the airways (Eapen and Sohal, 2019). In exacerbations of chronic obstructive pulmonary disease (COPD), the measures of patients' dyspnoea, cough, or sputum production change, which is enough to change disease management. The occurrence and recurrence of acute exacerbations is one of the most influential factors that affects the quality of life of patients (Seemungalet al., 1998, Doll & Miravitlles, 2005, Bourbeau et al., 2007). The number of episodes relate to hospital admission and readmission. These will impact daily activities and hence the total quality of life as well. There are several driving factors for COPD exacerbations; these include pathogens (bacteria, viruses) and air pollutants (David *et al.*, 2021). These factors are responsible for worsening the airway inflammation and eventually leading to a decline in lung function in COPD patients (**Figure 1**).

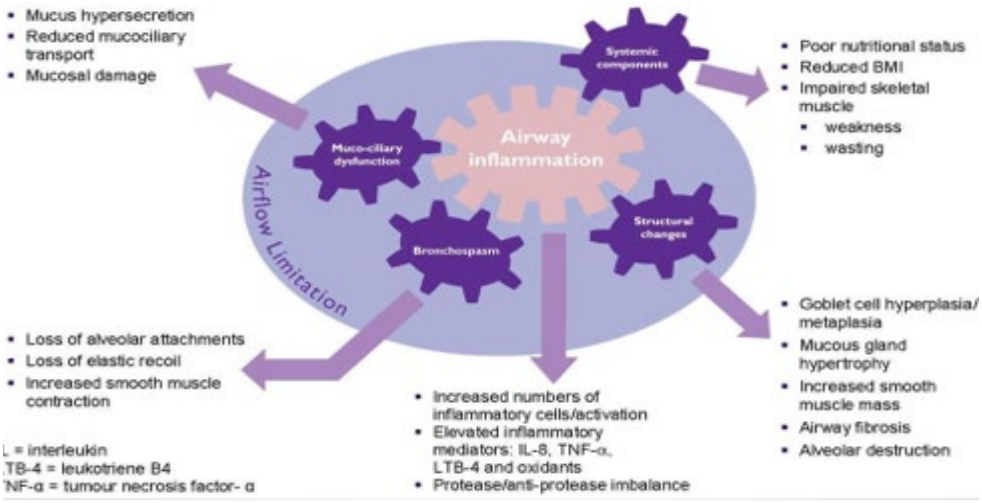

Figure 1. Pathophysiology of COPD (Cukic et al., 2012). ***This figure depicts the pathophysiology of COPD, which involves multiple structural and functional changes within the respiratory system. Key aspects of its pathology can be seen here such as: Structural Changes: COPD has been linked with many structural alterations of the respiratory system, such as airway remodelling, loss of lung tissue elasticity and expansion of air spaces. Bronchospasm: COPD can lead to increased smooth muscle contraction in the bronchi, narrowing airways and decreasing airflow. This condition, called Bronchospasm, causes airways to narrow further limiting their capacity and decreasing airflow. Mucociliary Dysfunction: With COPD comes impaired function of the Mucociliary escalator that normally assists with clearing away mucus and debris from the respiratory tract. This process must happen regularly for smooth functioning; otherwise COPD can worsen over time with significant increase in symptoms. COPD can also lead to systemic inflammation and stress on other organs in the body leading to potential organ and system dysfunctions.***

These changes include hypersecretion of the glycoprotein-rich gel-like secretion mucus, airflow obstruction, defects in gas exchange, increases in the pulmonary arterial pressure, and even systemic effects (MacNee, 2006). The first physiological outcome is mucous hypersecretion, which can cause chronic productive cough. Nonetheless, this outcome is not prevalent in all COPD patients (David *et al.*, 2021).The increase in mucous secretion can be attributed to an increased numbers of goblet cells and to the changes in submucosal glands (Hogg, 2004). The second outcome is airflow obstruction and air trapping, which takes place in small airways with less than 2mm diameter. Specifically, the alveolar walls which are responsible for lung elastic recoil, are destructed in these cases, which causes the airway obstruction (Maltais *et al.*, 2014; Garvey *et al.*, 2016). Upon expiration, the air is trapped due to airway closure and obstruction, and this leads to hyperinflation, which can cause breathlessness.

In AECOPD, airway obstruction caused the air to be trapped during expiration and this leads to Static hyperinflation (SH), which can be seen in severe cases. Static hyperinflation is caused by entrapment of air during expiration, due to peripheral airway obstruction. SH is combined with a decrease in inspiratory capacity (IC), causing severe dyspnoea, and an increase in functional

residual capacity (FRC). Another hyperinflation that occurs in severe cases of AECOPD is the dynamic hyperinflation (DH), which is characterised by an increase in end-expiratory lung volume. This type of hyperinflation can be used as a key predictor for activity tolerance.

In patients with moderate-to-severe chronic obstructive pulmonary disease (COPD), end-expiratory lung volume increases under conditions of greater minute ventilation (e.g. exercise). This abnormal response is termed dynamic hyperinflation (DH) and has now been recognised as a key determinant of symptomatology and exercise intolerance in COPD. The published literature shows that FEV1 does not give adequate diagnosis for COPD and more markers and parameters should be used for monitoring of COPD cases. These parameters comprise IC, FVC, and FVC. The third outcome is abnormal gas exchange, which is a result of respiratory anatomical changes found in this condition. The main feature for this phase is arterial hypoxaemia.

The nature and competency in gas transfer is crucial in lungs' function. Measuring the pulmonary diffusing capacity for carbon monoxide (CO) in COPD can give an indication of structural and functional status of lungs, given that COPD may cause severe damage to the alveoli, leading to deterioration of gas transfer.

The fourth outcome, which occurs simultaneously with the third one is pulmonary arterial hypertension (Qaseem *et al.*, 2011). This outcome can be caused by the construction or remodelling (hypertrophy of smooth muscles) of the respiratory arteries, destruction of the endothelium or the capillary beds **(Figure 2**) (Eapen and Sohal, 2019).

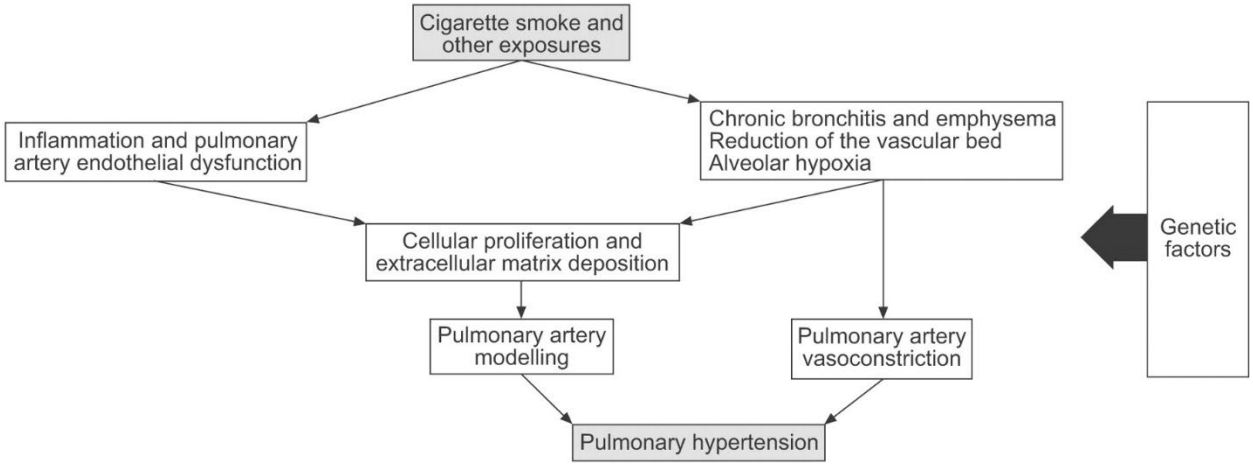

Figure 2. Pulmonary Hypertension in COPD (Chaouat, 2008). ***This figure depicts the pathophysiology of pulmonary hypertension, aserious medical condition characterized by increased resistance to blood flow within the pulmonary circulation. COPD is an important and under appreciated cause of pulmonary hypertension.. Two key mechanisms underlying pulmonary hypertension are depicted herein; Artery Remodelling: Pulmonary hypertension results from structural changes to pulmonary arteries that include thickening and narrowing of their lumen, increased smooth muscle proliferation and extracellular matrix deposition; all contributing to greater resistance to blood flow as well as elevated pulmonary arterial pressures. Vasoconstriction: Pulmonary hypertension not only leads to arterial remodelling but also involves vasoconstriction in pulmonary arterioles that leads to increased pressure in pulmonary arteries as well as resistance against blood flow. This further contributes to higher pressures within these arterioles as well as greater resistance against flow resistance.***

The final outcome is systemic effects, which can involve loss of skeletal muscle mass and capacity that reduces exercise tolerance. This is thought to arise as a result of systemic inflammation as shown by studies which show increased levels of inflammatory markers including CRP, IL-6, and fibrinogen levels. A previous study (Gan et al., 2004) concluded that impairment in lung's function was significantly associated with sharp increase in inflammatory markers levels, which may directly influence pharmacological and pathological features of patients with stable COPD. Similar to stable COPD, elevated levels of CRP, leukocytes, and fibrinogen are seen in AECOPD.

Asthma/COPD Overlap Patients

The aetiology and pathogenesis of the COPD in such patients may be different from that of patients with chronic bronchitis or emphysema. Subsets of patients with chronic bronchitis, COPD, emphysema, and asthma and their intersection with airflow obstruction or airflow limitation (AFL) and each other are shown in **(figure 3)**. Patients with asthma whose airflow obstruction is

reversible (normalizing) (subset 9), are not considered to have COPD. In some cases, it can be extremely challenging to distinguish between patients with asthma whose airflow obstruction does not fully recover and those with chronic bronchitis or COPD who have partly reversible airflow obstruction accompanied by airway hyper reactivity. Thus, some patients with unremitting asthma are classified as having COPD as shown by subsets 6, 7 and 8. Emphysema with AFL and chronic bronchitis with AFL comprise COPD patients, and are depicted in the darker circles labelled as subsets 3 and 4. Chronic bronchitis and emphysema with airflow obstruction often occur together as seen in subset 5, and some patients may have asthma associated with these two disorders as in subset 8. Individuals with asthma exposed to chronic irritation, as from cigarette smoke, may develop chronic productive cough, a feature of chronic bronchitis shown in subset 6. Such patients are often referred to in the United States as having asthmatic bronchitis or the asthmatic form of COPD. People with chronic bronchitis or emphysema without airflow obstruction, shown by subsets 1,2,11, are not classified as having COPD. Airflow obstruction can be totally reversible in the asthmatic patient, and the asthma patients are not considered sufferers from COPD. Whereas asthmatic patient with incomplete reversibility of airflow limitation may be considered to have COPD (Cukic *et al.*, 2012). Chronic bronchitis and emphysema with airflow obstruction frequently occur together and some of these patients may have asthma. Individuals with asthma may develop a chronic productive cough, either spontaneously or due to exposure; Asthmatic bronchitis, although this terminology has not been officially endorsed in clinical practice guidelines. Patients with asthma may develop a spontaneous chronic productive cough or it may be caused due to exposure to defined triggers e.g., cigarette smoke, or an allergen (Petty, Silvers and Stanford, 1987; Rosenbloom, 1991; Cukic *et al.*, 2012).

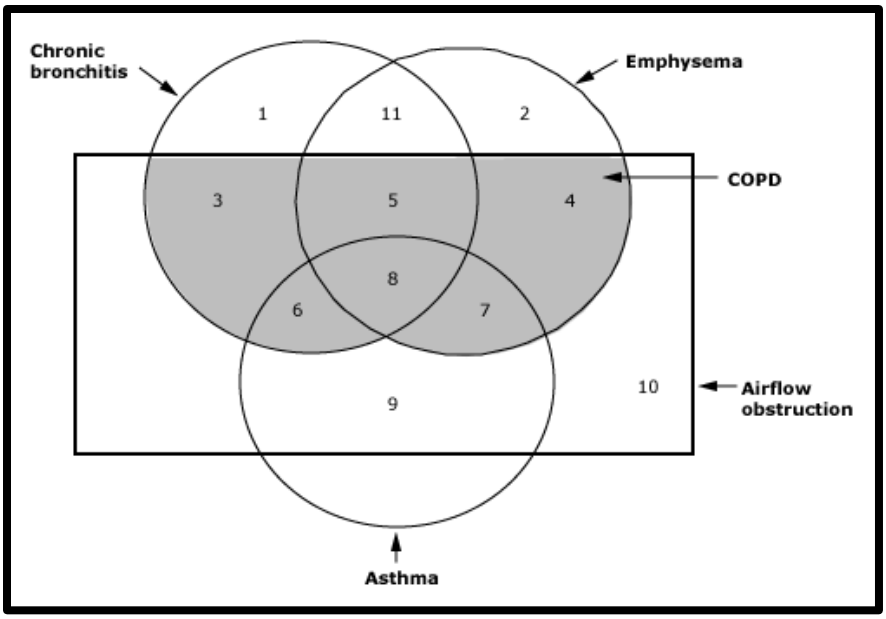

Figure 3. Interrelation between Asthma, Chronic Bronchitis, and Emphysema (Snider 1985).

This figure depicts the interrelation of three common respiratory conditions - asthma, chronic bronchitis and emphysema. Though each condition shares some similar features as depicted herein, each also presents uniquely in terms of pathophysiological mechanisms and clinical symptoms as shown herein. Asthma: Asthma is a chronic, inflammatory lung condition characterized by variable airflow limitation and hyperresponsiveness as well as respiratory symptoms like wheezing, coughing and shortness of breath. Asthma may coexist with chronic bronchitis or emphysema conditions but can exacerbate their symptoms over time. Chronic Bronchitis: Chronic bronchitis is a subtype of Chronic Obstructive Pulmonary Disease (COPD) marked by persistent cough with sputum production lasting at least three months in any two-year period, inflicting airflow restriction and leading to respiratory symptoms. Chronic inflammation narrows airways leading to airflow restrictions reducing airflow capacity as well as respiratory ailments exacerbated by airflow restrictions and symptoms related to respiratory health problems such as airflow limitation. Emphysema: Emphysema is another subset of COPD characterized by irreparable damage to alveoli in the lungs that results in loss of lung elasticity and destruction to alveolar walls, ultimately decreasing gas exchange and increasing shortness of breath symptoms. Subsets 1, 2, and 11: Individuals with chronic bronchitis or emphysema without airflow obstruction. They are not classified as having COPD. Subset 5: Chronic bronchitis and emphysema with airflow obstruction usually occurring together. Subset 6: Patients with unremitting asthma who are classified as having COPD. They may also have chronic productive cough due to exposure to chronic irritation, such as cigarette smoke. Subsets 7 and 8: Patients with asthma whose airflow obstruction does not remit completely and are classified as having COPD. Subset 9: Patients with asthma whose airflow obstruction is completely reversible and are not considered to have COPD. Subset 10: Patients with airway obstruction due to diseases with known etiology or specific pathology, such as cystic fibrosis or obliterative bronchiolitis. They are not generally included in the definition of COPD. Subset 6, 7, and 8: Patients with unremitting asthma who are classified as having COPD. Subset 8: Patients with asthma associated with chronic bronchitis and emphysema. Asthma is associated with reversible airflow obstruction, and special maneuvers may be necessary to make the obstruction evident. Subset areas in the Venn diagram are not proportional to actual relative subset sizes. Individuals with cough and sputum symptoms and normal lung function were classified as GOLD Stage 0 (at risk) in the original GOLD classification, but this stage was deleted in the 2006 revision due to uncertainties about its progression.

2.3. COPD Prevalence

There is recent considerable concern about the number of patients recorded globally. According to the WHO, COPD is the third leading cause of death worldwide, leading to more than 3 million deaths in 2019 (World Health Organization., 2019). The WHO reported that the most of mortality cases caused by COPD are in low-middle income countries. It is expected, that this population is going to inflate, as proved in high-income countries. Most deaths occurred mainly in low and middle-income categorised nations (May and Li, 2015). In the United States, a telephone-based survey reported that 6.3% of participants were diagnosed with COPD in their lives, indicating around 15 million patients may have been suffering from this disease in 2011 (Lange *et al.*, 2012). Another survey-based study found that the prevalence of COPD in the US was 13.5%, with mild to moderate severity (10). The estimates of prevalence of COPD in Europe range from 2% to 10% (Franchi M., 2010). A spirometry-based study conducted in Japan, found that the prevalence of COPD was 8.6% (Perera *et al.*, 2007).

The number of people who ever had a diagnosis of COPD has increased by 27% in the last decade in the UK, from a range of 1,600 to 2,000 per 100,000 population which indicates that more undiagnosed cases are being discovered, or that the disease is becoming more common. COPD-diagnosed cases make it the most threatening disease worldwide and Around 1.2 million people are diagnosed with COPD – markedly more than 835,000 estimated by the Department of Health in 2011

Hospitalization for acute exacerbations represents a major component of the socioeconomic burden related to COPD. Hilleman et al reported that hospitalization costs represent 40.4% of total health care costs for UK patients with mild COPD and 62.6% of total costs for patients with severe COPD and this is mentioned in COPD statistics by British Lung Foundation in 2012 (Snell et al., 2016). In addition to that, The Global burden of disease study addressed that the number of COPD cases worldwide reached 251 million cases in 2016. Around 5% of all deaths in 2015 were caused by COPD with an estimated 3.17 million deaths.

The burden of obstructive lung disease (BOLD) survey conducted an estimate standardised questionnaire in the adult population aged over 40 years old in Germany. This showed an overall prevalence of 10%; 11.8% for male and 8.5% for female (Rabe, 2013). Medicare beneficiaries

report revealed that 64% of readmitted patients happened after a discharge for a previous COPD exacerbation (Lindenauer *et al.*, 2017). The merged studies of 28 countries showed that the prevalence of COPD was 7.6% outlined from systematic review and meta-analysis throughout 1990-2004 (Halbert *et al.*, 2006). However, this analysis highlighted the geographical and methodological inequalities. Another study estimated the global prevalence of COPD with 10%. The variability in COPD statistics varies according to the area, sex and smoking. The onset of the disease was more prevalent in the following individuals: females, African Americans, and those with a family history of COPD. It is thought that underrating of the disease's severity and/or serious outcomes at advanced ages, occurs due to erroneous coding and/or inconsistent coding mechanisms in healthcare systems (Halbert *et al.*, 2006).

At the beginning of the 21st century, the United Kingdom reported that COPD reached its peak rate among the male population and started to grow in the females (Soriano *et al.*, 2000). COPD was observed in 5.2% of males and in 1.8% of females (Tageldin *et al.*, 2012). Contrary to expectation, In Austria, no significant difference in COPD were found in both sexes (Schirnhofer *et al.*, 2007). Therefore, it is possible that the number of women suffering from COPD may soar through the following years (Mannino and Braman, 2007). In Cape Town, South Africa, the prevalence had the highest rates of COPD, 22.2% of men and 16.7% of females. Hannover in Germany had a minimum per cent of COPD, 8.6% of males and 3.7% of females (Geldmacher *et al.*, 2008). This is in contrast with a study conducted in the United States, which prove that the number of women with COPD has started to increase (Mannino *et al.*, 2002). Overall data are consistent with variation in the trend of smoking between both sexes and the high susceptibility of women to the effects of smoking (Rycroft *et al.*, 2012).

Smoking and COPD dependant outcomes are recognised as an evolving epidemic in the Arabian Gulf and Middle East countries (Mahboub *et al.*, 2017; Masjedi *et al.*, 2018). The estimate of the prevalence is not exact, as some cases are undiscovered yet. This is illustrated by the existence of unreported exacerbation cases, which have not been seen or examined lately by a physician due to the patient's adaptation to his health condition (Yawn *et al.*, 2014). Accurate data are also hampered by the lack of COPD statistics in some global regions, which may have higher death rates. Therefore, the true COPD distribution worldwide is still unrecognized.

The estimated prevalence of COPD data may not be reliable as part of population is still underdiagnosed. For example, the findings of two studies conducted in the UK showed two different estimations for the COPD prevalence (Casanova *et al.*, 2011). The prevalence of airway obstruction in the UK was found to be higher in people aged over 35 than previous studies (Castagna *et al.*, 2008). The overall prevalence survey from a large international report represented that 4/5 smokers aged above 50 years have undiagnosed COPD (Cavarra *et al.*, 2009; Castaldi *et al.*, 2011) (**Figure 4**)

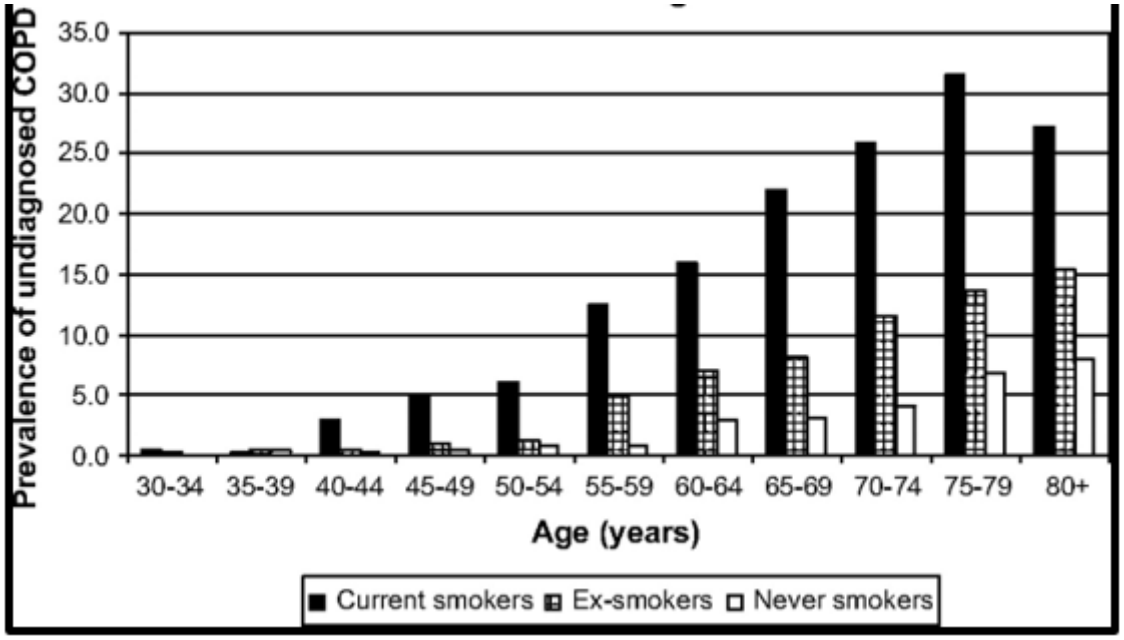

Figure 4. Prevalence of Undiagnosed Chronic Obstructive Pulmonary Disease Cases Stratified by Smoking Categories (Jordan et al., 2010). ***This figure shows the prevalence of undiagnosed COPD cases stratified by smoking categories, based on data from a population-based survey. The x-axis represents different age categories. The y-axis represents the percentage of individuals in each smoking category with undiagnosed COPD. The highest percentage of undiagnosed COPD was found in smokers aged between 75 and 79 years.***

There are several reasons why COPD remains underdiagnosed; first, because patients are unconscious about the disease symptoms, they may gradually get used to the symptoms without seeking healthcare consultation. A study indicated that while other health conditions such as stroke, cancer, and cardiovascular disease are increasingly well understood (Celli *et al.*, 2004), COPD still remains misunderstood among the general public (Celli *et al.*, 2011). Second, misdiagnosis, which occurs when clinicians face a difficulty in symptom identification and differentiation. A previous study screened patient records in UK primary care and found that clinicians had the chance to make early diagnoses in 80% of COPD cases. Reasons for underreporting of COPD may include poor disease management and inappropriate medical procedures. (Celli *et al.*, 2005). Also COPD diagnoses may suffer from both missed diagnoses as well as misdiagnosis and over diagnosis (Chapman *et al.*, 2005). This can be overcome by good training of healthcare professionals to obtain high standards of quality in using spirometers to make an accurate diagnosis.

2.3.1. COPD in the MENA Region

The disease is creeping into the Middle East and North Africa (MENA) nations. The prevalence of COPD in the Gulf Cooperation Council (GCC)-MENA regions is unknown because it depends on several factors; involving genetic and environmental factors and there are limited studies. Moreover, there is inadequate genetic research on COPD. The prevalence of COPD is related to the population of smokers. The BREATHE – study determined that the COPD patients were more prevalent in Levant and Turkey communities in the MENA (Khattab *et al.*, 2012). This disease is more prevalent in the high-risk smokers' population who attended the clinics and hence may lead to selection bias (Al Ghobain, Al-Hajjaj and Wali, 2011). This may contribute to a miss-estimation of COPD prevalence. There were some variations in the prevalence estimation of COPD across studies in the Middle East. A survey-based study found that the prevalence of COPD in the region ranges from 7.2% (UAE) to 19.1% (Algeria) (Tageldin *et al.*, 2012). They found that COPD is more prevalent in men than women. There were two other studies which assessed the COPD prevalence in the UAE and found that the prevalence of COPD in the UAE ranges from 3.7% to 12.9% (Al Zaabi *et al.*, 2011; Mahboub *et al.*, 2014). The variation is prevalence can be attributed to the plethora in COPD definitions and scales. For example, some definitions focused on the

disease outcomes such as ATS definition of COPD (Celli *et al.*, 2015). Others focused on symptoms and aetiology such as the ERS definition (Celli *et al.*, 2015).

In Saudi Arabia, studies indicated that the prevalence of COPD ranges from 2.4% to 14.2% (Al Ghobain, Al-Hajjaj and Wali, 2011; Tageldin *et al.*, 2012; Al Ghobain *et al.*, 2015). The variation in prevalence estimation was also noted in Jordan, where several studies reported that the prevalence of COPD ranges from 5.4% to 8.2% (Tageldin *et al.*, 2012; Al Omari *et al.*, 2014). Additionally, a survey-based study scanned the high-risk groups in Egypt. This found a COPD prevalence (9.6%) that is different from the BREATH study (3.5%) (Tageldin *et al.*, 2012; Said *et al.*, 2017). A study operated for those in higher risk groups involved the following: smoke; workplace exposure, and biomass fuel combustion. This indicated a tripled, more significant prevalence, than in BREATH-study (Said *et al.*, 2017). In Abu Dhabi, the Capital of UAE, A Cross-sectional survey in a population of 40-80 years-old, showed the prevalence of 3.7% COPD sufferers and correlated with smoking tobacco and other harmful materials (Al Zaabi *et al.*, 2011). In the Middle East and North Africa- MENA countries, smoking is carried out in various forms; Shisha, Medwakh; tobacco pipe with herbs, and tobacco pipes. All these forms are considered entertainment habits in before mentioned countries. Young individuals suffer from a lack of knowledge and awareness and restrictions from the regulations arm and are unaware of the future dangers of smoking; all these conditions are supportive of increasing the smoker's population and encouraging this habit in men and women. Moreover, the newly launched electronic pipe mitigates the smokers' guilty feelings toward smoking; they think it is less risky than conventional habits; cigarettes. The fallacy beyond this new addiction, is that is less harmful than cigarettes, because the smoke is clear and the dangerous materials are dissolved in water (Maziak, Eissenberg and Ward, 2005). Currently, the UAE government imposes a tobacco tax (50%) in addition to the original price. The law includes strict controls and there are standards and also educational campaigns and clinics, both ordinary and mobile to restrict the burden of chronic respiratory illnesses associated with smoking (Ekpu and Brown, 2015).

2.4. Causes of COPD

The main cause of COPD is the long-term exposure to certain lung irritants such as cigarette smoke (active or passive), dust, chemicals, cooking with biomass fuel and air pollution. In detail, around 90% of COPD cases were caused by smoking (NIH, 2021). In addition, in rare cases, COPD is

secondary to Alpha-1 antitrypsin deficiency, a protein that can protect the lungs. Specifically, up to 3%of COPD patients have alpha-1 deficiency (Greulich, 2017; Wells *et al.*, 2019).

2.5. Risk Factors for COPD

While risk factors of COPD can be classified into clinical and genetic, investigating these risk factors and their potential association with the disease may help in improving diagnosis and management of the disease, and thus reduce its prevalence (Postma, Bush and van den Berge, 2015). Not all individuals exposed to the risk factors, will develop COPD. There are several risk factors for COPD. First, smoking. Cigarettes have high level of oxidants, which can trigger an inflammation chain leading to lung injuries and chronic inflammatory changes (Saetta *et al.*, 1993; Brody and Spira, 2006; Yang *et al.*, 2017). According to the WHO, more than a hundred million deaths in the last century were associated with tobacco, and if this habit moves in the same direction, the expected cases of deaths will highly increase up to one billion in the 21st century. Half of these deaths were attributed to health conditions induced by tobacco. This risk factor can influence several systems within human body, including the respiratory, heart, and nervous systems. There is rising evidence that the incidence of COPD can be significantly decreased if an individual quits smoking. Additionally, smokers have a 50% chance of developing COPD disease during their lifetime (Laniado-Laborín, 2009). Genetic factors will increase individuals' susceptibility toward the detrimental effects of cigarette smoke. The lung responsiveness, which can predict its decline, was correlated with people who had first degree relatives with severe early-onset COPD (Lundbäck*et al.*, 2003). Therefore, smoking cessation should be considered as the main intervention plan and preventive measures to limit the popularity of COPD. Second, airway responsiveness, which can be defined as a high level and early response of the airway to stimuli, has been related to COPD, with an inflated airway response to bronchial spasmogens. So, the rise in the airway responsiveness could be considered as a risk factor to COPD (Rijcken *et al.*, 1995). The mechanism of developing COPD from the relationship between AHR and COPD may not be the same as those with other diseases such as asthma. Third, exposing to multiple stimuli, dust, fumes, vapour, or organic antigen also can be considered as risk factors for COPD (Wang et al., 2018).

COPD is more common in exposed persons than those who are not frequently exposed to environmental stimuli (Torres-Duque *et al.*, 2008). Fourth, mild to moderate asthmatic patients have the chance of developing COPD. In a study done by the Childhood Asthma Management Cohort, it was shown that FEV1 growth has categories associated with reduced growth, early decline, or both reduced growth and early decline, defined by GOLD spirometric criteria of level 1 or 2 of COPD (McGeachie *et al.*, 2016). Fifth, lack of antioxidants and vitamins (C and E) in our bodies may be considered as a contributing factor for COPD (Cantin and Crystal, 1985). Insufficiency of antioxidant leaves the host unable to protect itself against the catastrophic effect of oxidative radicles, which are acquired from both exogenous substances in cigarette smoke and endogenous sources such as activated lung phagocytes. Sixth, tuberculosis has been correlated with airway obstruction through endobronchial infection and consequent Broncho stenosis. Pulmonary Tuberculosis enhances airway obstruction, regardless of cigarette smoking, biomass fuel exposure, and prior diagnosis of asthma (Lam *et al.*, 2010). Seventh, socioeconomic status, specifically, the level of education is a factor in COPD. The published literature reported that individuals with low levels of education are at high risk of developing COPD (Gershon *et al.*, 2011; Beran *et al.*, 2015). This could be attributed to the fact that these people live and work in conditions that lack healthcare protection. Additionally, some studies report that allergic history may increase the risk for COPD (Hospers *et al.*, 2000; Sørheim *et al.*, 2010). However, further research is necessary to establish a strong relationship between allergic history and developing COPD. History of respiratory infection during the childhood period was another potential risk factor according to a meta-analysis (De Marco *et al.*, 2011; Yang *et al.*, 2017). Recurrent respiratory infections and lack of ventilation were also mentioned in the published literature as risk factors for COPD (Park *et al.*, 2005; Mattiello *et al.*, 2010; Zhou *et al.*, 2014).

The regulation of antioxidant enzymes may be considered a contributing factor for COPD given the genetic differences among these enzymes: glutathione S-transferases P1 and M1, glutamate cysteine ligase, and superoxide dismutase. (Bentley, Emrani and Cassano, 2008). The published literature indicated that genetic polymorphisms may decrease the enzymes responsible for smoking detoxification, and thus contribute to developing COPD (Yim *et al.*, 2002; Cheng *et al.*, 2004). Additionally, decreased level of enzymes that help in the glutathione synthesis such as glutamate cysteine ligase (GCL) may lead to increased risk of COPD (Bentley, Emrani and Cassano, 2008).

Nevertheless, this was not supported by all authors. For examples He et al (He *et al.*, 2004), concluded that there is no established association between decreased level of glutathione S-transferase M1 (GSTM1) and developing COPD. Some researchers highlighted the impact of dysregulation and abnormal activity of metalloproteinase enzymes in COPD (Cataldo *et al.*, 2000; IMAI *et al.*, 2001; Leco *et al.*, 2001; Churg and Wright, 2005) (**Figure 5**). MMP-9 is an elastolytic enzyme and overexpressed by alveolar macrophages in patients with COPD (Russell *et al.*, 2002). Selective MMP-9 inhibitors are considered as a potential treatment in emphysema (Dahl *et al.*, 2012). Suppression of this enzyme could inhibit the multiple activities of this protease which relate to COPD pathophysiology. Other authors suggest that COPD may occur as a result of excess elastase activity. In detail, they stated that deficiency in elastase inhibitors (i.e. alpha-1 antitrypsin) may induce emphysema (Dean *et al.*, 1997).

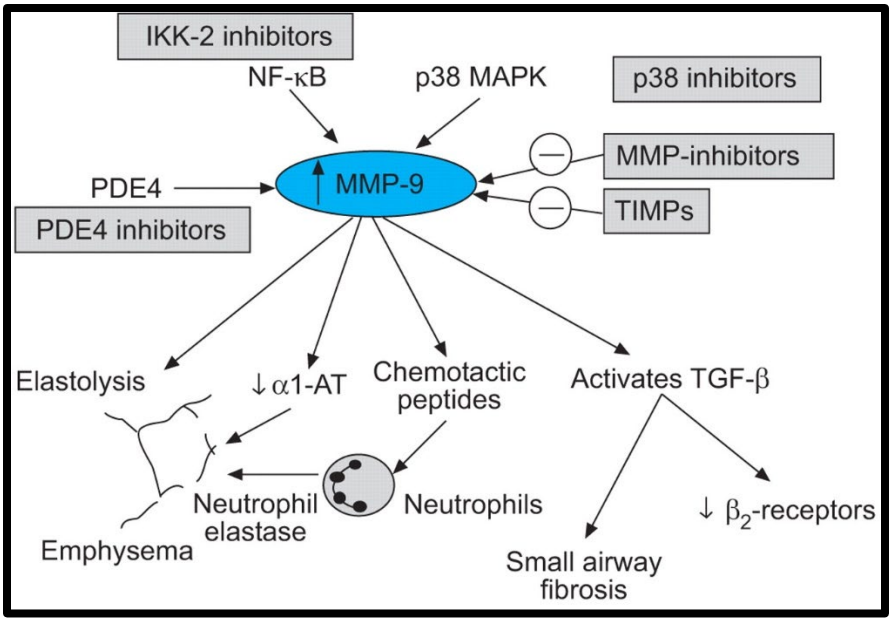

Figure 5 . The Mechanism of Metalloproteinase Dysregulation (Wang et al, 2020). ***This figure depicts how dysregulation of metalloproteinase enzymes contributes to cancer, arthritis and cardiovascular diseases. These enzymes play an essential role in tissue remodelling and repair by breaking down extracellular matrix (ECM) proteins; however, when dysregulated they can lead to excessive tissue destruction as well as disease progression. Figure shows the intricate network of signalling pathways and regulatory mechanisms which regulate metalloproteinase activity, including: Transcriptional Regulation: Gene expression for metalloproteases is controlled by several transcription factors, such as Nuclear Factor-Kapa protein, Activator Protein 1 and Activator Protein 1 (NF-kB, AP-1 and SP-1) which can be activated by various***

stimuli including cytokines, growth factors and other stimuli. IKK inhibitors: IKK stands for IκB kinase. PDE4 inhibitors: PDE4 refers to Phosphodiesterase 4, an enzyme that breaks down cyclic adenosine monophosphate (cAMP). MMP-9: Matrix Metalloproteinase 9 is an enzyme involved in the breakdown of extracellular matrix components, including collagen and gelatin. alpha-1-AT: Alpha-1-Antitrypsin is a protein primarily produced in the liver and secreted into the bloodstream. TGF-beta: Transforming Growth Factor-beta is a multifunctional cytokine involved in regulating cell growth, differentiation, and development. TIMPs: Tissue Inhibitors of Metalloproteinases are a family of proteins that regulate the activity of matrix metalloproteinases (MMPs). -38 inhibitors: p-38 refers to p38 mitogen-activated protein kinase (MAPK)

2.6. Impact of COPD on Daily Life

The published literature shows that COPD symptoms occur at night-time and in daylight and can substantially influence the patients' quality of life (Price *et al.*, 2013; Stephenson *et al.*, 2015). For example, a multicentre study followed 791 COPD patients for one year and found a significant association between COPD symptoms (i.e., dyspnoea) and impaired quality of life (Monteagudo *et al.*, 2013). More specifically, cough, fatigue, and shortness of breath accounted for the most frequent symptoms that can deteriorate patients' quality of life (Miravitlles *et al.*, 2007). Miravitlles M et al, used the COPD Assessment Test (CAT) and found that health status was negatively correlated with the appearance of COPD symptoms (Miravitlles, Worth, *et al.*, 2014). The following sections summarise the impact of COPD on physical activity, sleep, mental status, and disease prognosis.

2.6.1. Impact of COPD on Physical Activity

The symptoms and markers of COPD are significant determinants of physical activity. For example, COPD symptoms can limit a patients' capacity to perform normal physical activity at any time of the day. Several studies assessed patients' perception of COPD impact on their daily activity (Partridge, Karlsson and Small, 2009; Kessler *et al.*, 2011; Lopez-Campos, Calero and Quintana-Gallego, 2013; O'Hagan and Chavannes, 2014; Stephenson *et al.*, 2015). Patients reported that COPD symptoms can lead to workplace absenteeism (Roche *et al.*, 2013). Additionally, some patients felt themselves a burden on their relatives, because they need their assistance to perform daily activities such as "Going up and down stairs", "doing heavy household chores", "going shopping", and "taking part in sports and hobbies" (Kessler *et al.*, 2011). In some cases, patients decrease their physical activity to avoid COPD symptoms such as shortness of breath, and this leads to muscle deconditioning (Pleguezuelos *et al.*, 2016). Additionally,

performing physical activities was linked with reduced mortality and hospitalization (Lopez-Campos, Calero and Quintana-Gallego, 2013). Therefore, doing more physical activities is important even in mild cases of COPD.

2.6.2. Impact of COPD on Sleep

It is well-known that sleep quality is a significant predictor of quality of life and thus sleep problems have been associated with negative health outcomes (Omachi *et al.*, 2012). Because COPD patients experience symptoms throughout the 24 hours, the vast majority of those patients have sleep problems (Scharf *et al.*, 2010). These problems include difficulties in initiating and maintaining sleep (Scharf *et al.*, 2010). This could be attributed to COPD symptoms including sputum, cough, and shortness of breath, chest pain, heartburn, and anxiety (McNicholas, Verbraecken and Marin, 2013). As a result of these problems, patients experience difficulties in getting up in the morning (Nunes *et al.*, 2009). A European study reported that COPD patients experience "trouble falling asleep", "wake up several times per night", "trouble staying asleep", and "wake up feeling tired and worn-out after usual amount of sleep" (Price *et al.*, 2013).

2.6.3. Impact of COPD on Mental Health

The published literature indicates that COPD patients are at high risk of developing psychological distress, anxiety, and depression (Pumar *et al.*, 2014; Dury, 2016). These mental illnesses are significant determinants of COPD parameters including hospitalization, length of hospital stay, severity of symptoms, prognosis of the disease, and mortality (Dury, 2016). Although it is extremely difficult to establish causality between COPD symptoms and mental illnesses (anxiety and depression) given the complexity of the relationships, some evidence demonstrates a potential association between dyspnoea and mental illnesses. This includes evidence which has emerged from two observational studies that investigated mental illnesses in COPD. Miravitlles M and colleagues (Miravitlles, Molina, *et al.*, 2014) used the BECK depression scale and found the depressed COPD patients have greater dyspnoea. Another observational study reported a significant association between depression and COPD symptoms (Martinez Rivera *et al.*, 2016). The Newcastle UK group have shown a high burden of anxiety and depression in people with COPD and that cognitive behavioural therapy delivered by respiratory nurses can be a cost effective healthcare intervention in patients (Marshall et al, 2018)

2.6.4. Impact of COPD Symptoms on Disease Prognosis

The Appearance of COPD symptoms has a negative impact on disease prognosis. A previous study found that night-time symptoms (i.e. breathlessness) were associated with increased hospitalization (Hazard ratio: 3.2), exacerbations (Hazard ratio: 2.3), and mortality (Hazard ratio: 1.7). Another study found that day-time symptoms are significant risk factors for future exacerbations (Miravitlles *et al.*, 2016). Nishimura et al (Nishimura *et al.*, 2002), investigated the association between COPD symptoms and mortality. They found that breathlessness is a significant predictor for 5-year death.Cough was also found to be a significant determinant of disease prognosis, hospitalisation, and mortality (Putcha *et al.*, 2014; Lindberg *et al.*, 2015).

2.7. Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD)

AECOPD is a serious clinical issue that occurs in more than half of COPD patients and poses severe clinical outcomes (Burge and Wedzicha, 2003). According to the nature of the symptoms and events encountered by COPD patients, there are various definitions for AECOPD. GOLD has defined an acute exacerbation of chronic obstructive pulmonary disease as an event occurring within its natural course that results in changes to baseline dyspnoea, cough and/or sputum production that go beyond usual day-to-day variations and have an abrupt onset, as well as may prompt changes to regular medication in those diagnosed with COPD. The GOLD's definition of AECOPD focuses on the nature and causes of the condition (Global Initiative for Chronic Obstructive Lung Disease, 2020; Halpin *et al.*, 2020). The WHO's definition emphasises the outcomes of the disease. The published literature identified two types for AECOPD: frequent, which occurs more than two times per year and infrequent, which occurs less than that (Wedzicha *et al.*, 2013). While the infrequent AECOPD patients can be stable for years, frequent AECOPD causes recurrent inflammation and attacks, which need longer and more intense medical

interventions (Bhowmik *et al.*, 2000; Perera *et al.*, 2007). Based on the type of treatment and the necessity for hospitalisation, AECOPD can be classified into mild, moderate, and severe (Global Initiative for Chronic Obstructive Lung Disease, 2020). The AECOPD cases that can be managed by short-acting bronchodilators are described as mild (Wedzicha *et al.*, 2016). A moderate AECOPD, which may cause respiratory failure, requires antibiotic therapy. A severe AECOPD requires hospitalisation and urgent care. The classification of AECOPD severity is different from the severity of COPD, which depends on airflow obstruction to grade the disease from mild to very severe (Global Initiative for Chronic Obstructive Lung Disease, 2020).

2.7.1. Diagnosis of AECOPD

The early diagnosis COPD is a key element in disease management and can help in reducing lung deterioration, increasing survival, and improving patients' quality of life. Additionally, it helps in saving healthcare resources. While COPD can be firstly linked with several risk factors, Spirometry is the only test that can detect airflow obstruction and differentiate COPD from asthma and chronic bronchitis. (Qaseem *et al.*, 2011; Spyratos, Chloros and Sichletidis, 2012). **Figure 6** summarises the differential diagnosis for COPD according to the GOLD. In cases of AECOPD, chest imaging scans are crucial for optimizing drug therapy. This is necessary to exclude pneumothorax (accumulation of air between parietal and visceral pleurae), embolism (blocking an artery in the lung), pulmonary effusion (accumulation of fluid around the lung), and pneumonia (inflammation of lung tissues caused by an infection). The published literature indicates that chest imaging can improve disease management in up to 33% of patients (Celedón *et al.*, 2004; Wu *et al.*, 2004; DeMeo *et al.*, 2009; Pillai *et al.*, 2010; Artigas *et al.*, 2011; Zhou *et al.*, 2012; Ruvuna and Sood, 2020).

Because AECOPD often comes with pneumonia, which has overlapping symptoms and similar clinical outcomes among hospitalised patients, differentiation between the two conditions is difficult (Müllerova *et al.*, 2012; Steer, Gibson and Bourke, 2012; Hurst, 2018). The published literature indicated a discrepancy in estimation of pneumonia diagnosis in AECOPD. Additionally, they reported that AECOPD patients who have been diagnosed with pneumonia should have

different treatment plans from those experiencing AECOPD without pneumonia (Rizkallah, Man and Sin, 2009). Specifically, they also found that the symptoms of those with pulmonary embolism overlap with those who did not have the condition (Finney *et al.*, 2019). In summary, misdiagnosis of complexities in AECOPD is a probable event, which could lead to failure in the treatment plan (Müllerova *et al.*, 2012).

Differential diagnosis of COPD

Diagnosis	Suggestive features*
COPD	Onset in mid-life; onset in early adulthood should prompt suspicion for alpha-1 antitrypsin deficiency
	Symptoms slowly progressive
	Long smoking history, although can occur in nonsmokers
	Dyspnea during exercise
	Largely irreversible airflow limitation
Asthma	Onset early in life (often childhood)
	Symptoms vary from day to day
	Symptoms at night/early morning
	Allergy, rhinitis, and/or eczema also present
	Family history of asthma
	Largely reversible airflow limitation
Central airway obstruction (eg, bronchogenic or metastatic cancer, lymphadenopathy, scarring from endotracheal tube)	Monophonic wheeze or stridor
	Variable inspiratory or fixed slowing on flow volume loop
	Chest radiograph often normal
	Airway narrowing on three dimensional reconstruction of HRCT scan
Heart failure	Fine basilar crackles on auscultation
	Chest radiograph shows dilated heart, pulmonary edema
	Pulmonary function tests typically indicate volume restriction, but airflow limitation can sometimes be seen
Bronchiectasis	Large volumes of purulent sputum
	Commonly associated with recurrent or persistent bacterial infection
	Coarse crackles on auscultation, clubbing of digits
	Chest radiograph/HRCT shows bronchial dilation, bronchial wall thickening
Tuberculosis	Onset all ages
	Chest radiograph shows upper lung zone scarring and/or calcified granulomata
	Positive PPD or IGRA
	High local prevalence of tuberculosis
Obliterative bronchiolitis	Onset in younger age, nonsmokers
	May have history of rheumatoid arthritis or fume exposure
	HRCT on expiration shows hypodense areas, mosaic pattern
Diffuse panbronchiolitis	Most patients are male and nonsmokers
	Highest prevalence in East Asia
	Almost all have chronic sinusitis
	Chest radiograph and HRCT show diffuse small centrilobular nodular opacities and hyperinflation

Figure 6. Differential Diagnosis of Chronic Obstructive Pulmonary Disease (Halpin et al, 2021). ***This figure shows how to differentiate COPD from asthma, heart failure, tuberculosis and other conditions. HRCT: High-Resolution Computed Tomography. PPD: Purified Protein Derivative. IGRA: Interferon-Gamma Release Assay***

2.7.2. Triggers of AECOPD

AECOPD can be induced by several factors; infections, poor ventilation and air pollution (Donaldson and Wedzicha, 2014). The frequency of AECOPD episodes can vary depending on patients and disease characteristics. Nonetheless, the incidence of AECOPD is two times higher in winter than summer given the spread of viral infections in that season (Aaron *et al.*, 2012; Jenkins

et al., 2012). Additionally, winter AECOPD is considered more severe and requires longer period for recovery than summer episodes (Sama *et al.*, 2017). A UK study found that AECOPD was more frequent in winter than in summer, and was linked with more severe inflammations (Han *et al.*, 2017). **Figure 7** Summarises contributing factors for AECOPD. These comprise socio-demographic factors (sex, specifically females), disease symptoms and features (such as shortness of breath, declined lung function, and frequent exacerbation), concurrent health conditions, and biomarkers (e.g. increased white blood total cell count) (Hurst *et al.*, 2010; Wedzicha *et al.*, 2013). While the increased level of eosinophil counts in the blood was considered a contributing factor for AECOPD (McGarvey *et al.*, 2015).The published literature suggests a potential association between airflow limitation and AECOPD showing that the annual frequency of AECOPD was significantly correlated with the severity of airflow limitation (Overbeek *et al.*, 2015; Merinopoulou *et al.*, 2016). A further potential risk factor that was mentioned by the literature is gastroesophageal. Reflux disease (GERD, which was correlated with increased frequency of AECOPD (Hurst *et al.*, 2010; Kim *et al.*, 2013). In detail, a case-control study found that many of COPD patients were previously diagnosed with GERD (Terada *et al.*, 2008). Nevertheless, evidence suggested that treating COPD patients with proton pump inhibitors (PPIs) has no beneficial impact on AECOPD risk and survival rate (Baumeler *et al.*, 2016). PPIs are a drug class that used to antagonise the stomach's acid production (Nehra *et al.*, 2018). In addition to GERD, pulmonary hypertension is another condition that may increase the risk for developing AECOPD. Specifically, in chest imaging, if the ratio of the diameter of the pulmonary artery to the diameter of the aorta is higher than 1, that indicates the occurrence of pulmonary hypertension and increases the risk for AECOPD (Wells *et al.*, 2012).

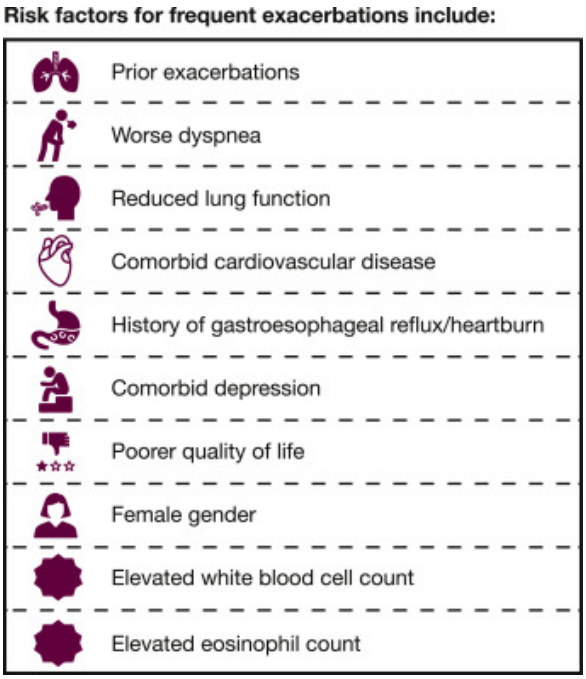

Figure 7. Risk Factors for Acute Exacerbation of Chronic Obstructive Pulmonary Disease (Miravitlles et al, 2007). ***This figure illustrates the risk factors for acute exacerbation of COPD, an important and frequently fatal complication which often necessitates hospitalization and causes increased mortality rates. Modifiable and non-modifiable risk factors both interact to increase likelihood of exacerbations.***

It was noted that AECOPD can be triggered by viral and bacterial infections, which is challenging given the likelihood of these infections. In detail, up to 60% of AECOPD cases were triggered by viral infections (such as Wild-type rhinovirus), which increase interleukin (IL)-6 levels. There are other viruses linked with the occurrence of AECOPD: respiratory syncytial virus and human metapneumovirus (Falsey *et al.*, 2005; Hamelin *et al.*, 2005).

The mechanism by which these viruses work is that they attack the airway epithelial cells and damage the receptors, and activate the release of inflammatory mediators such as cytokines (Mallia and Johnston, 2006). In this regard, the published literature reported that COPD patients have high levels of epithelial expression of ICAM-1, which is a key receptor of rhinovirus. This may explain how AECOPD patients suffer from lower airway symptoms (Seemungal *et al.*, 2000). It was estimated that infections due to bacteria account for half of the infections in AECOPD patients. The main bacterial responsible for triggering AECOPD were *Moraxella catarrhalis* and *Streptococcus pneumoniae*, which have been investigated in AECOPD patients. The studies found that colonization by these types of bacteria is significantly associated with the severity of AECOPD (Sethi and Murphy, 2001). The published literature identified two main markers for bacterial infections in AECOPD patients; FEV1<50 and sputum purulence (Finney *et al.*, 2014;

Shimizu *et al.*, 2015). As mentioned above, AECOPD can be triggered by viral, bacterial, or both infections (Bandi *et al.*, 2003; Wilkinson *et al.*, 2006). The worst clinical scenario for AECOPD patients is co-infections, because their length of hospital stay, bacterial load, FEV1, inflammations, will be worsened (Papi *et al.*, 2006; Molyneaux *et al.*, 2013).

2.7.3. AECOPD Risk Reduction

The risk factors which likely develop COPD and its impacts cannot be easily measured. The modification of risk factor target is to reduce lung function decline. Smoking cessation has the greatest effect on reducing COPD incidence. Physical activity and avoidance of inhalational exposures and vaccinations may also reduce the incidence of COPD as well. In detail, declines in lung function can be substantially improved if the COPD patient quits smoking (Løkke *et al.*, 2006; Eisner *et al.*, 2010; De Marco *et al.*, 2011; Perret *et al.*, 2013). The mechanism of triggering COPD was investigated. Smoking increases the production of interleukin (IL-8) and interleukin B4 by activating respiratory macrophages. Eventually, the connective tissue of the respiratory tract will be damaged and emphysema will be induced. Furthermore, this chain of events will lead to mucus hypersecretion as well. The impact of smoking in developing COPD was investigated by a retrospective cohort study (n = 8045), which concluded that the incidence of COPD was strongly correlated with smoking. The study was conducted over 25 years and found that incidence of COPD was less among patients who had never smoked or stop smoking than among patient that are currently on smoking. Avoiding exposure to dust, gases, vapours, fumes, and toxic chemical is another strategy to reduce AECOPD occurrence. Although this will be less efficient than smoking cessation, avoiding exposure to dusts will slow the decline in lung function. This illustrated by a retrospective cohort study (n = 9651), which indicated that a small decline in the annual rate of the particulate matter concentration was associated with a small reduction of the annual rate of decline in forced expiratory volume in one second (FEV1) through 11 years (Downs *et al.*, 2007; Lippmann, 2007). Another prospective cohort study performed over 9 years, reported that good kitchen ventilation and using biogas rather than biomass fuel will also associate with a reduction of FEV1 decline (Zhou *et al.*, 2014). The published literature also highlighted the importance of physical activity in mitigating the decline in lung function, especially among smokers. A longitudinal retrospective study followed thousands of individuals for 11 years and

found that smokers who perform moderate to high physical activity on a regular basis were less likely to develop COPD than those with a low level of physical activity (Garcia-Aymerich *et al.*, 2007).

Because influenza vaccination has proved to be effective in minimising the incidence and severity of respiratory symptoms, it has been considered as an important approach to reduce the risk for developing AECOPD (Calderón-Larrañaga *et al.*, 2011; Walters JAE and Wood-Baker, 2017).

The public health measures implemented such as masks, hand washing and social distancing in the last pandemic disease reduce hospitalization and symptoms worsening of AECOPD patients. Tan and colleagues report significant outcomes that have achieved from public health measures during SARS-COV-2 and COVID-19, major outcome decrease community transmission and therefore reduce respiratory viral infections that triggers of exacerbation of AECOPD (Tan et al., 2021). During COVID-19 lockdowns reduce hospital admission rate of AECOPD with increase health preventative measurements (masks wearing, using disinfectant and dependence on web application services). Lawless and colleagues show no changes on mortality rate of AECOPD patients during COVID-12 pandemic period (Lawless et al., 2022).

2.7.4. Management of AECOPD

To reduce negative outcomes and prevent subsequent conditions, the management of AECOPD should take place with maximum care (Prieto-Centurion *et al.*, 2014). The management of AECOPD has impact on hospital hospitalization and readmission. In the US, Hospitalised AECOPD cost the economy more than 13 billion $ per year with 22% readmission rate (Kong and Wilkinson, 2020).

Furthermore, the management plan should consider failure in treatment, which occurs in almost one-fifth of AECOPD cases. The predictors for treatment failure were the disease severity, increased level of C-reactive protein at admission, and the use of penicillin-based antibiotics (Crisafulli *et al.*, 2016).

The first step in AECOPD management is assessing the need for hospitalisation. The published literature indicates that baseline parameters should determine whether AECOPD patients need hospitalisation or not (Crisafulli et al., 2016). Additionally, the literature suggested several indicators that alert the need for hospitalisation. These indicators include severe underlying COPD disease, severe shortness of breath even with little activity, peripheral oedema (accumulation of

fluids in the leg tissues), confusion, major comorbidities, less than 90% oxygen saturation, and treatment failure (Vestbo, 2006). In the case of AECOPD management outside the hospital setting, patients are usually treated with bronchodilators and oral glucocorticoids. Because of its rapid relief and high efficacy, short-acting beta-adrenergic agonists are considered the cornerstone for AECOPD management. Sometimes, these agents are combined with short-acting anticholinergic agents to improve their performance. Nonetheless, the first-choice combination is oral glucocorticoids with bronchodilators, which can minimise the severity of the symptoms, and reduce the deterioration of lung function, and decrease the need for hospital admission (Walters and Walters, 2014). The preferable dose prednisone 40mg or equivalent. The severity of the exacerbation determines if the patient requires a higher dose of prednisolone than 40 mg or longer duration (Global Initiative for Chronic Obstructive Lung Disease, 2020). The GOLD guideline noted that due to absence of adequate evidence, inhaled steroids cannot replace systemic glucocorticoids in AECOPD management. Additionally, outpatients with moderate to severe AECOPD are advised to take antibiotics (**Figure 8**), if dyspnoea, increased sputum purulence or volume were are encountered (Seemungal *et al.*, 2008; He *et al.*, 2010). The most common targeted bacteria in antibiotic plans are *Haemophilus influenza*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae.* In addition to drug therapy, home-treated patients should be provided with adequate supportive care and a set of non-pharmacological interventions including but not limited to; smoking cessation, balanced diet, maintaining oxygen supplies

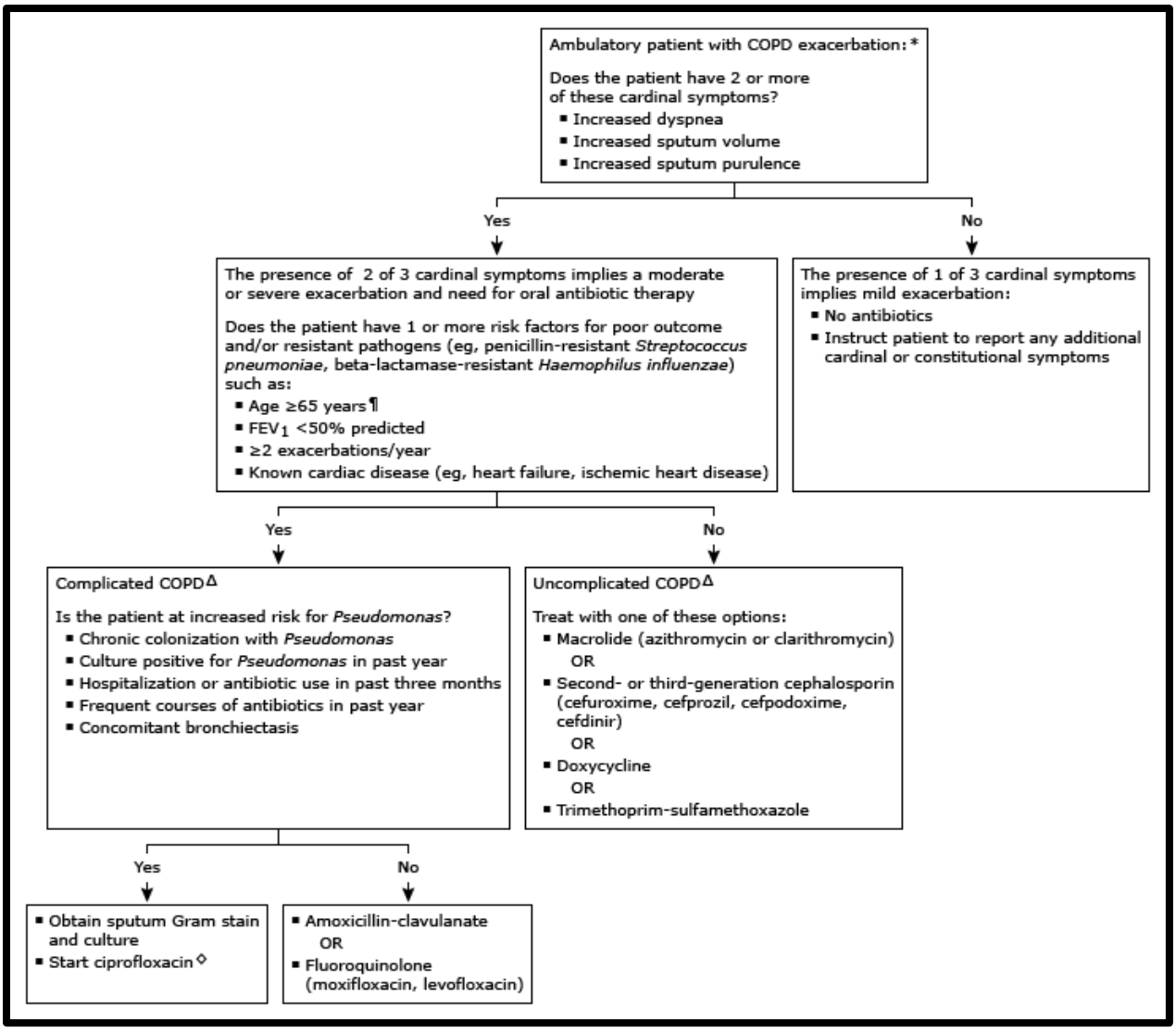

Figure 8. Antibiotics Plan for Acute Exacerbation of Chronic Obstructive Pulmonary Disease (Siddiqi and Sethi, 2008). ***This figure illustrates the proposed antibiotics plan for treating acute exacerbations of COPD as described by Siddiqi and Sethi in 2008. The figure includes a flowchart of the recommended antibiotic therapy based on the severity of the exacerbation and the presence of risk factors for antibiotic resistance. FEV1: Forced Expiratory Volume in 1 second.***

The main aim for inpatient management of AECOPD is maintaining adequate oxygenation, reducing the inflammation, and fighting the infections. Therefore, clinicians initiate short-acting bronchodilators, systemic steroids, and antibiotics. Moreover, they add thromboembolic therapy to avoid any difficulty in immobilization complication that normally occurs in AECOPD patients. According to the GOLD standards, this would prevent bacterial infection and help avoid mechanical ventilation. AECOPD patients admitted to the hospital require close monitoring of

several parameters including; heart rate, rhythm, fluid levels, oxygen saturation, and respiratory rate. In addition, clinicians suggest monitoring arterial blood gas to assess potential respiratory acidosis and hypercapnia as well, especially in deteriorated patients. For AECOPD patients admitted to the hospital, the percentage saturation (SpO_2) and arterial oxygen tension (PaO_2) should be kept between 88 and 92 and between 60 and 70 mmHg, respectively. This would help in preventing hypercapnia (an increase in the partial pressure of carbon dioxide), especially if an oxygen-driven nebulizer is used during bronchodilator treatments (Stoller, 2002; Austin et al., 2010; Edwards et al., 2012). However, other guidelines such as the BTS suggest using conventional air supply (O'Driscoll, Howard and Davison, 2008). The recommended dosage for Ipratropium is 500mcg up to six times per day. Additionally, antibiotic and antiviral-based therapies are recommended for AECOPD patients admitted to the hospital, particularly for those with severe AECOPD. Antiviral medication is necessary in occurrence of influenza infection and confirmed by clinical and laboratory inspection in hospital settings (Bach et al., 2001; MacIntyre and Huang, 2008; Halpin et al., 2020). Zanamivir/Oseltamivir is preferred except in local possibility of oseltamivir-resistant influenza. AECOPD hospitalized patients need supportive care (i.e., smoking cessation) and palliative care, which are crucial to gain more than 1-year life expectancy after hospital discharge for an exacerbation (Fried, Vaz Fragoso and Rabow, 2012). There are some medications that have a lack of evidence regarding their effectiveness against the disease; mucoactive agents, methylxanthines, and mechanical techniques to augment sputum. Lack of evidence supporting the consumption of the mucoactive agents and anti-oxidants in exacerbations of COPD are illustrated by a double-blind trial through selection random samples of 50 subjects with AECOPD who received N-acetyl cysteine (600 mg, twice daily) or placebo for seven days. The results showed no change in the rate of change of FEV1, vital capacity, oxygen saturation, breathlessness, or length of stay between the two groups (Black et al., 2004). Despite the finding that nebulized magnesium has a good impact in severe asthmatic patients, it has not shown benefit on FEV1 in exacerbated COPD patients. Mechanical procedures that might be used to clear the sputum in the chest such as chest physiotherapy or coughing have not been shown to be effective in exacerbations of COPD (Snow, Lascher and Mottur-Pilson, 2001; Ram et al., 2004).

The main pharmacological interventions used in AECOPD include bronchodilators, corticosteroids, antibiotics, and mucolytics (O'Reilly, 2013).

Bronchodilators are medications often employed in treating acute exacerbations of chronic obstructive pulmonary disease (AECOPD) (O'Reilly, 2013). They work by relaxing smooth muscle around airways to open them up and increase airflow; there are two major categories of bronchodilators available: beta-agonists and anticholinergics. Beta-agonists are medications which work by stimulating beta-receptors in the lung to relax smooth muscle around airways and relieve symptoms quickly and efficiently. These are available as both short-acting and long-acting forms, beta-agonists may be taken using inhaler or nebulizer; salbutamol and terbutaline are frequently prescribed first for managing AECOPD; these SABAs work quickly to alleviate breathlessness, wheezing, coughing as quickly as short-acting beta-agonists (SABAs); long acting beta-agonists such as formoterol and salmeterol are recommended only during an acute exacerbation. Anticholinergics are medications are designed to block the action of acetylcholine; a neurotransmitter responsible for airway constriction. Anticholinergics come in short- and long-acting varieties and may also be administered using inhalers and nebulizers for easy administration. Short-acting forms like Ipratropium bromide may be combined with SABAs in treating AECOPD symptoms for additional bronchodilation; long-acting forms like Tiotropium and Aclidinium may provide maintenance therapy options rather than acute exacerbations (O'Reilly, 2013).

Bronchodilators are essential components of AECOPD management pharmacologically. Short-acting anticholinergics (SABAs) and short-acting β2-agonists (SABs) should typically be prescribed first as relief treatments during an exacerbation, while long-acting β2-agonists (LABAs) and long-acting anticholinergics (LAMAs) should be used long-term as maintenance therapy to prevent future exacerbation episodes. Ultimately, the choice of medication will depend on the severity of the condition, patient preferences, and any related coexisting medical issues or comorbidities present.

Corticosteroids are strongly recommended by international guidelines such as those provided by GOLD (Global Initiative for Chronic Obstructive Lung Disease) and BTS. Corticosteroids may be taken orally or intravenously depending on severity and patient ability to take medications. Studies have demonstrated the value of early corticosteroid treatment during AECOPD can lead to shorter hospital stays and reduce treatment failure, treatment escalation, and relapse risks. A shorter course (5-7 days) of corticosteroids should generally be advised because long-term use could result in osteoporosis, weight gain, increased infection risks, and further damage. Corticosteroid selection

and dosage depend on the severity of an exacerbation; typically, oral prednisolone should be sufficient in treating mild-to-moderate exacerbations while intravenous methylprednisolone may need to be given in cases requiring hospitalization. Patients experiencing frequent exacerbations are also recommended inhalable corticosteroids for maintenance therapy to reduce future exacerbation risk (O'Reilly, 2013).

Antibiotics and mucolytic can also play an essential role in managing AECOPD. Antibiotics may be necessary in cases when bacterial infection, which often exacerbates symptoms of COPD, is suspected. Antibiotic treatments typically last from 7-14 days depending on severity, medical history and local resistance patterns; and should only be given when truly necessary (and unnecessary use can increase risks for antibiotic resistance). Antibiotic treatment should only be considered necessary under clinical circumstances and is not often advised in all AECOPD cases as overuse increases resistance risks significantly. Mucolytics are medications designed to thin out mucus and make coughing and clearing from airways easier, making sputum production excessive or thick, or expectoration difficult and difficult. Mucolytics should usually be inhaled on an as-needed or regular maintenance therapy basis and include such substances as Acetylcysteine and Carbocisteine which have proven particularly useful when managing AECOPD symptoms. While antibiotics and mucolytics may help in managing AECOPD, their usage should only be when necessary. Overusing either could result in antibiotic resistance while overuse of mucolytics can irritate airway tissue leading to further symptoms worsening. (O'Reilly, 2013).

2.8. Predictors of Mortality in COPD

COPD is a major cause of death and in fact, respiratory dysfunction driving COPD is considered the third leading cause of death worldwide (Pahal, Hashmi and Sharma, 2022), which indicates that research efforts should be focused on how specific symptoms and markers can be used to predict COPD-related mortalities. Regarding the cause of death in COPD patients, the published literature showed varied findings. A previous study was conducted on 5887 smokers found that the mortality rate was 12% over 14 years follow-up, the main causes of death were cancer and cardiovascular diseases (CVDs) (Anthonisen *et al.*, 2005). However, in more severe COPD, the main cause of death was respiratory disorders as a 26-month follow-up study showed (Sin *et al.*, 2005). Another study (Calverley *et al.*, 2007) reported that respiratory disorders are the main cause

of death in COPD, followed by CVD and cancer. In this section, we review the current predictors of mortality in COPD.

2.8.1. Forced Expiratory Volume in 1 Second (FEV1)

COPD inflammatory process is multifactorial. FEV1 level is an important factor to determine respiratory function disorders and it relates with patients worsening symptoms leads to death. In the 1970s, Fletcher and Peto's landmark study (Fletcher and Peto, 1977), followed more than 2000 men over a period of 25 years to investigate the potential relationship between airflow obstruction and mortality. Their study was divided into two parts; an initial survey, which found that FEV1 is a strong predictor of mortality in COPD, whereas, longitudinal data demonstrated a weakness in that relationship. FEV1 has been utilized in COPD as a prime measure determining the presence of disease, its severity, and the response to different therapies. Undoubtedly, smoking is the most important factor that contributes to FEV1 declining in annual follow up. Although the FEV1 remains the most used in COPD prediction and severity measuring of COPD. (Celli *et al.*, 2008). Since then, several studies have reported the statistically significant, yet weak association between FEV1 and death due to COPD (Beaty *et al.*, 1982; Bang *et al.*, 1993; Hole *et al.*, 1996; Schünemann *et al.*, 2000).

2.8.2. Exercise Capacity

One of the COPD manifestations that can predict mortality is the patients' exercise capacity. The impairment in physical function and decreased exercise capacity are strong predictors for a severe decline in COPD (Oga *et al.*, 2003). The decreased exercise capacity can indicate respiratory or cardiovascular deterioration, and the ability of both systems to maintain oxygen supply (Pinto-Plata *et al.*, 2004). The published literature showed that measuring exercise capacity was the strongest determinant of the mortality among COPD patients. Other studies found that exercise capacity is a stronger predictor of mortality than BMI and FEV1. Clinically, exercise capacity can be helpful in assessment of many comorbidities and optimise clinical interventions (Oga *et al.*, 2003).

2.8.3. Body Mass Index

Body mass index is a strong contributing factor to COPD. There is a negative correlation between BMI and mortality; as decreasing body mass is associated with increased mortality (Wilson *et al.*, 1989; Gray-Donald *et al.*, 1996; Schols *et al.*, 1998). Whereas, further weight loss will enhance mortality risk and weight gain will help the prognosis (Landbo *et al.*, 1999; Prescott *et al.*, 2002). The fat-free mass index (FFMI) another indicator which provides further information than BMI has been investigated in COPD. It can determine an increase in mortality in such groups with their normal BMI. A prospective cohort study of COPD patients through a mean of seven years of following up (Vestbo *et al.*, 2006) showed that FFMI is a good predictor for disease severity prediction. Both are interrelated with the six-minute walk test, while FFMI correlates with severity of chronic dyspnoea.

2.8.4. Eosinopenia

Eosinophil count is a predictive marker commonly used to shape clinical decisions about the management and therapy of many conditions. The presence of proinflammatory mediators such as IL3 and IL5 triggers the migration of eosinophils from the blood to the site of inflammation, in which the main features of the condition take place (Conroy and Williams, 2001; Smit and Lukacs, 2006; George and Brightling, 2015). Specifically, when the eosinophil migrates into the lungs, proinflammatory mediators, namely eosinophil-derived neurotoxin, IL3 and IL5 initiate the inflammation and tissue damage (Moqbel, Levi-Schaffer and Barry Kay, 1994; George and Brightling, 2015). There are other mechanisms for mediating the lung inflammation, including, the thymic stromal lymphopoietin, (Ziegler *et al.*, 2013), which can play a role in eosinophil biology to regulate inflammatory cytokine expression. Eosinopenia is measured when the blood level of eosinophils is less than 0.01×10^9/l. The published literature reported a considerable association between eosinopenia and negative outcomes of AECOPD patients. Overall, eosinopenia can reflect the nature and severity of the inflammatory response. Thus, eosinopenia can be a useful, easy-to-detect, and low-cost test for predicting the prognosis of patients with AECOPD. Studies found that eosinopenia and other factors lead to significant alteration in blood cell counts, blood urea and serum creatinine (Sangwan et al., 2017). Blood eosinophilia can be employed as an indicator in AECOPD patients to predict all-cause mortality risk (Zhang *et al.*, 2020).

2.8.5. Consolidation

COPD causes alterations and remodelling to the physical structure of the lungs, which can be seen by CT scanning or chest radiography. These alterations may indicate consolidation, which can be defined as "evacuation, exudate, or other disease discharges that supersede alveolar air and render the pulmonary parenchyma airless" (Panse *et al.*, 2013). The published literature indicates that many AECOPD patients who were admitted to hospitals confirmed complicated consolidation (Confalonieri *et al.*, 2005; Wildman *et al.*, 2007; Tabak *et al.*, 2009). In terms of scanning, chest radiography is not the preferred choice given its poor accuracy. (Lieberman *et al.*, 2002; Hagaman *et al.*, 2009). Moreover, a previous study confirmed the increased inpatient mortality in patients who experienced chest consolidation with AECOPD either at admission or during follow-up sessions (Saleh *et al.*, 2015).

2.8.6. Acidaemia

The published literature shows that acid-base disorders and Acidaemia influence long-term survival of COPD patients. Several studies linked acid-based conditions with increased mortality rates in COPD patients (Bruno and Valenti, 2012). Acid-base disorders have been explored as potential factors affecting long-term survival for COPD patients through various studies that employ various study designs such as retrospective cohort, prospective cohort and case-control designs. Bruno and Valenti (Bruno and Valenti, 2012) conducted an impressive retrospective cohort study by analysing 338 COPD patients over ten years and found an association between acid-base disorders and COPD mortality rates; their research observed those with lower pH and greater carbon dioxide levels had an increased risk than those who maintained normal pH levels. Overall, experimental data indicates that acid-base disorders play a vital role in long-term survival of COPD patients; however, their exact nature remains poorly understood. Thus further investigation must be done into this relationship to uncover any underlying mechanisms or any possible interventions which might help improve COPD patients with acid-base disorders' outcomes.

2.8.7. Atrial Fibrillation

COPD patients with severe symptoms are at high risk of mortality, which can be associated with a broad range of comorbidities. COPD is linked with certain changes in electrocardiography in conjunction with an enhanced occurrence of cardiac arrhythmias, which comprise atrial flutter (AFL), atrial fibrillation (AF), multifocal atrial tachycardia (MAT), and non-sustained ventricular tachycardia (NSVT) (Bhatt and Dransfield, 2013). There are a variety of reasons why arrhythmias can happen in COPD, due to risk factors, and the effects of changing cardiopulmonary physiology in the treatment of COPD. Smoking, airway inflammation, hypoxia, hypercapnia, pulmonary hypertension, β-adrenergic agonist and steroids all lead to or worsen AF (Kinoshita *et al.*, 2009). Studies reveal atrial fibrillation as a predictor of exacerbation of COPD and linked with hospitalization and increased mortality rate (Steer et al., 2012). In addition, many studies have demonstrated that atrial fibrillation enhances the risk of death in 1-year (Chen and Liao, 2018).

2.9. Assessment Scores and Scales

In the attempt to provide a compressive assessment of COPD consequences, multifactorial indices that comprise several COPD variables have been developed and assessed. One of these indices is the BODE index, a multidimensional 10-point index that signals the risk of mortality in COPD patients. The BODE score includes four respiratory and systemic variables; BMI, FEV1, dyspnoea, and exercise capacity. The BODE score is superior over other unidimensional mortality prediction scores based on just FEV_1 monitoring (de Torres *et al.*, 2009). Furthermore, the BODE score can be utilized to anticipate the hospitalization as well. This score was validated and assessed by several authors (Celli and MacNee, 2004; Tashkin, 2011). Another multidimensional score called the COPD assessment test (CAT) has been suggested to measure and monitor health status of AECOPD patients by assessing the appearance of cough, sputum, shortness of breath, and chest tightness. A 3.5-unit change is the best indicator to assess the patient's responsiveness to the treatment. It is easy to use to facilitate the monitoring of the health status of the patient with AECOPD (Zhou *et al.*, 2018). This questionnaire showed good predictive performance.

Another multifactorial index called "DOSE score" was suggested to predict risk of mortality and deterioration in COPD patients. This index uses the available data reported and stored in the

electronic patient records to generate an estimate of patient' status (Jones *et al.*, 2009). A previous study tested this index and reported that DOSE index can significantly and accurately predict the prognosis of AECOPD (Jones *et al.*, 2016). Short and long-term readmission is one of the parameters that should be considered in COPD management given how it affects patients and healthcare facilities as well. In this regard, the PEARL score was developed to anticipate 90-day readmission in COPD patients. The importance of this score can be explained in the context of its effectiveness in shaping the treatment strategies for COPD patients (Echevarria *et al.*, 2017). This index comprises five factors; history of admissions, shortness of breath, patient age, right and left heart failure. A higher PEARL score means higher risk for readmission or mortality of COPD patients (Recio Moreno *et al.*, 2019).

2.9.1. The Dyspnoea, Eosinopenia, Consolidation, Acidemia, and Atrial Fibrillation (DECAF) Score.

As mentioned above, prognostic tools have been developed and validated for COPD. Nevertheless, in AECOPD, there have been few efforts to establish a valid predictive tool developed for the hospital setting. In 2012, a comprehensive prognostic index was developed and called the "DECAF score". This index includes five variables; "dyspnoea (D)", "eosinopenia (E)", "consolidation (C)", "Academia (A)", and "atrial fibrillation (F)" (**Figure 9**). In this scale, the most predominant parameter is dyspnoea, which can be assessed according to the extended Medical Research Council Dyspnoea score (eMRCD) **Table 2**. Eosinopenia is measured when the eosinophil count is less than 0.05×10^9/L. Consolidation can be identified by chest imaging. Acidemia is measured when the pH is less than 7.3. The DECAF score can be used to predict inpatient death in AECOPD. This tool has been shown to be applicable and efficient and can be helpful in identifying high risk groups, thus enabling clinicians to perform the most appropriate medical interventions. Additionally, DECAF score can identify patients who are eligible for early discharge and reduce burden and costs of healthcare (**Figure 10).**

Variable	Points
Dyspnea limiting the patient to home (MRCD 5) and	
Independent in bathing and/or dressing (eMRCD 5a)	1
Requires assistance with bathing and dressing (eMRCD 5b)	2
Eosinopenia (<0.05 × 10^9/L)	1
Consolidation (on chest X-ray)	1
Acidemia (pH < 7.30)	1
Atrial Fibrillation (on admission EKG)	1
Total score	6

Figure 9. The DECAF Score Calculation (Echevarria et al., 2015)

Table 2. Extended Medical Research Council Dyspnoea Score (EMRCD) (ECHEVARRIA ET AL., 2016)

"In the past 3 months, when you were feeling at your best, which of the following statements best describes your level of breathlessness?"	Grade
"Only breathless on strenuous exertion"	1
"Breathless hurrying on the level or walking up a slight hill"	2
"Walks slower than contemporaries, or stops after walking on the level for 15 min"	3
"Stops for breath after walking 100 m, or for a few minutes, on the level"	4
"Too breathless to leave the house unassisted but independent in washing and/or dressing"	5a
"Too breathless to leave the house unassisted and requires help with washing and dressing"	5b

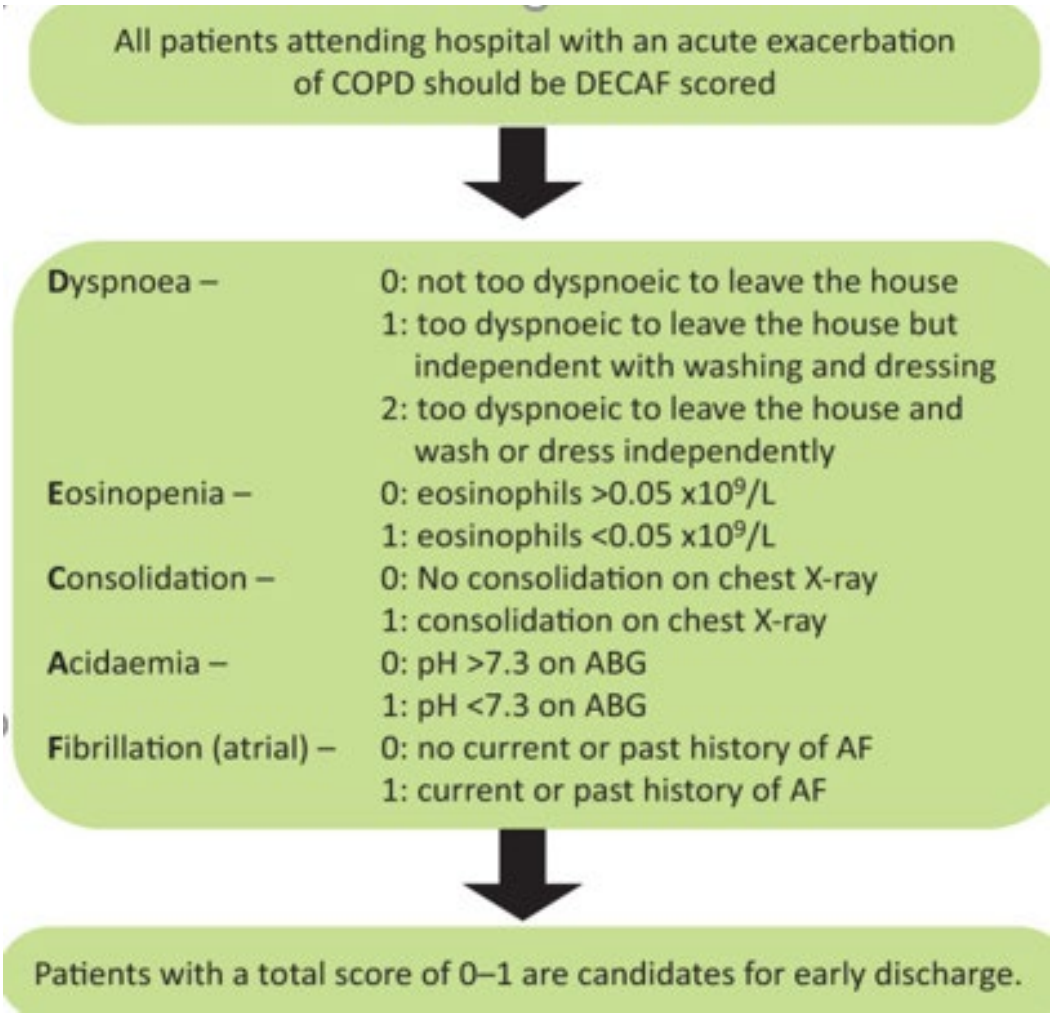

Figure 10. DECAF Flow for Early Discharge. COPD = Chronic Obstructive Pulmonary Disease. AF = Atrial Fibrillation. ABG = Arterial Blood Gases (Nadeem et al., 2021).

2.9.2. EXACT-PRO Tool

In the attempt to provide clinicians with a valid tool for early prediction of AECOPD and recovery, the Exacerbations of Chronic Obstructive Pulmonary Disease Tool-Patient-Reported Outcomes (EXACT-PRO) was developed and validated. The key principle of this tool is measuring the occurrence, severity, and duration symptoms of AECOPD. Furthermore, EXACT-PRO was used in research efforts to assess the effectiveness of AECOPD therapies. A previous study concluded that EXACT-PRO tool can significantly identify the severity of AECOPD. However, Mackay and colleagues raised a concern regarding the accuracy of this tool (Mackay *et al.*, 2014). They thought that this tool may ignore the nature of AECOPD symptoms, and thus fail to predict mortality and other factors.

2.9.3. BAP-65 Score

In 2015, Kumaraguru (Kumaraguru and Anur Ramakrishnan, 2015) believed that well-scored disease severity will assist effective therapy and ease the decisions made at triage. Therefore, they utilised the BAP-65 score in a prospective observational study among tertiary care hospital in South India. Hospital admissions were based on the BAP-65 severity scoring. This included risk factors such as elevated Blood Urea Nitrogen ≥ 25 mg/dl, altered mental status, Pulse ≥ 109/ and age > 65 years during time of admission until their discharge. Subjects were classified; as patients without any risk factors and, those less than 65 years of age are under class I. Patients with no risk factors who are above 65 years of age are classified as class II. Classes from III to V are then derived according to numbers of risk factors. The results found that a patient with a BAP-65 score of 3 and above were at greater risk, and more prone to die or might need ventilation, with a sensitivity of 71.9% and specificity of 86.9%.

2.9.4. Using Technology for Early Detection of AECOPD Severity

An innovative and creative study (Fernandez-Granero, Sanchez-Morillo and Leon-Jimenez, 2015) supports a new era of technology- associated symptoms prediction of severe disease. As acute exacerbations are one of the main causes that reduce health-related quality of life and lead to hospitalizations guided early prediction of exacerbations could reduce both adverse impacts and reduce the high costs incurred from COPD cases. Electronic records of daily respiratory sounds of 16 telemonitored acute exacerbated COPD patients were studied through an electronic sensor in an ad-hoc design for 6 months. The new model could predict an early acute exacerbation with evidence present an average of 4.4 days before the AECOPD clinical event. Thirty-two out of 41 exacerbations were detected early. The authors finally concluded that the machine-learning techniques significantly supported the early detection of COPD exacerbations (Fernandez-Granero, Sanchez-Morillo and Leon-Jimenez, 2015, 2018)

2.9.5. ProPal-COPD

The need for identifying COPD patients who require palliative care is challenging given the acute exacerbations episodes and absence of a valid tool that is intended for this purpose. The ProPal-COPD tool, which was developed by RG Duenk et al (Duenk *et al.*, 2017), can be used to predict the need for palliative care in COPD. This tool was basically constructed using multivariate

regression. The dependent variable was death within one year and independent variables were; Hypoxemia, using non-invasive ventilation, the need for homecare services, say "no" to this question "Would I (as pulmonologist) be surprised if this patient would die in the next year?", having severe comorbidity (cancer, heart failure, neuropathy induced by diabetes mellitus, or renal failure), Clinical COPD Questionnaire (>3), <30% FEV1, dyspnoea, BMI less than 21, and previous admission due to AECOPD. Overall, this tool was found promising in predicting the prognosis of COPD.

2.9.6. Malnutrition Universal Screening Tool (MUST) for AECOPD

Malnutrition Universal Screening Tool (MUST) is a nutritional screening tool that scores BMI, weight change and disease effect equally and determines a malnutrition risk score (Karsegard, 2004). Steer and colleagues (Steer *et al.*, 2010), investigated the malnutrition risk in AECOPD patients admitted to the hospital. One of the main observations was the change in body weight and BMI. They observed a dramatic change in BMI among this population and most with low body mass index (BMI) died. The MUST index provides a comprehensive assessment of malnutrition risk through a 6-month monitoring of BMI and weight loss. Specifically, this tool has 5 major steps; obtaining BMI, reporting the unplanned weight loss, establishing the influence of an acute disease on BMI, calculate the overall score, and use guidelines to develop a care strategy. Marco et al, reported that malnutrition is highly prevalent in AECOPD patients, and associated with 4 times death risk after two years follow up (Marco *et al.*, 2019). Steer and colleagues (Steer *et al.*, 2010) investigated whether the MUST index can predict inpatient death and readmission by recruiting 608 patients, half of them were females. The study concluded that the nutritional status and the highest risk of malnutrition (MUST score ≥2) can be considered as an important predictor for either in-hospital death or early readmissions as well for AECOPD hospitals patient.

2.9.7. Salzburg COPD-Screening Questionnaire (SCSQ)

A study was conducted in Austria by a group of scientists to conduct a series of studies to diminish the number of under-diagnosed cases. They used an initial questionnaire to identify which of the subjects required spirometer and therapy thereby identifying under-diagnosed cases. Questions from the Salzburg chronic obstructive pulmonary disease screening-questionnaire were selected using a logistic regression model, and risk scores depended on the regression coefficients. Eight hundred subjects were selected as a training sub-sample to create the score and another subgroup

of 458 samples used for testing. The Salzburg chronic obstructive pulmonary disease screening questionnaire was consisted of components related to “breathing problems”, “wheeze”, “cough”, “limitation of physical activity”, and “smoking”. At the >=2 points cut-off of the Salzburg chronic obstructive pulmonary disease screening questionnaire, sensitivity was 69.1% [95%CI: 56.6%; 79.5%], specificity 60.0% [95%CI: 54.9%; 64.9%], the positive predictive value 23.2% [95%CI: 17.7%; 29.7%] and the negative predictive value 91.8% [95%CI: 87.5%; 95.7%] to detect post-bronchodilator airflow obstruction. The external validation study in primary care confirmed these findings. This validated and self-administered questionnaire could therefore help to increase the efficiency of chronic obstructive pulmonary disease case-finding (Weiss *et al.*, 2017).

2.9.8. COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk (CAPTURE)

Martinez and his team used a case-control study design approach to develop a method to detect undiagnosed COPD with FEV1 <60% predicted or those at risk to develop an exacerbation of COPD in the US (Martinez *et al.*, 2016). The study groups were either a case, which consisted of patients with at least one exacerbation in that year or who had an FEV1 less than 60% predicted, or a control group, which consisted of healthy individuals or COPD patients with mild symptoms and severity (FEV1>60%). The primary outcomes for their study were peak expiratory flow (PEF) and optimal sensitivity (SN). Data mining was used to adopt the most approximate questions of the study questionnaire. The study led to the development of the CAPTURE score, which comprises five yes/no questions to generate a summated score. Martinez concluded that the CAPTURE score is a specific and sensitive diagnostic tool that could be easily implemented to primary care settings to provide information about the risk of AECOPD.

2.10. Healthcare in the United Arab Emirates and the United Kingdom

The UAE is a Middle Eastern country, which has the biggest economy in the region after Saudi Arabia (UNDP, 2015). As all aspects of life in the UAE, healthcare has seen considerable investment for decades, with notable expansion and improvements over recent years. Oil revenues are used to fund healthcare infrastructure development as well as attract and retain skilled medical staff. Recently, one significant development in Abu Dhabi is the establishment of the Abu Dhabi Health Services Company (SEHA), which oversees public healthcare facilities within Abu Dhabi. SEHA has overseen construction projects at several new hospitals and medical centres such as

Sheikh Shakhbout Medical City and Al Ain Hospital - two notable projects managed by SEHA. UAE healthcare systems have not only expanded in infrastructure terms, but have also taken great strides toward raising public awareness on public health matters such as obesity prevention or smoking cessation campaigns by the Ministry of Health and Prevention. Furthermore, Dubai Health Insurance Scheme was implemented nationwide which provides residents with affordable health coverage options. Investment in healthcare has also drawn top professionals from around the globe to work in UAE healthcare institutions and clinics, such as Cleveland Clinic Abu Dhabi which opened as part of their world-famous Cleveland Clinic network in 2015 to offer world-class medical services here in UAE.

According to data compiled by United Nations Development Program in 2015, the UAE population stood at 9.4 million while UK was home to 63.8 million residents; as per UNDP statistics in 2015, UK was placed 14th on Human Development Index while UAE came 41st; life expectancy for both nations is significantly different; UK having an 81 year lifespan as opposed to 79 for UAE residents. The UK spends 9.1% of GDP on public health spending while UAE devotes only 3.2%. As for health quality rankings, both countries rank 20th and 28th respectively; UK DTP vaccination rates stand out with only two percent of infants failing to be immunized in the UK while six percent lack DTP immunization in the UAE; healthcare in UAE is funded through revenues generated from capital, oil sales taxes and individual contributions while insurance acts as pooling agent while both public and private health service providers offer healthcare. Meanwhile in UK NHS is primary provider. Healthcare provision in the UAE is governed by both federal and emirate legislation, including licensing requirements and training programs for healthcare professions and clinical practices. Established in 1971, the Ministry of Health and Prevention (MOHAP) provides guidelines and licensing/training programs related to these practices; while in Abu Dhabi's capital city DOH and SEHA act as regulatory bodies.

Abu Dhabi's healthcare system has seen dramatic improvements due to collaborations with international health groups. Notable institutions that currently manage numerous facilities and hospitals include Johns Hopkins Medical, Cleveland Clinic, and Bangkok-based Bumrungrad International Limited (BIL). Health systems across the UK (England, Northern Ireland, Scotland, and Wales) differ in terms of policies, funding, and practice. Similar to the UAE, the UK provides healthcare to all permanent residents (Grosios, 2010). However, the private healthcare sector in the UK is substantially smaller than the public sector (Doyle and Bull, 2000).

Chapter 3. Detailed Literature Review on the DECAF Score

3.1. A Brief Statement about the Detailed DECAF Literature Review

The cornerstone of this thesis is the assessment of the DECAF score capacity and accuracy to predict AECOPD severity, inpatient mortality, and readmission due to AECOPD in Middle Eastern countries. Therefore, this chapter focuses on reviewing relevant studies, cases, and trials published in journals. Specifically, this chapter examines whether the DECAF score can play a role in predicting hospital mortality, AECOPD severity, readmission, early discharge, and potential associations between DECAF score and patient outcomes. Furthermore, this chapter summarises the relevant studies discussing strengths, limitations, patient groups, and settings. The studies investigating the DECAF score are summarised in **Table 3**.

Table 3. Literature Summary

First author's last name	Study method	Study aims	Country	Sample size (number of patients)	Findings
Huang (2020)	Systematic review and meta-analysis	To examine the association between DECAF score and the prognosis of AECOPD	China	8329	the DECAF score is more effective in predicting short-term mortality than other prognostic scores
Steer (2012)	Systematic review	To develop and assess the DECAF score in AECOPD	UK	920	the DECAF score was a stronger predictive index than APACHE II, BAB-65, and CURB-65, indices
Echevarria (2016)	observational study	to compare the predictive performance of the DECAF index with other indices such as CURB-65, BAB-65, and others, for predicting inpatient death	UK	1725	DECAF score had higher predictive performance for inpatient mortality and 30-day death than other indices
Echevarria (2019)	observational study	to compare the DECAF score with the National Early Warning Score 2 (NEWS2)	UK	2654	DECAF score does not replace repeated measures of NEWS2 during hospitalisation to detect the deteriorating patient.
Sharma (2020)	observational study	to investigate association between the DECAF index and patient outcomes in AECOPD	India	160	DECAF score is sensitive and specific in predicting in-hospital mortality in AECOPD patients
Sangwan	A prospective,	to compare between the DECAF score and BAB-65 index in predicting inpatient mortality in AECOPD	India	50	Both DECAF and BAP-65 scores were found to be good predictors of mortality and need for ventilation

First author's last name	Study method	Study aims	Country	Sample size (number of patients)	Findings
	observational study				
Memon	a prospective observational study	to assess the predictive performance of the DECAF score in AECOPD	Pakistan	162	the study did not compare the DECAF score with other indices
Nadeem	Retrospective observational study	to facilitate the early discharge of AECOPD patients with low DECAF score (0-1)	UK	20	DECAF score can facilitate the early discharge of low-risk patients
Rabbani	a retrospective observational study	to evaluate the accuracy and validity of the DECAF score for AECOPD patients	UK	159	DECAF score showed strong prediction for inpatient death and 30-day mortality
Collier (2015)	a prospective observational study	to evaluate the accuracy and validity of the DECAF score for AECOPD patients	UK	78	the DECAF score succeeded in predicting the need for NIV in addition to inhospital mortality

First author's last name	Study method	Study aims	Country	Sample size (number of patients)	Findings
Shi (2019)	a prospective observational study	to assess whether a newly modified DECAF score called "v-DECAF" can predict 90-day mortality in AECOPD	China	112	The v-DECAF score had good discriminatory power in predicting 90-day all-cause mortality in AECOPD patients requiring IMV
Shafuddin (2018)	Cohort study	to measure the 30-day mortality predictive performance of four tools: The DECAF score, BAB-65, CRP-65, and CURB-65	New Zealand	423	BAB-65, CRP-65, and CURB-65 were able to predict up to one year inpatient death, whereas, DECAF score predicted only 30-day mortality
Zidan (2015)	observational study	to measure the effectiveness of the DECAF score in predicting inpatient mortality in the emergency room in a large hospital in Egypt	Egypt	100	The DECAF score is a powerful score to predict in-hospital mortality from eCOPD
Yousif (2016)	observational study	To compared the DECAF score and other prognostic tools in predicting AECOPD mortality	Egypt	264	BAP-score had higher AUROC and was more accurate in predicting in-hospital mortality than DECAF
Nafae (2014)	observational study	To predict hospital mortality in patients with acute exacerbation of COPD	Egypt	200	The DECAF Score is a simple and effective clinical tool that can risk stratify hospitalized patients with AECOPD

3.2. The DECAF Score in the Literature

Prognosis studies, include assessments of the association between a disease outcome (endpoint) and its baseline state in order to enhance the well-being and health of patients. These studies are important to understand the nature of the disease and thus design approaches to prevent it (Hemingway et al., 2013). Prognostic studies may use one or more of the following themes; using biomarkers that are linked with health outcomes of the disease, the quality of the current care, statistical validation, and stratified clinical approaches (Hemingway et al., 2013).

Huang (Huang et al., 2020) conducted a meta-analysis to examine the association between DECAF score and the prognosis of AECOPD. This research included patients with specific criteria (patient above 18 years, diagnosis of AECOPD based on latest reference standard and original articles were included). The findings of meta-analysis showed that the DECAF score is more effective in predicting short-term mortality than other prognostic scores. The area under the receiver operating characteristic curves (AUROC) for 30-day and inpatient death were 0.79 and 0.83, respectively. Therefore, this meta-analysis indicates that the DECAF score has good predictive performance for 30-day death and overall excellent predictive performance for inpatient death. These findings demonstrate the value of the DECAF score as an effective tool in clinical assessment.

Steer and colleagues (Steer, Gibson and Bourke, 2012) were the first to develop and assess the DECAF score in AECOPD. The study included 920 patients, of which more than half (53.9%) were females and 34.2% were housebound. The AUROC for predicting inpatient death was 0.86 (95% CI 0.82-0.89), which reflects a strong predictive performance. Additionally, they indicated that the DECAF score was a stronger predictive index than APACHE II, BAB-65, and CURB-65, indices. Steer and colleagues found that the higher the DECAF score for AECOPD patients, the higher the severity of the disease. The findings of Steer's study are strengthened by the recruitment of a large number of AECOPD patients with a broad range of sociodemographic characteristics.

Echevarria and colleagues (Echevarria *et al.*, 2016) conducted an observational study to validate the DECAF score in six hospitals in the UK and to compare the predictive performance of the DECAF index with other indices such as CURB-65, BAB-65, and others, for predicting inpatient death. The statistical method to assess the predictive performance of the DECAF index was the area under the receiver operator characteristic (AUROC) curve. Their findings showed that the

DECAF index had an AUROC value of more than 0.8 in all settings included, which indicates a strong prognostic value for this index. Additionally, their findings showed that the DECAF score had higher predictive performance for inpatient mortality and 30-day death than other indices. The study reported that high values of DECAF score are significantly associated with longer hospital stay and more severe symptoms. However, Echevarria's study had two major limitations. First, part of the internal validation cohort was retrospective in nature, which could incorporate bias. Second, their study only included 6 NHS hospitals in the UK, which may raise concerns regarding the generalisability of the findings in other worldwide health care settings. Although their study proved to some extent the validity and accuracy of the DECAF score in predicting inpatient death in AECOPD, further outcome-based research investigating the clinical and economic values of the DECAF index is still necessary.

Echevarria and colleagues conducted another study on DECAF score in AECOPD. This time, they aimed to compare the DECAF score with the National Early Warning Score 2 (NEWS2). The AUROCs for DECAF score and NEWS2 were 0.82 and 0.73, respectively. Overall, the DECAF score had higher consistency, accuracy, and validity than other indices. Nonetheless, NEWS2 is necessary in early warning of AECOPD symptoms and consequences.

Sharma et al (Sharma *et al.*, 2020), conducted a study in a secondary care hospital in India to investigate association between the DECAF index and patient outcomes in AECOPD. In their study design, they divided patients into low-risk (0-2 DECAF score values), moderate risk (3 DECAF score value), and high risk (4-6 DECAF score values) groups. They reported that inpatient mortality rate in the high-risk group reached 70%. This percentage dropped into 7% in the moderate-risk group and into 0% in the low-risk group. Of the 160 patients included in their study, 137 were male and 142 were smokers. Among participants, 50 had a pH value of less than 7.3, 42 had consolidation, and 21 had eosinophil counts of less than 50 cells/mm^3.However, their study had several limitations. First, they did not use a robust statistical test (i.e. AUROC) to measure the validity of the DECAF score and they did not compare the DECAF index with other indices. Second, their study design was not adequate to assess whether the DECAF score can be used to make clinical decisions such as the need for urgent care or early discharge of patients. Third, they included one hospital and a small number of patients compared to other studies, which may limit the generalisability of their findings, especially in a huge country like India.

Another Indian study was carried out by Sangwan et al, (Sangwan, Chaudhry and Malik, 2017) to compare between the DECAF score and BAB-65 index in predicting inpatient mortality in AECOPD. The study was prospective in nature, with a relatively small number of participants (n=50). Among participants 9 (18%) died during their hospital stay. Overall, the study reported that both indices were good predictors for inpatient mortality in AECOPD, with no significant differences in predictive performance across the indices. However, with this methodology and sample size, it is extremely difficult to provide strong evidence regarding the predictive performance of these indices.

Memon et al (Memon *et al.*, 2019), performed a prospective observational study to assess the predictive performance of the DECAF score in AECOPD in the intensive care unit (ICU) of a large hospital in Pakistan between 2016 and 2018. Of the 162 patients included in their study, 69 (42.5%) were females and 21 (13%) died in the hospital. They found that patients who died were older and more likely to have a lower FEV1. Additionally, they reported that the mortality rate was between 60% and 70% for people with DECAF score 4 and 5, respectively. However, the Memon's study should be considered in the context of its limitations. First, the statistical tests used were descriptive and may not be adequate to assess the DECAF score and more sophisticated measures such ANOVA and AUROC are recommended. Second, the study did not compare the DECAF score with other indices. Third, some of the findings were not statistically significant, which can be attributed to the small sample size included. Additionally, they did not address the relationship between the DECAF score and other patient outcomes such as length of hospital stay.

Nadeem et al (Nadeem *et al.*, 2021), implemented the DECAF score in a general hospital in the UK to facilitate the early discharge of AECOPD patients with low DECAF score (0-1). The study nature was retrospective and the study design adopted was the plan, do, study, act (PDSA) strategy. They found that the DECAF score can facilitate the early discharge of low-risk patients. Nonetheless, there were no statistically significant findings regarding 30-day readmission and 30-day mortality. The Nadeem study had several limitations. First, the low number of patients, n=20 may limit the validity of the statistical analysis of the data. Second, the study was interrupted by the Coronavirus disease 2019 (COVID-19), which led to temporary suspension of the data collection. This could induce bias given the difficulty in determining the impact of the pandemic on the clinical status of patients included in the study. Additionally, the findings presented in the

Nadeem study may not be generalizable to other international settings given that they included patients from one hospital in the UK.

Two other studies were conducted in the UK to evaluate the accuracy and validity of the DECAF score for AECOPD patients. The first one was carried out by Rabbani and Brammer (Rabbani and Brammer, 2014) using a retrospective study design of n=159 patients. The outcomes of the study were inpatient death and 30-day mortality. While the DECAF score showed strong prediction for inpatient death and 30-day mortality, it failed to predict the need for non-invasive ventilation and 90-day readmission. The second study was conducted by Collier and colleagues (Collier *et al.*, 2015) using a prospective study design in 78patients. They reported that the DECAF score succeeded in predicting the need for NIV in addition to inhospital mortality. However, both studies were limited by their small sample size (n=159) and single setting.

Shi et al (Shi *et al.*, 2019), performed a prospective observational study in a single medical centre in China to assess whether a newly modified DECAF score called "v-DECAF" can predict 90-day mortality in AECOPD. Of the 112 patients included, 39 were females and 38 (33.9%) died during their hospital stay. Using logistic regression, Qi-Fang Shi et al reported that age, FEV1, urea, and albumin were significant predictors for 90-day mortality. The highest AUROC for 90-day death was reported in v-DECAF (0.85) and APACHE II (0.84), then the DECAF score (0.77). The main limitation for the study by Qi-Fang Shi et al, is that it included a single centre and a relatively small sample size, which could influence several parameters. For example, there was no significant difference in the prevalence of eosinopenia across patients.

Shafuddin and colleagues (Shafuddin, Chang and Hancox, 2018) carried out a comparative study in New Zealand to measure the 30-day mortality predictive performance of four tools: The DECAF score, BAB-65, CRP-65, and CURB-65. The study included 423 patients, of which 233 (55%) were females and 126 (30%) were smokers. Overall, there was no statistically significant difference in predictive performance across the four tools. However, BAB-65, CRP-65, and CURB-65 were able to predict up to one year inpatient death, whereas, DECAF score predicted only 30-day mortality. A potential explanation for their findings is the primary assumptions for the data analysis, in which they removed several parameters concerning the DECAF score including acidemia and eosinopenia data. The main limitation of the study by Shafuddin is missing information, which may incorporate bias into the study findings.

In the Middle East, Zidan and colleagues (Zidan *et al.*, 2015) conducted a study to measure the effectiveness of the DECAF score in predicting inpatient mortality in the emergency room in a large hospital in Egypt. The total number of patients included in their study was 100, of which 42% were females and 15% were older than 65 years. More than 60% of the patients had at least one admission to the hospital in the previous year and this was a significant determinant of inpatient mortality. The mean DECAF score was 1.3 (SD: 1.32). Among the study participants, 87 had Eosinopenia, 49 had consolidation, 12 had Academia, and 12 had AF. Older patients were more likely to die during their hospital stay. Additionally, they reported that there was a statistically significant association between the DECAF score and inpatient mortality. Zidan added the frequency of admission to the DECAF score and called it a "modified DECAF score". They found that this modified score is better than the DECAF score. Specifically, the AUROCs for the DECAF score and the modified DECAF score were 0.84 and 0.87, respectively. Another Egyptian study conducted by Yousif and El Wahsh (Yousif and El Wahsh, 2016) compared the DECAF score and other prognostic tools in predicting AECOPD mortality. Specifically, the modified DECAF score, the BAB-65, and the DECAF score were calculated and assessed using the AUROC. The study included 264 patients, of which 20 died during their hospital stay. The highest AUROC was found in the BAB-65 (0.86). Whereas, the AUROCs for the DECAF score and the modified DECAF were 0.82 and 0.77, respectively. These findings are contrasted by Nafea et al (Nafae, Embarak and Mostafa, 2014) who reported that the DECAF score is superior to other indices such as APACHE II, CAPS, and CURB-65.

In summary, the DECAF score showed a strong predictive performance for the severity and mortality of AECOPD in several settings and countries. Nevertheless, given the variation in data collection, inclusion criteria, and diagnosis of AECOPD, further multicentre studies with a larger sample size are required to highlight not only the advantages of the DECAF score, but also the gaps.

Chapter 4. Methodology

4.1. Introduction to the Methodology Chapter

This chapter of the thesis summarises the methodological procedures followed to answer the research questions addressed in my PhD. In detail, after the ethics approval statement, the first part of this chapter provides a closer look into the research methods mentioned in the published literature and justifies the methodological approaches for this research. Then, more details about the study design, settings, and participants are provided. These details include a description of the geographical, organizational, and professional structures of the study setting, and a summary for the inclusion and exclusion criteria of the research participants. Additionally, this chapter describes the processes of sampling, recruitment of participants, and data collection. A statement about the entities that approved the ethical part of the study was also provided. Finally, a detailed description of the statistical procedures adopted for the research data is provided. To illustrate the research flow, this chapter also contains a schematic diagram that shows the flow of the study in each methodological step.

4.2. Ethics Approval

The ethical aspects of the research programme were approved by the federal and local ethics committees; The Research Ethics Committees in the Emirates Health Services (EHS) (EHS/DXB-REC/JAA/No.29.2019) and Dubai Health Authority (DHA) (USRRC12-38/PhD/2020). (Appendix 1).

4.3. Research Approach in the Literature

To answer a specific research question or a set of questions, there are several study designs that can be adopted, modified, and used for collecting and analysing the data. In this section, I describe the strengths and limitations of several methodological approaches and their classifications. A study design can be defined as "a *framework, or the set of methods and procedures used to collect and analyse data on variables specified in a particular research problem*" (Ranganathan and Aggarwal, 2018). Study designs can be classified into observational versus experimental research designs (Ranganathan and Aggarwal, 2018). In observational studies, the research team documents a routine relationship between two or more variables or between the exposure (independent variable) and the outcome (dependent variable) without intervening or influencing the probability

of any variables. On the other hand, in experimental studies, the research team assesses an intervention that could influence the study variables. This intervention can be designed in several forms. For example, a drug that can be administered to patients or an administrative procedure such as implementation of digital health or clinical pharmacy services in a particular setting (Ranganathan and Aggarwal, 2018). Observational study designs can be analytical or descriptive. In descriptive-based study designs, the research outcomes describe the characteristics of a study variable without linking these features to other variables (Ranganathan and Aggarwal, 2018). On the other hand, in analytical-based study design, the research team attempts to test a relationship between two or more variables (Ranganathan and Aggarwal, 2018). More specifically, the research team tests the impact of the exposure variable on the outcome variable. From a classification point of view, analytical studies can be observational and interventional. Study designs also can be classified based on their directions into "*forward-direction*" or "*backward-direction*" (Ranganathan and Aggarwal, 2018). In forward direction-based studies, the research team firstly identifies the exposure variables and then measure the probability of outcome occurrence in a specific point in the future. This type of the studies is called a "*cohort study design*". In terms of timeline, study designs can be classified into "prospective" and "retrospective" studies (Ranganathan and Aggarwal, 2018). In prospective studies, the research team follow the participants or the study sample to observe or identify the study outcomes, which have not been occurred yet. On the other hand, in retrospective studies, the research team extracts information or data about an outcome that has already occurred in the past (Ranganathan and Aggarwal, 2018). A retrospective research method enables the research team to design hypotheses about potential relationships between an outcome and an exposure and to further assess the possible associations. Nevertheless, this type of study designs cannot lead to decisive statements regarding causal relationships between two or more variables. In a retrospective study design, the research team typically utilises electronic medical databases or surveying participants with a history of the study outcomes (Salkind, 2010). In terms of the type of data needed to answer the research questions, study designs can be classified into qualitative, quantitative, or mixed approaches. The textual display of the data is the core element of this type of quantitative study designs. In contrast, quantitative-based study designs include performing statistical tests to translate numerical data into meaningful findings (Steven et al, 2015; Mukhalalati and Ibrahim, 2019).

The main aim of this thesis was to investigate the newly designed DECAF score in acute exacerbation COPD patients in the UAE. This involves assessing potential association between the score and other variables such as disease severity and mortality. To fulfil this aim, I needed to look into patients' medical profiles and collect data without performing any intervention. Therefore, our study can be described as a Multicentred retrospective, observational study. This study design allowed us to observe the study variables and assess potential associations using minimum financial and humanistic resources. Given that validating the DECAF score was the main aim of this thesis, patient medical records needed to be accessed and no intervention by the researcher needed to be performed. Thus, reviewing the medical records retrospectively was appropriate to fulfil the research purposes.

4.4. Study Design and Setting

This was a retrospective, observational study conducted between 2019 and 2021 in 19 hospitals in the UAE. Data were retrieved from the electronic records of patients admitted due to an acute exacerbation of chronic obstructive pulmonary disease (AECOPD) units in Al-Amal, Al-Kuwait, Al-Qassimi, Al-Dhaid, Khorfakkan, Kalba, Kuwait, Ibrahim Bin Hamad Obaidullah, Abdullah Omran, Obaidalla Geriatric, Shaam and Saqr, Masafi, Dibba, Fujairah, Dubai, Rashid, Latifa Women and Children and Hatta hospitals. These hospitals were distributed in six UAE Emirates: Dubai, Sharjah, Ajman, Umm Al-Quwain, Fujairah, and Ras Al Khaimah. In research, choosing the appropriate setting for conducting the study is crucial to achieve the maximum favourable outcomes of our results. Hence, the research questions should be considered when choosing the suitable setting. Therefore, we choose these research hospitals from the leading health entities; the Dubai Health Authority and the Emirates Health Services- the executive health arm belongs directly to the umbrella of all health sectors in the UAE. The Ministry of Health and Prevention (MOHAP), Based in 1970, is a healthcare regulatory system in the UAE. It raises, updates and enforces healthcare policies that are followed across all the clinical establishments in the country and most of the regulations and laws. The UAE population is condensed more in Dubai and Sharjah, as reported by global media insight (GMI). Dubai has the largest population among the seven emirates, at around 3,551,734. Sharjah, with a population of 1,831,000, is the next largest city and has a north-eastern people of over 1,155,000. The total number of people in Dubai, Sharjah and the north-eastern is above 6,537,000 (GMI Blogger, 2023). This population overreaches to

Abu Dhabi's population by about 4,970,000 individuals. The Emirates Health Services and the Dubai Health Authority cover the majority of the population, and people with COPD. In this study, data collection from selected locations was simple and accessible. When choosing research settings, it's essential to take limitations into consideration, depending on factors like research question, area of interest, options available to them and constraints; all this allows researchers to confidently select an ideal site. As members of MOHAP organization where our research took place, it made accessing and including sufficient individuals with AECOPD easier. Furthermore, accessing help was simpler as membership of this institution meant quicker responses when seeking assistance or accessing sites for our research.

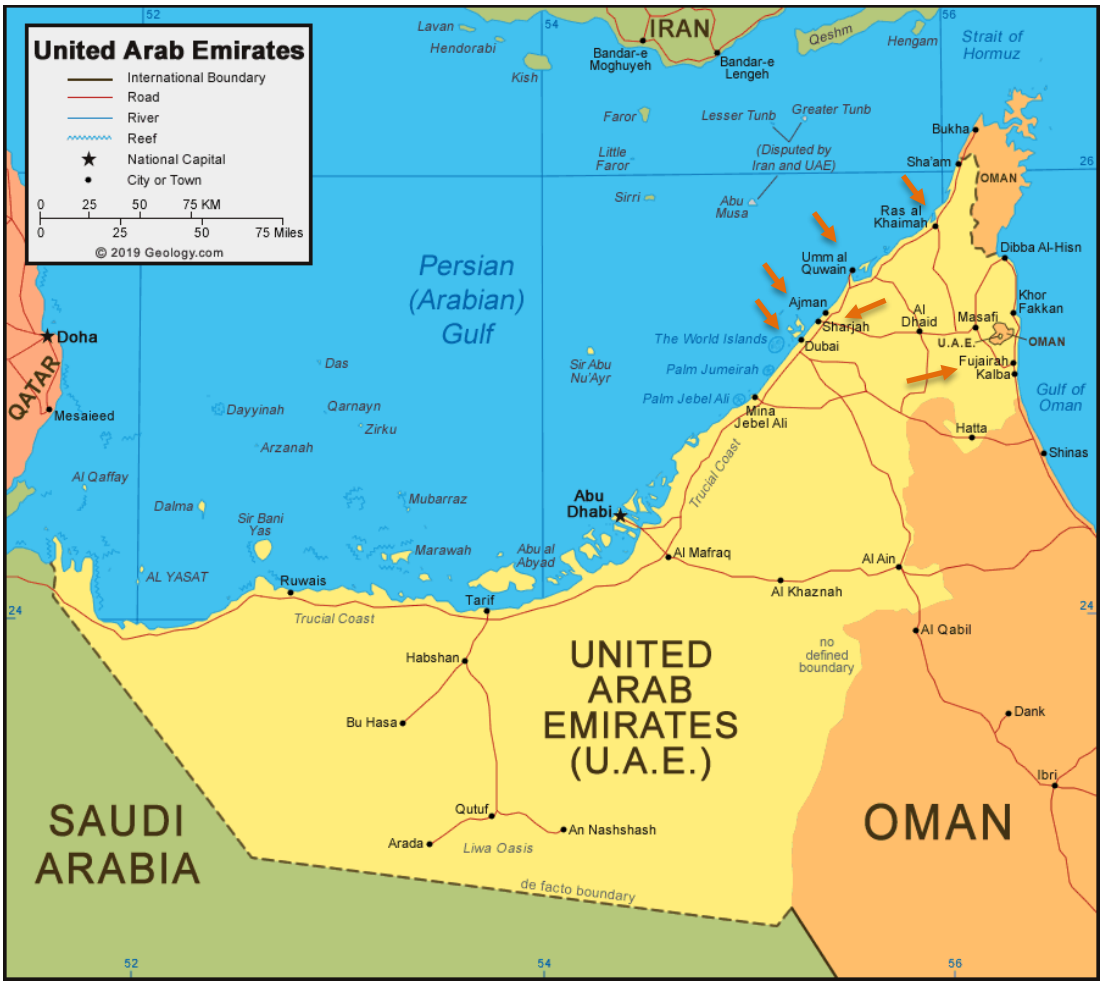

Figure 11. The United Arab Emirates Map (Geology, 2022). ***This figure shows the map of the UAE with arrows pointing to the cities where the hospitals were included in the study: Dubai, Um Quawin, Sharjah, Fujairah, and Ras Al Khaimah.***

4.5. Participants and Data Collection

In this thesis, patients who were diagnosed with AECOPD (non-pneumonic or pneumonic), aged more than 35 years, and heavy smokers were included. Patients who had other illnesses that could limit survival to less than one year were excluded from the study. Electronic records of all patients who met the above criteria were screened, retrieved, and analysed. The screening was identified by searching the visit number of the patients (admitted with COPD exacerbation) and then checked on the routinely recorded admission DECAF indices and the mortality which were frequently updated.

This observational retrospective DECAF validation study included 512 UAE nationals in a period between (Septembers 2018 – 2021) in the United Arab Emirates. This study involved patients admitted with AECOPD from 11 hospitals in the Emirates Health Services (EHS; 438 patients) and four hospitals from the Dubai Health Authority (DHA; 74 patients). The included hospitals were Sharjah/ Al-Qassimi hospital, Sharjah/Dhaid hospital, Sharjah/Kalba hospital, Sharjah/Khorfakkan hospital, Fujairah/Dibba hospital, Fujairah/ Fujairah hospital, Ras Al-Khaimah/ Saqr hospital, Ras-Al-Khaimah/ Abdullah Omran, Ras-Al-Khaimah/ Ibrahim Hamad bin Obaidullah hospital, Dubai Hospital, Rashid Hospital, Latifa Women and Children's Hospital, and Hatta Hospital.

Table 4 presents information about the participants of the study. Data for gender, age and smoking status for all 512 study participants from five locations within United Arab Emirates: Dubai, Sharjah, Ras Al Khaimah, Fujairah and Umm Al Quwain can be seen. A total of 67% of participants were male (67.0%), with Umm Al Quwain recording the highest male participation (90.0%) while Dubai recorded 43.8 % male participants, and 56.2 % of females being involved respectively (43.8% vs 10.0% in Umm Al Quwain and Umm Al Quwain, respectively. The mean age of participants was 73.3 with a standard deviation of 11.9 years; median age was also 74.3; mode age 64.0 was reported on an overall basis but not specific regions, and no age range information was made available by either region. Concerning their smoking status, most participants (68.7%) were former smokers with Dubai having the highest percentage (42.5%) and Sharjah having the lowest (16.0%). Sharjah saw 62.4%) current smokers while Umm Al Quwain (80.0%) only had 10 participants total and thus 80.0%) current as opposed to never smokers accounted for most participants (35.6%) with Umm Al Quwain (0%) having none at all.

When comparing males and females, the mean age differs slightly, with males having a mean age of 72.4 and females having a mean age of 75.2 ($p>0.05$) **(Figure 12)**. When cluster the mean age by sex and location **(Figure 13)**, the mean age of males in Dubai (65.2 years) was significantly lower than mean age of males in other regions. Also, the mean age of females in Umm Al Quwain (87.1 years) was significantly higher than mean age of females in other regions.

Table 4. Characteristics of Participants

Parameter	Total	Dubai	Sharjah	Ras Al-Khaimah	Fujairah	Umm Al Quwain
Gender						
Female	169 (33.0%)	42 (56.2%)	61 (33.7%)	47 (30.5%)	28 (29.8%)	1 (10.0%)
Male	343 (67.0%)	32 (43.8%)	120 (66.3%)	107 (69.5%)	66 (70.2%)	9 (90.0%)
Age (years)						
Mean (SD)	73.3 (11.9)	79 (9.2)	71.6 (11.8)	71.4 (12.7)	75.8 (11.2)	67.4 (7.6)
Median	74.3	--	--	--	--	--
Mode	64.0	--	--	--	--	--
Range	83.7	--	--	--	--	--
Smoking Status						
Current	64 (12.5%)	16 (21.9%)	113 (62.4%)	89 (57.8%)	55 (58.5%)	8 (80.0%)
Former	352 (68.7%)	31 (42.5%)	29 (16.0%)	44 (28.6%)	27 (28.7%)	2 (20.0%)
Never	96 (18.8%)	26 (35.6%)	39 (21.5%)	21 (13.6%)	12 (12.8%)	0 (0.0%)

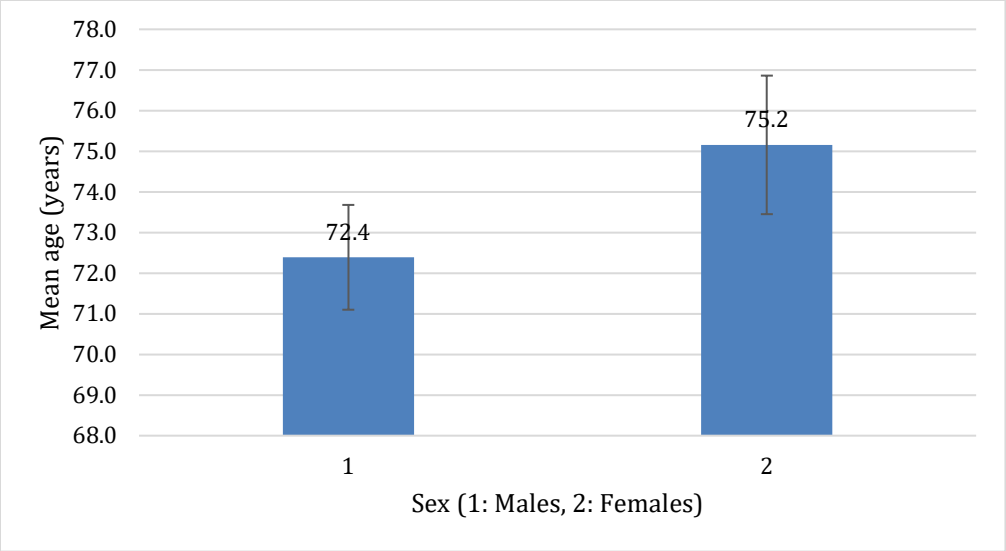

Figure 12. The Mean Age across Males and Females

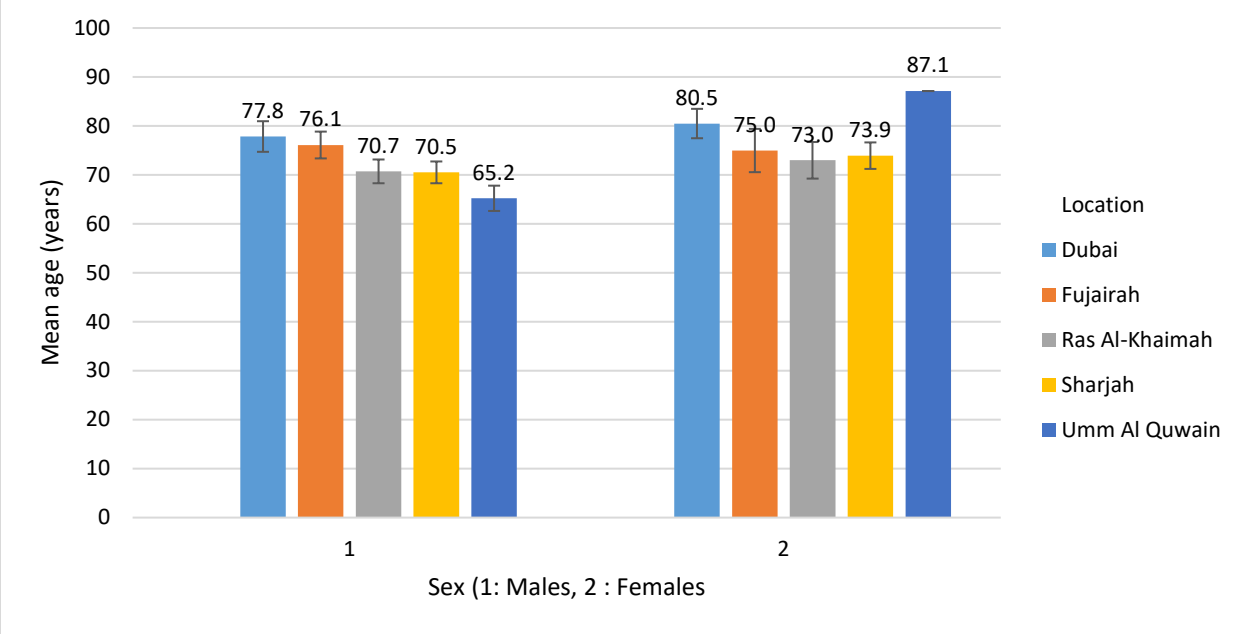

Figure 13. Mean Age by Sex and Location

4.6. Study Outcomes

There were three major outcomes prospectively designated for this thesis; 1) the validation of the DECAF Score for inpatient death, 30-days death, and 90-day readmission, 2) an analysis of the patient length of stay across DECAF score, and 3) differences in means of pH, Eosinophil numbers, CRP, and Urea levels across patients with different DECAF scores. Secondary outcomes were the proportions of patients with atrial fibrillation across DECAF score and the differences in needing assistance for doing activities across DECAF score. Additionally, the thesis provides a description of the sex, age, smoking status, mortality rate, markers of disease severity, exercise tolerance, body mass index (BMI), vital signs, laboratory findings (sodium, potassium, Urea, Creatinine, Albumin, Bilirubin, Troponin, C- reactive protein, Haemoglobin, WBC, Haematocrit, Platelet, Neutrophil Eosinophil, pH, PaO2, PaCO2, HCO3, and medical history (medications and comorbidities) of participants.

4.6. Data Management and Statistical Analysis

After the completion of the data collection step, data were entered into an Excel sheet (Microsoft Corporation, 2018) and cleaned. Data cleaning was performed to remove duplicates or any faulty data from the database. The data cleaning protocol was adopted from Broeck's framework and included three main steps; screening, diagnosis, and editing (Broeck, 2005). In this study, screening in data cleaning involved the identification and deletion or flagging of any outliers or errors found within a dataset, such as duplicate records or missing values that could potentially indicate error. Also included in data cleansing processes are efforts aimed at eliminating duplicate entries while checking for missing values that might represent gaps, and noting any unusual values which might represent potential sources of discrepancies that warrant further analysis. Diagnosing data involved reviewing flagged data to ascertain its integrity or invalidity based on cross-referencing with other data sources or statistical analysis to detect patterns and trends. Editing is the act of making adjustments to data in order to correct for any identified errors and inconsistencies, including imputing missing values, correcting data entry mistakes or eliminating outliers that appear as potential sources of inaccuracy.

Then, the excel sheet was imported into the Statistical Package for the Social Sciences (SPSS) version 24 (Armonk, NY: IBM Corp). The first step in data analysis was assessing the missing

values patterns and dropping all variables with more than 50% missing data. Then, the Markov Chain Monte Carlo (MCMC) approach to impute the data into the study variables was applied. MCMC is a multiple imputation method used to solve the problem of missing data by generating several plausible imputed datasets (Li XS, 2005). The second step was to perform a descriptive analysis of data, in which demographic and medical information of participants were described as absolute numbers (n) with proportions (%). Continuous variables were presented as means with standard deviations. The third step was comparing the means length of stay and laboratory markers (pH, Eosinophil counts, CRP, and Urea levels) across patients with different DECAF scores using ANOVA test (p values of less than 0.05 were considered significant results). The Tukey post-hoc analysis was used to make pairwise comparisons between group means. The error bars test with 95% confidence interval (CI) was used to measure differences in the proportions of patients with atrial fibrillation and the level of needing assistance across DECAF score. Chi-square and Fisher's exact tests were used to measure differences in the DECAF score across sex, locations, diabetes, and smoking status. A p value of less than 0.5 was considered a significant finding.

4.6.1. Area under the Receiver Operating Characteristics Analysis

The validation of the DECAF score was performed using the Area under the Receiver Operator (AUROC) curve for inpatient death, 30-days death, and 90-day readmission. AUROC is an effective test to evaluate the accuracy of the DECAF predictions by graphing sensitivity versus one minus specificity. Sensitivity measures the ability of tests or models to correctly identify individuals who possess an illness (true positives). It can be calculated as the proportion of these people who test positive. Specificity measures a test or model's ability to correctly identify individuals who do not meet its criteria (true negatives). AUROC is an indicator of diagnostic test or prediction model performance, calculated by graphing sensitivity (true positive rate) against specificity (false positive rate) at various thresholds and measuring its area under the curve. A score of one indicates perfect discrimination, while scores below half indicate no discernibility at all, equivalent to performing no better than chance.

To perform the AUROC analysis, the DECAF score variable was coded from 0 to 6 and identified as a state variable. Inpatient death, 30-days death, and 90-day readmission were the test variables. The Hosmer–Lemeshow test was used to test whether the data fits the AUROC model and measure whether the observed event rates match the expected event rates in the population subgroup. The

Hosmer-Lemeshow test is a goodness-of-fit test used to measure the calibration of predictive models. It evaluates whether the predicted probabilities match the observed frequencies from data. If such tests indicate poor calibration of the predicted probabilities, this suggests possible bias and the need for correction.

AUROC curve analysis and Hosmer-Lemeshow tests serve as invaluable tools in evaluating the accuracy and calibration of predictive models. While AUROC analyses discrimination power of models, Hosmer-Lemeshow assesses calibration properties. Both tests are essential in gauging overall DECAF model performance. A p-value of more than 0.05 indicates a good fit.

Sensitivity (also referred to as recall, hit rate, or true positive rate) measures the proportion of actual positives that were correctly identified by a binary classification model. It can also be calculated as the ratio between true positives (TP) and the sum of true positives and false negatives (FN). Sensitivity ranges from 0 to 1; higher values indicate better performance. Specificity measures the proportion of actual negatives correctly identified by a binary classification model, expressed as a ratio between true negatives (TN) and the sum of true negatives and false positives (FP). Specificity ratings range from 0 to 1; higher numbers indicate better performance of the model.

Sensitivity and specificity are two essential metrics used to assess the performance of binary classification models, with sensitivity measuring how well a model identifies positive cases while specificity assesses its ability to correctly classify negative ones. Both metrics provide invaluable measurements of performance - prioritization will depend on which problem needs solving first.

	Disease	
Test	**Present**	**Absent**
Positive	True Positive (TP)	False Positive (FP)
Negative	False Negative (FN)	True Negative (TN)

Figure 14. Sensitivity and Specificity of the Area under the Receiver Operator (AUROC) Curve. ***Sensitivity refers to the percentage of true positives (TP) identified correctly by a model; specificity measures the proportion of true negatives (TN) correctly identified by it. Sensitivity can be calculated by dividing true positives by total true***

positives plus false negatives as follows: Sensitivity = TP/ (TP +FN); specificity can then be computed similarly but by taking their opposite: specificity = (TN / (TN+FP).

Chapter 5. Results

DECAF score calculation was possible in 472 (92.2%) of patients, In the UK DECAF study, there were no DECAF missing data found (Echevarria *et al.*, 2016). In patients where, DECAF score could not be calculated, this occurred due to lack of recorded data for eMRCD score in 20 (3.9 %) patients, eosinophil count was absent in 36 (27.3%) patients, in 37 (7.2%) patient's chest X-ray information for consolidation was not available. The following data were missing from the study: n= 40 (7.8%) of DECAF scores, 20 (3.9%) of eMRCD, and 277 (54.1%) of 30-day death after admission data were missing. There was no missing inpatient mortality data. The proportions of missing data in length of stay, comorbidities, and 90-day readmission data were 21.5%, 15.4%, and 2.1%, respectively.

5.1. Missing Data

As a routine a lot of different data is meant to be collected in standard UAE practice .The first finding was that a lot of this information was not collected effectively in real world practice and there was a lot of missing data. Despite the significant improvements in setting up guidelines, for example, HAAD Guidelines for the Diagnosis and Management of Chronic Obstructive Pulmonary Disease (COPD), several challenges have arisen affecting the quality of health services. The missing or shortage of data may be the need for a well-established system and strong incorporation between the healthcare system and the level of public knowledge in expressing their symptoms and delivering accurate information to the healthcare providers (Mohammad Sharif, 2016).We found no established cut-off from the literature regarding an acceptable percentage of missing data in a dataset for valid statistical inferences (Dong and Peng, 2013). Overall, 40 (30.5%) of variables included in the study had at least one missing value and 30.8% (20636) of values included in the dataset were missing. As shown in **Table 5**, 40 (7.8%) DECAF scores could not be calculated, 20 (3.9%) patients were missing eMRCD scores. For 277 (54.1%) patients30-day death after admission data were missing. There was no missing inpatient mortality data. The proportions of missing data in Length of stay, comorbidities, and 90-day readmission data were 21.5%, 15.4%, and 2.1%, respectively.

Table 5. Analysis of Missing Data

Variables	Missing values, N, (%)
Resus IPPV	506 (98.8%)
CRP	505 (98.6%)
Resus: NIV treatment	505 (98.6%)
IPPV	500 (97.7%)
NIV respiratory acidosis during admission	497 (97.1%)
ABG deemed unnecessary and sats >92% on room air	496 (96.9%)
Dementia	496 (96.9%)
NIV treatment	493 (96.3%)
Number of smoking years	487 (95.1%)
BUN	482 (94.1%)
Cigarettes/day	475 (92.8%)
Sats (respiratory aids)	471 (92.0%)
Glucose fasting	466 (91.0%)
No. of admission 6months (non-R)	464 (90.6%)
No. of admission 12 months (non-Resp)	461 (90.0%)
No. of AE visits in past 6 months(0-R)	449 (87.7%)
No. of AE visits in past 12 months(non-R)	445 (86.9%)
ABG; FiO_2	444 (86.7%)
No.of AE visits in past 6 months(R or non-R)	423 (82.6%)
CO_2 sat art	422 (82.4%)
No.of AE visits in past 12 months(R)	420 (82.0%)
Asthma	399 (77.9%)

Variables	Missing values, N, (%)
Weight change 3-6 monthsago more than 10%	390 (76.2%)
Weight (3-6 mons)	383 (74.8%)
nutrition intake for more than 5 days	380 (74.2%)
O_2 sat art	378 (73.8%)
Attend pulmonary Rehab	362 (70.7%)
IHD	358 (69.9%)
SPO_2	354 (69.1%)
Exercise tolerance	343 (67.0%)
No. of exacerbation past 12 months	341 (66.6%)
admission GCS	340 (66.4%)
social history	340 (66.4%)
No. of admission 6months (Resp)	338 (66.0%)
No. of admission 12 months (Resp	336 (65.6%)
Age at diagnosis	331 (64.6%)
Current age	326 (63.7%)
Diabetes	279 (54.5%)
30-days of death after admission	277 (54.1%)
HTN	264 (51.6%)
Smoking history	249 (48.6%)
pO_2 (mmHg)	186 (36.3%)
Troponin (ng/mL)	186 (36.3%)
HCO_3 (Mmol/L)	183 (35.7%)
pCO_2(mmHg)	174 (34.0%)
Ph	172 (33.6%)
Creatinine(umol/L)	161 (31.4%)
Height (m)	141 (27.5%)

Variables	Missing values, N, (%)
Weight admission(Kg)	121 (23.6%)
Bilirubin (umol/L)	115 (22.5%)
Albumin (gm/L)	113 (22.1%)
LOS	110 (21.5%)
Serum	95 (18.6%)
CRP (mg/L)	93 (18.2%)
Comorbidities	79 (15.4%)
Previously inclusion in the validation study	69 (13.5%)
admission Temp	65 (12.7%)
Discharged Deceased in this admission	56 (10.9%)
Urea(Mmol/L)	42 (8.2%)
Confusion	41 (8.0%)
DECAF SCORE	40 (7.8%)
Feeding	38 (7.4%)
Dressing	38 (7.4%)
Consolidation	37 (7.2%)
Washing	37 (7.2%)
Eosinophils ($10^{(3)}$)/mcL)	34 (6.6%)
Neutrophils Absolute	30 (5.9%)
WBC$10^{(3)}$)/mcL	28 (5.5%)
Eosinophil Absolute	27 (5.3%)
Baseline Cr (umol/L)	24 (4.7%)
Cough;	22 (4.3%)
Admission on RR	20 (3.9%)
eMRCD	20 (3.9%)
Neutro %	13 (2.5%)
Plt ($10^{(3)}$)/mcL)	13 (2.5%)
Hct (%)	12 (2.3%)
90-day readmission	11 (2.1%)

Variables	Missing values, N, (%)
Haemoglobin (gm/dL)	10 (2.0%)
Admission pulse rate (bpm)	10 (2.0%)
admission Systolic (mmHg)	9 (1.8%)
admission Diastolic (mmHg)	8 (1.6%)
Admission	8 (1.6%)
K (Mmol/L)	6 (1.2%)
Na (Mmol/L)	6 (1.2%)
Steroids 2 weeks preadmission	1 (0.2%)

IPPV: Intermittent positive-pressure ventilation. BUN: Blood urea nitrogen, HTN: hypertension, Hct: haematocrit Plt: platelet CRP: C - reactive protein LOS: length of stay. IHD: ischemic heart disease. EMRCD: exacerbation modified Medical Research Council Dyspnoea Scale. Cr: creatinine. WBC: white blood cells

5.2. Descriptive Findings

In this section, we describe the data after imputation using frequencies, means, and medians. The means (SD) age and length of stay at hospital of our 512 participants were 73.3 (11.9) years and 14.3 (32.5) days respectively **Table 6**. Among participants, 169 (33.0%) were females and 64 (12.5%) were smokers. The incidence of inpatient death and 90-day readmission was high 24.40% and 35.9%, respectively. The median DECAF score was 3. The top three comorbidities were hypertension (48.3%), diabetes (45.4%), and atrial fibrillation (45.2%) (**Figure 15)**.The findings of this study showed that more than half of patients 56.4% had DECAF score between 3 and 6. Across the study participants, 195 (38.1%) had eMRCD score (0-4), 165 (32.4%) had eMRCD (5a), and 152 (29.6%) had eMRCD (5b). Of the 512 participants included in this study, 303 (59.6%) needed assistance in washing, 300 (58.5%) needed assistance in dressing, 312 (60.8%) needed assistance in feeding, and only 39 (7.6%) tolerated exercise. Upon admission, the means (SD) BMI and pulse rate were 30.7 (13.6) kg/m^2 and 106.4 (32.2) beat per minute, respectively. Furthermore, 14.6% had acute confusion, 46.0% had lung consolidation, and 62.9% had pH less than 7.35. Of the 512 patients included in this study, 61.3% were on diuretics, 39.6% were on statins, and 30.1% were on beta blockers **(Figure 15).**

Table 6. Descriptive Findings (N=512)

Parameters	Total, n (%)
Sex	
Male	343 (67.0%)
Female	169 (33.0%)
Age, mean (SD)	73.3 (11.9)
Smoking	
Yes, current	64 (12.5%)
Yes, former	352 (68.7%)
No, never	96 (18.8%)
Inpatient death	125 (24.4%)
90-days readmission	184 (35.9%)
DECAF, median (range)	3 (6)
DECAF (0-1)	112 (21.9%)
DECAF (2)	111 (21.7%)
DECAF (3-6)	189 (56.4%)
Markers of disease severity	
eMRCD score (0-4)	195 (38.1%)
eMRCD (5a)	165 (32.4%)
eMRCD (5b)	152 (29.6%)
Needing assistance in performing activities	
Washing, yes	303 (59.6%)
Dressing, yes	300 (58.5%)
Feeding, yes	312 (60.8%)
Exercise tolerance, yes	39 (7.6%)
Clinical data on admission	
BMI, kg/m^2, mean (SD)	30.7 (13.6)
Acute confusion	75 (14.6%)
Pulse rate (bpm), mean (SD)	106.4 (32.2)
sBP, (mm Hg), mean (SD)	126.2 (36.1)

Parameters	Total, n (%)
dBP, (mm Hg), mean (SD)	77.8 (20.7)
Temperature, (C^{o}), median (range)	36.9 (4.9)
Oxygen saturation, median (range)	91 (60.0)
Length of stay at hospital (days), mean (SD)	14.3 (32.5)
Lung consolidation, yes, n (%)	236 (46.0%)
Lab findings on admission	
Na (Mmol/L), mean (SD)	136.6 (5.7)
K (Mmol/L), mean (SD)	4.6 (7.7)
Urea (Mmol/L) mean (SD)	16.1 (21.3)
Creatinine (umol/L), mean (SD)	157.4 (248.3)
Albumin (gm/L), mean (SD)	31.9 (19.6)
Bilirubin (umol/L), mean (SD)	16.4 (18.5)
Troponin (ng/mL), mean (SD)	631.9 (1573.2)
CRP (mg/L), mean (SD)	74.6 (83.7)
Haemoglobin (gm/dL), mean (SD)	12.6 (9.4)
WBC ($x10^{(3)}$/mcL), mean (SD)	10.5 (5.0)
Haematocrit (%)	37.2 (11.0)
Platelet ($x10^{(3)}$/mcL),	252.9 (98.8)
Neutrophil ($x10^{(3)}$/mcL),	11.8 (48.3)
Eosinophil ($x10^{(3)}$/mcL),	2.1 (2.4)
pH, median (range)	7.3 (1.3)
PaO2 (mmHg), median (range)	70.0 (49.9)
PaCO2 (mmHg), median (range)	55.8 (21.9)
HCO3 (Mmol/L)	28.1 (7.4)
PH<7.35, n (%)	322 (62.9)

Data are presented as n (%), unless otherwise indicated. SD: standard deviation. DBP: systolic blood pressure, dBP; diastolic blood pressure. CRP: C-reactive protein. SD: Standard Deviation. DECAF: Dyspnoea, Eosinopenia, Consolidation, Acidemia, and atrial Fibrillation. eMRCD: modified Medical Research Council Dyspnoea Scale. BMI: Body Mass Index. bpm: Beats per Minute. C^{o}: Degrees Celsius. Na: Sodium. K: Potassium. WBC: White Blood Cell. HCO3: Bicarbonate. PaO2: Partial Pressure of Oxygen. PaCO2: Partial Pressure of Carbon Dioxide.

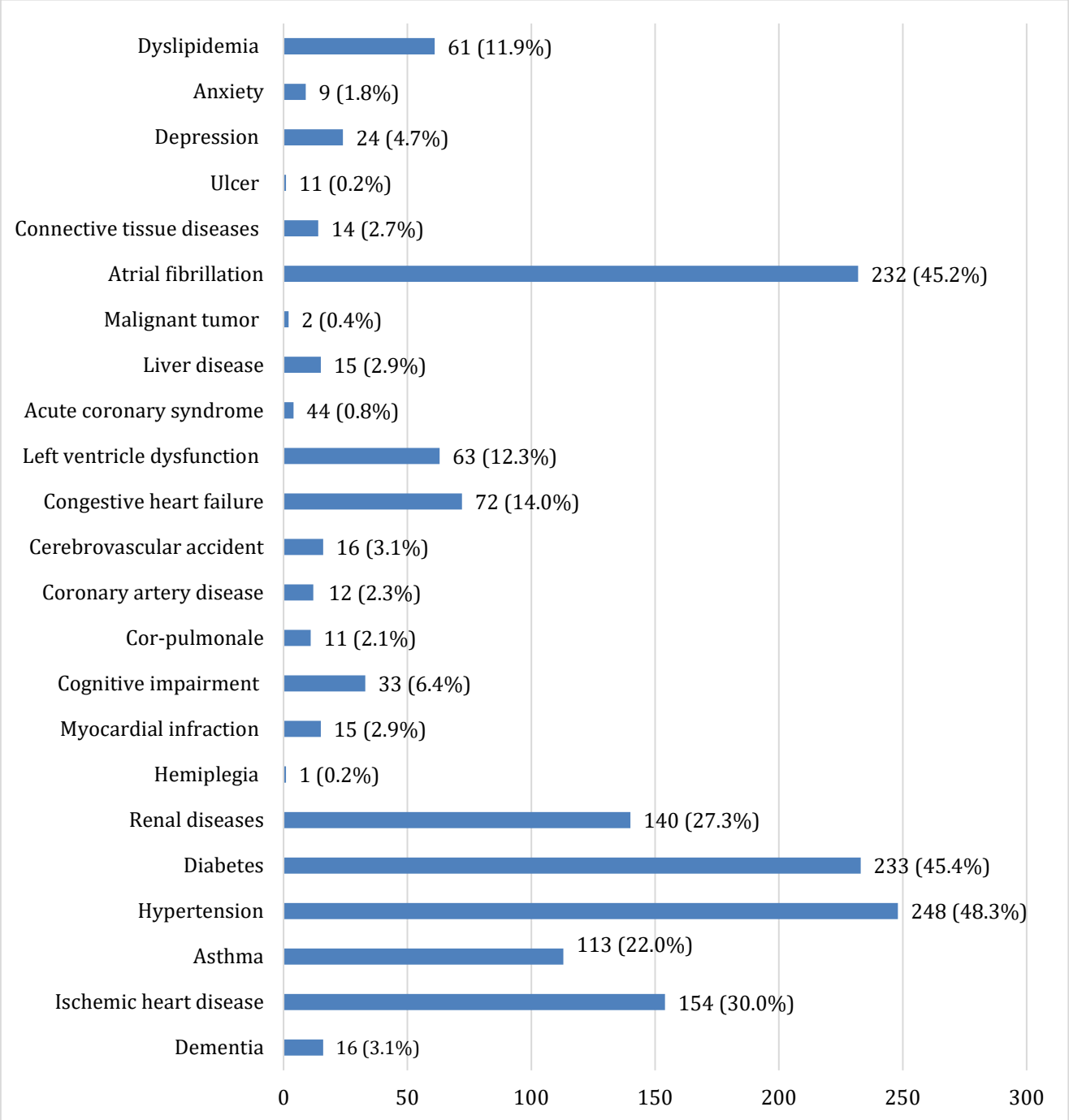

Figure 15 .Comorbidities, data are presented as n (%). Denominator is 512.

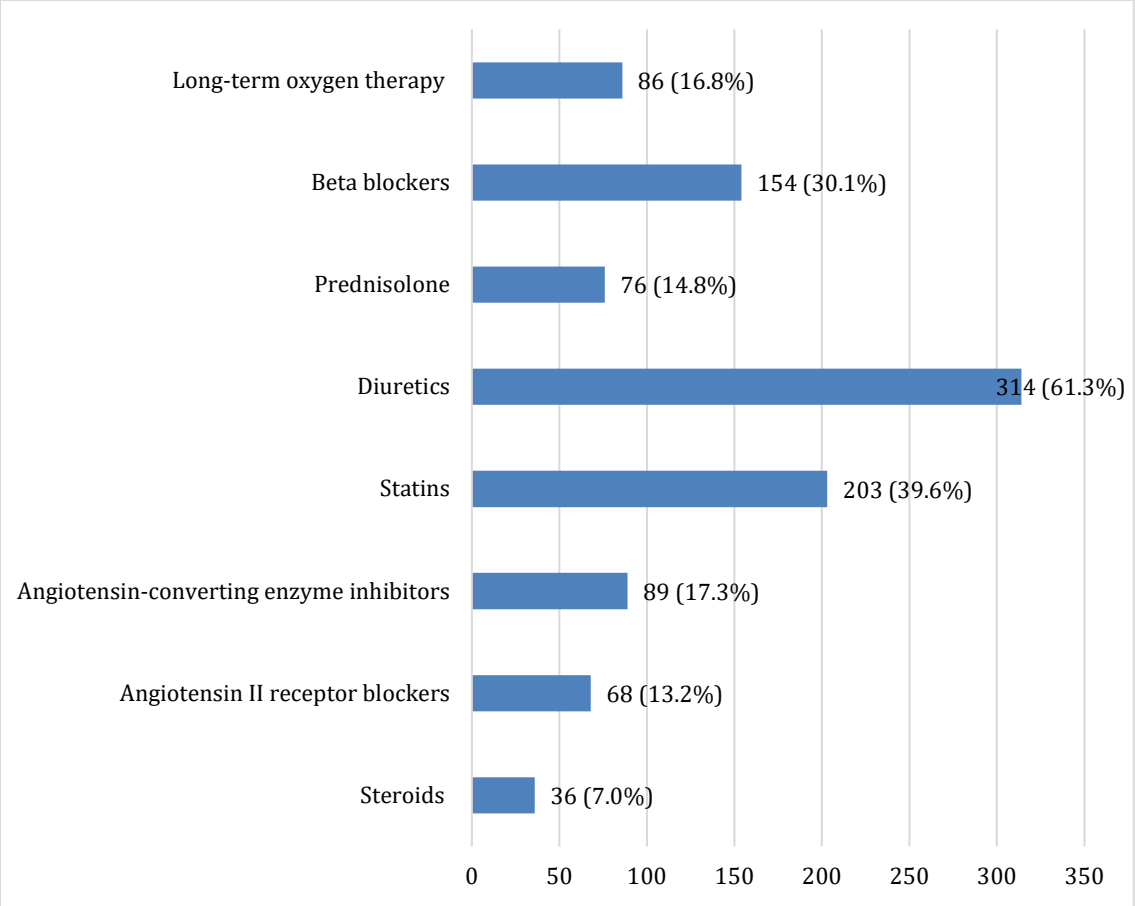

Figure 16. Frequency of Medications Used

5.3. Validation of the DECAF Score.

The AUROCDECAF curves for inpatient death, 30-days death, and 90-day readmission were 0.8 (95% CI: 0.8-0.87), 0.8 (95% CI: 0.7-0.8), and 0.8 (95% CI: 0.8-0.8), respectively (**Table 7 and figure 17, 18, 19**). These values are derived from the AUROC curves plotted for the respective outcomes, and they indicate that the model has a good discriminatory ability for predicting these outcomes.

The model was a satisfactory fit to the data (Hosmer–Lemeshow statistic=0.195, Nagelkerke R^2=31.7%). The Hosmer-Lemeshow test is a goodness-of-fit test used to assess the agreement between the predicted and observed outcomes of a logistic regression model. In the given statement, the Hosmer-Lemeshow statistic is reported as 0.195, indicating that the model fits the data well. Additionally, the Nagelkerke R2 value of 31.7% indicates that the model explains a considerable amount of the variation in the outcome variable.

Table 7. Validation OF DECAF Score against Inpatient Death, 30-Day Death, and 90-Day Readmission

Score	AUROC curve (95% CI) inpatient death		AUROC curve (95% CI) 30-days death*		AUROC curve (95% CI) 90-days readmission	
DECAF	0.8 (0.8-0.87)		0.8 (0.7-0.8)		0.8 (0.8-0.8)	
	Sensitivity	1-Specificity	Sensitivity	1-Specificity	Sensitivity	1-Specificity
1	0.992	0.910	1.000	0.941	0.989	0.896
2	0.960	0.724	0.966	0.831	0.978	0.671
3	0.888	0.460	0.897	0.559	0.870	0.393
4	0.712	0.204	0.701	0.305	0.620	0.165
5	0.400	0.018	0.359	0.034	0.207	0.058
6	0.152	0.003	0.145	0.000	0.065	0.024

30-day death had more than 50% missing values. AUROC: Area Under the Receiver Operating Characteristic curve.

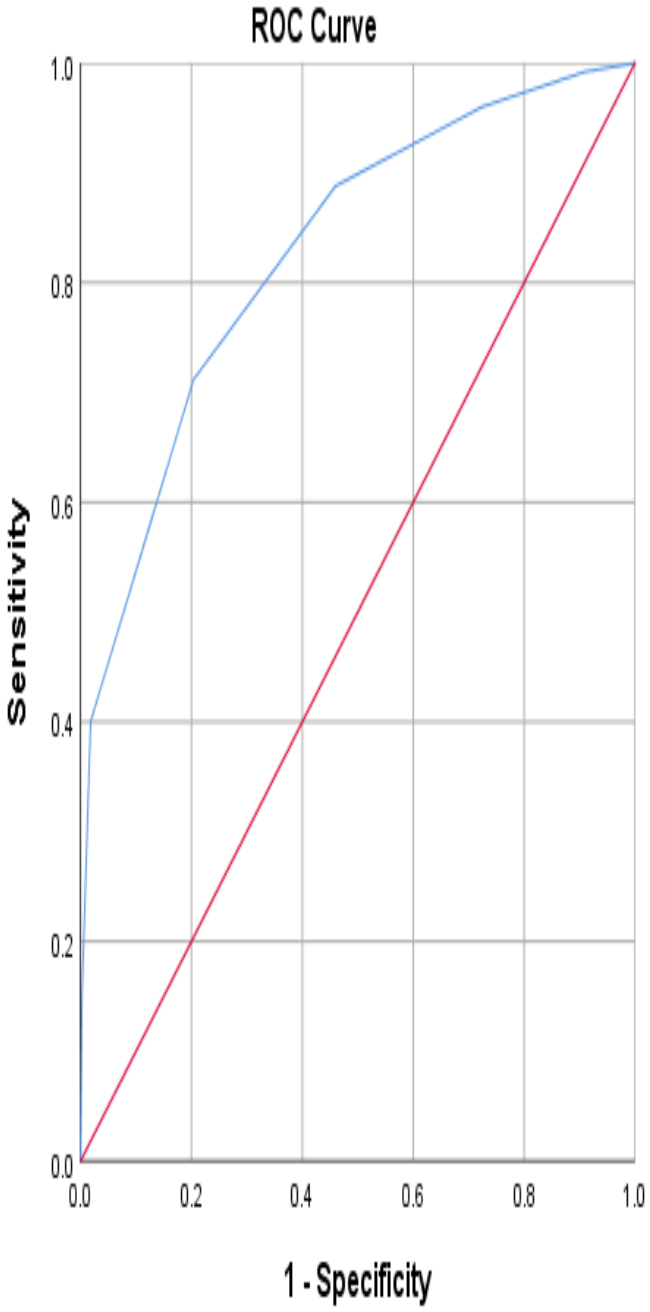

Figure 17. Receiver Operator Curve (ROC) for Inpatient Death.

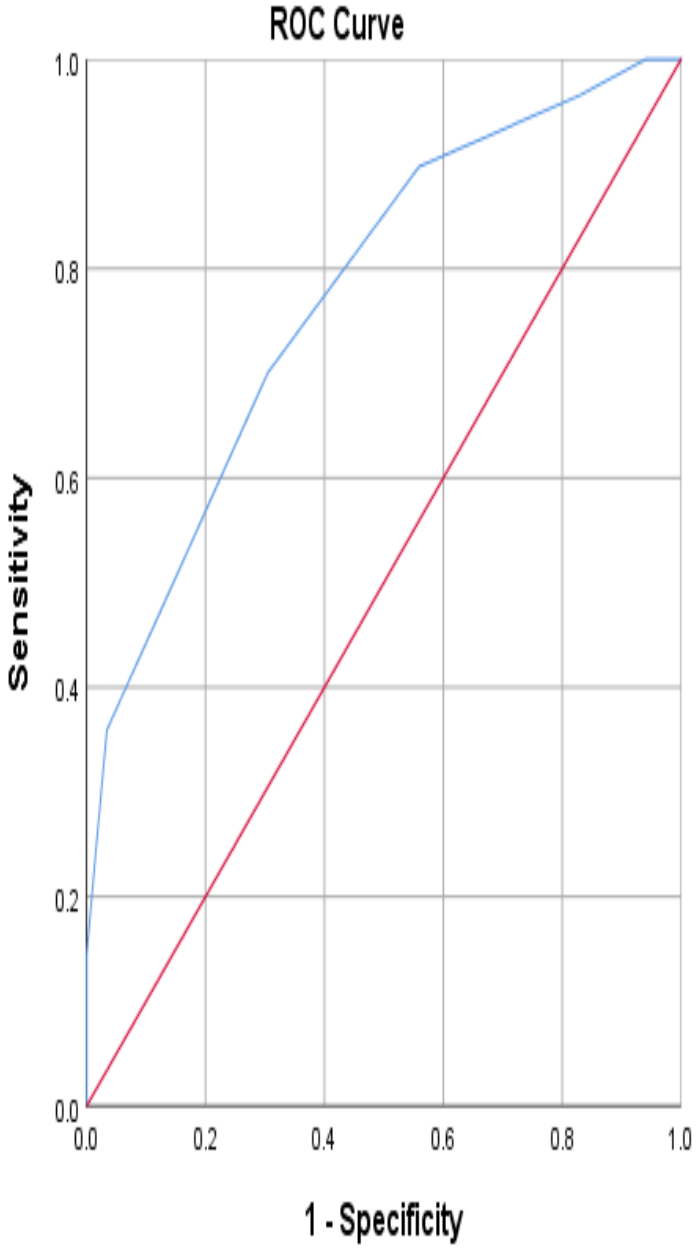

Figure 18. Receiver Operator Curve (ROC) for 30-Day Death.

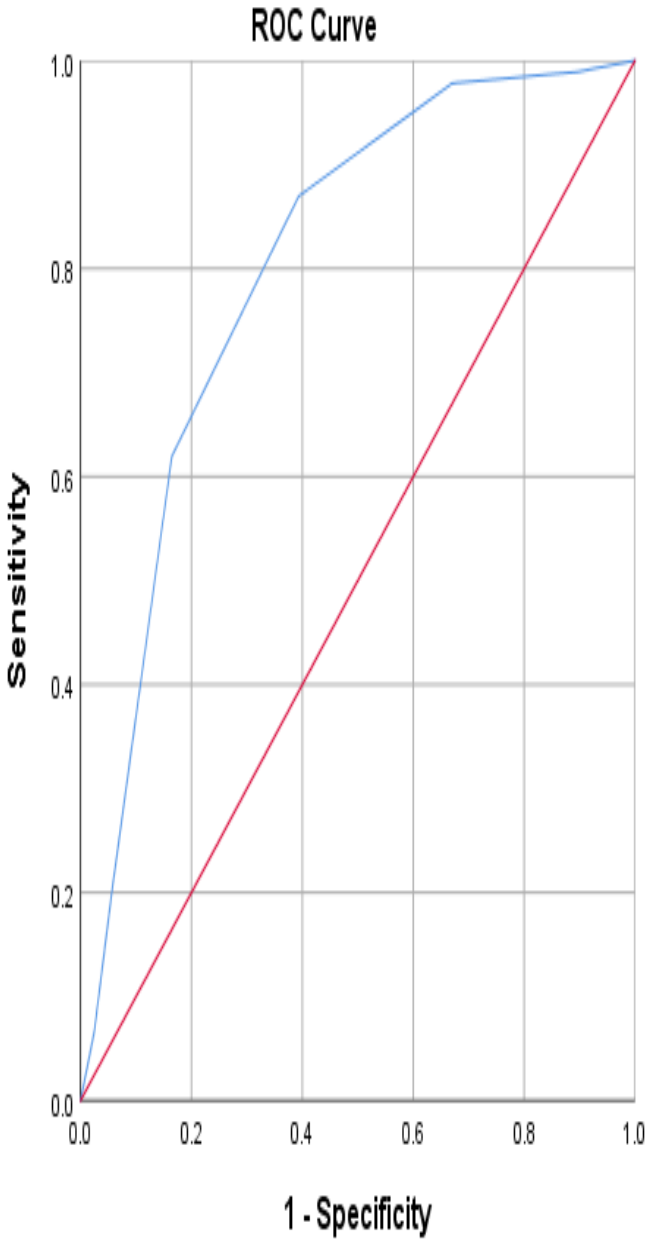

Figure 19. ROC Curve for 90-Days Readmission.

Length of Stay versus DECAF Score

We compared the mean length of stay across patients with different DECAF score using ANOVA. As shown **in Table 8 and Figure 20**, a dramatic increase in mean of length of stay was found with increasing DECAF score. More specifically, there were significant differences in means of length of stay across patients with different DECAF score (p=0.0108). The highest mean (SD) length of stay was seen patients with 6 DECAF score 29.8 (31.4) and the lowest value was reported in patients with 0 DECAF score 3.6 (2.0).The threshold for the difference in men of length of stay was found between patients with 27.3 (16.3) and patients with 3 DECAF score 20.0 (51.8).

Post-hoc analyses conducted on length of stay data against DECAF score revealed significant variance in mean length of stay between DECAF score groups for some comparisons as shown below:

DECAF score 0 vs 4: The mean difference in length of stay was -9.0 days and its associated p-value was 0.013; whilst when considering DECAF scores of 5 against 4, mean differences increased further by 90.7 days; this led to its associated p-value also reaching 0.013.

DECAF scores 1 and 5 were associated with an average difference in length of stay of -4.7 days; their p-value was also significant at being less than 0.001. For DECAF scores 1 and 6, the difference in mean length of stay between these groups was 12.9 days, with both outcomes having significant significance (p=0.001).

DECAF score 2 vs 5: The mean difference in length of stay was -7.7 days and its associated p-value was 0.001, whilst for DECAF scores of 2 and 6, this mean difference was 15 days - this time with its associated p-value being 0.003.

DECAF score 4 vs 0: The mean difference in length of stay was 9.0 days and its associated p-value was 0.013; by contrast, for DECAF scores 5 and 1, this difference decreased to only 4.7 days with its associated p-value being just 0.001.

DECAF score 5 vs 2: The mean difference in length of stay was 7.7 days and its associated p-value was 0.001, whilst for DECAF scores 6 and 1 this number increased to 12.91 days with no significant statistically significant differences found.

DECAF scores 6 and 2 yielded mean length differences of 15.9 days; their respective p-values were both significant at 0.003.

These findings indicate significant variations in length of stay depending on DECAF score group; those with higher DECAF scores could require longer hospital stays, making this information valuable for healthcare providers and researchers to better manage COPD exacerbations patients.

Table 8. Association of DECAF Score with Length of Stay

DECAF	Number of patients	Mean length of stay (SD)	95% CI (lower-upper)	ANOVA p value	DECAF	Post-hoc analysis	Mean difference	P value (post-hoc)
0	27	3.6 (2.0)	2.8-4.4	**.0108**	0	1	-5.0	.984
						2	-2.0	1.000
						3	-11.8	.382
						4	-9.0	.013
						5	-9.7	.013
						6	-17.9	.007
1	48	4.9 (5.2)	3.4-6.4		1	0	5.0	.984
						2	3.0	.994
						3	-6.8	.722
						4	-4.0	.973
						5	-4.7	.001
						6	-12.9	.001
2	77	7.3 (16.3)	3.5-11.0		2	0	2.0	1.000
						1	-3.0	.994
						3	-9.8	.174
						4	-7.0	.598
						5	-7.7	.001
						6	-15.9	.003
3	99	20.0 (51.8)	9.7-30.4		3	0	11.8	.382
						1	6.8	.722
						2	9.8	.174
						4	2.7	.993
						5	2.0	1.000

						6	-6.0	.182
4	86	14.5 (22.8)	9.6-19.4		4	0	9.0	.013
						1	4.0	.973
						2	7.0	.598
						3	-2.8	.993
						5	-.7	1.000
						6	-8.8	.294
5	22	20.8 (27.9)	8.5-33.3		5	0	9.7	.013
						1	4.7	.001
						2	7.7	.001
						3	-2.1	1.000
						4	.7	1.000
						6	-8.1	.261
6	10	29.8 (31.4)	7.4-52.4		6	0	17.9	.007
						1	12.9	.001
						2	15.9	.003
						3	6.0	.182
						4	8.8	.294
						5	8.1	.261

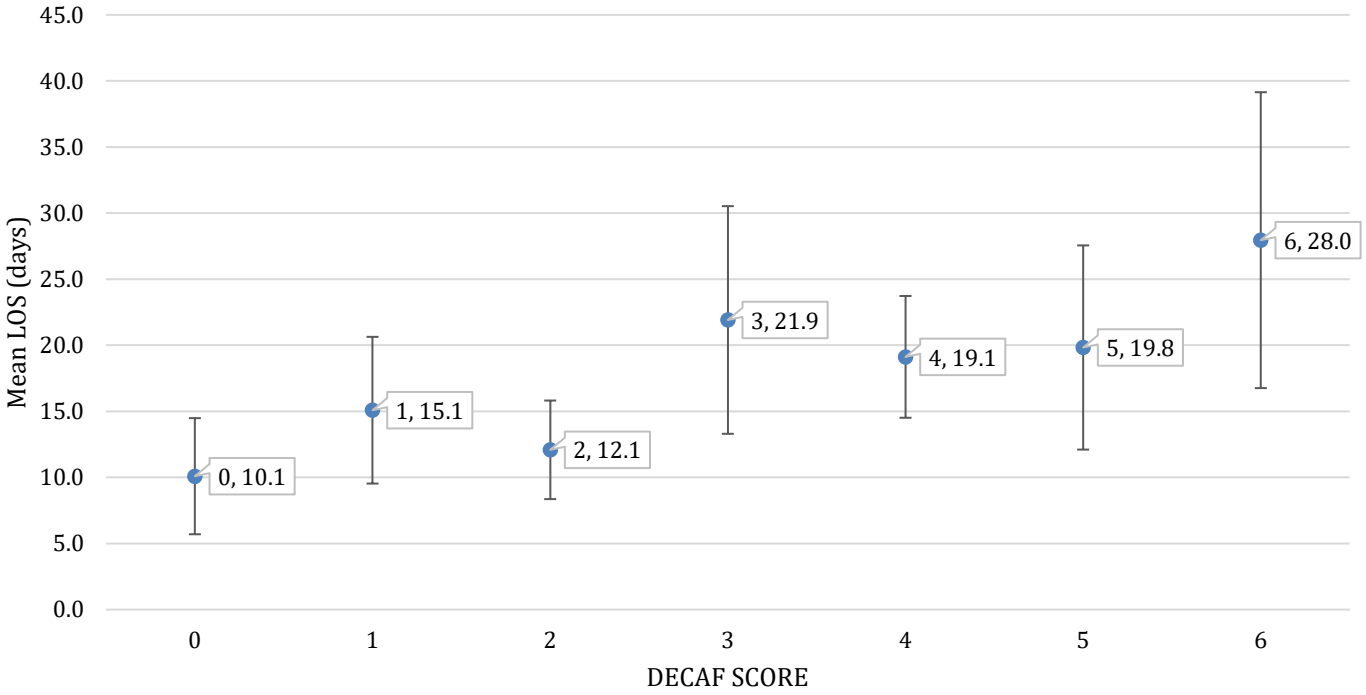

Figure 20. Length of Stay versus the DECAF Score

5.5. Laboratory Markers versus DECAF Score

To measure differences in means of pH, eosinophil counts, CRP, and Urea levels across patients with different DECAF scores, we performed ANOVA test. As shown in **Table 9 and Figure 21a**, the mean pH was significantly decreased with the increase in DECAF score (p=0.001). The lowest mean (SD) pH was reported in patients with 6 DECAF score 7.2 (0.1) and the highest among patients with 0 DECAF score 7.4 (0.03). The pH value dropped below 7.35 between DECAF scores 1 and 2 (7.36 versus 7.34). There was a significant difference in mean eosinophil counts across DECAF scores (p=0.041) (**Figure 21b**). The lowest mean of eosinophils ($x10^{(3)}$/mcL) was found in patients with a DECAF score of 6, $0.01x10^{9}$/L (0.1) and the highest was seen in patients with 0 DECAF score 0.4 (1.1). The mean of CRP (mg/L) was significantly increased with the increase in DECAF score (p=0.004) (**Figure 21c**). The highest mean (SD) of CRP (mg/L) was seen in patients with 6 DECAF score 117.0 (92.3) and the lowest in patients with 0 DECAF score 33.1 (32.8). The level of CRP (mg/L) exceeded 60 between 2 and 3 DECAF score. Finally, the mean of urea (Mmol/L) was significantly increased with the increase in DECAF score (p=0.001) (**Figure 21d**). The threshold for the difference in urea (Mmol/L) levels was estimated to be between 3 and 4 DECAF scores (14.0versus 21.9). Patients with 6 DECAF score had 47.7 (74.9) a mean (SD) of Urea.

Post-hoc analysis revealed significant variations in pH levels across certain DECAF scores. DECAF score 5 had significantly higher pH levels when compared with scores 1 and 6, at both p-values of 0.012 and 0.002, while DECAF scores 3, 4 and 5 all displayed significant mean differences of at least two points between DECAF scores 5 and 6, 4 and 6, and 3 and 6, all having significant mean difference coefficients greater than zero as shown below (p = 0.002, 4 to 6, and 3 and 6, respectively, with significant mean differences at each step between DECAF score 6 and 1, 0, 1, 0, 1, 1 2 or between DECAF scores 5 and 1 or between DECAF scores 0, 1 2, or between 3 or 4. Please keep in mind there were no significant variations between DECAF scores 0 and 1, between DECAF scores 0, 1 2 or between 3 or 4, as shown here as there were no such significant variations found.

This post-hoc analysis for mean differences among DECAF score groups for Eosinophils revealed statistical significance between DECAF score groups 1 and 4 (p = 0.002), 1 and 5 (p = 0.027), and 1 and 6 (p = 0.001). Comparing between DECAF groups 2 and 6 (p = 0.031) as well as 6 and 1

did not reach statistical significance ($p > 0.05$). The lowest mean of eosinophils was found among patient with 6 DECAF score and the highest was among those with 1 DECAF score.

Post-hoc analysis contrasted DECAF scores to CRP levels. This comparison revealed a statistically significant (p 0.05) variation among DECAF scores 1 through 5, where DECAF 6 produced lower CRP levels than scores 1, 2, 3, 4 or 5 as per analysis -the mean differences ranged between 49.904 to -69.902. No other significant variations could be detected and their exact p-values for comparisons range from 0.206 (vs score 6 = 0.206) through 6 to DECAF score 1 against scores 2 through to 5 against score 6 (p = 0.115); 3 against score 6 (p = 0.115); 3 against score 6 (p = 0.115); 4 against score 6 (0.599); 5 against score 6 (p =0.752); DECAF score 5 against score 6 (p = 0.772) while for DECAF score 0, the exact opposite pattern could also exist (p =0.043).

Tukey HSD tests were utilized to analyse mean differences of Urea levels among different DECAF scores and to detect significant variance in Urea concentration levels across DECAF score ranges. Results revealed statistically significant variance in levels across DECAF score groups. DECAF scores 0, 1, 2, 3, and 4 were shown to have significantly higher mean Urea concentration levels compared to DECAF score 6 with respective p-values being 0.029, 0.029, 0.079, 0.003 and 0.001 respectively. DECAF scores 1 and 2 had significantly higher mean Urea levels compared to DECAF score 4, as evidenced by significant p-values of 0.029 and 0.000 respectively. DECAF scores 3 and 4 had significantly higher mean Urea levels compared to DECAF score 6, as evidenced by significantly greater p-values (0.000 and 0.004, respectively). Notably, DECAF score 5 did not show any notable variations in mean Urea levels compared to any of its DECAF counterparts. DECAF score 6 was significantly associated with significantly reduced mean Urea levels when compared with all the other DECAF scores; its p-value was less than 0.005. These findings demonstrate the significance of considering DECAF when interpreting Urea levels among patients, since it can identify those who possess either higher or lower concentrations of Urea in their systems.

Table 9. Association of DECAF Score with Laboratory Markers

DECAF	Number of patients				Mean (SD)				95% CI (lower-upper)			
	pH	Eos*	CRP	Urea	pH	Eos*	CRP	Urea	pH	Eos*	CRP	Urea
0	6	32	26	31	7.39 (0.03)	0.42 (1.1)	33.14 (32.84)	9.70 (8.36)	7.35-7.43	0.02-0.83	19.87-46.40	6.64-12.77
1	36	64	54	59	7.36 (0.07)	0.28 (0.38)	47.77 (55.73)	10.90 (15.84)	7.34-7.39	0.18-0.37	32.55-62.98	6.78-15.03
2	66	96	87	90	7.34 (0.09)	0.31 (0.97)	59.30 (79.71)	14.05 (16.69)	7.31-7.36	0.12-0.51	42.31-76.29	10.56-17.55
3	80	111	93	105	7.30 (0.09)	0.20 (0.24)	65.07 (75.27)	14.00 (16.30)	7.28-7.32	0.16-0.25	49.57-80.57	10.85-17.16
4	87	108	90	104	7.29 (0.10)	0.14 (0.20)	85.97 (109.39)	21.93 (25.67)	7.27-7.32	0.10-0.18	63.06-108.88	16.93-26.92
5	28	30	25	31	7.24 (0.14)	0.10 (0.15)	78.07 (90.13)	21.69 (20.53)	7.18-7.29	0.04-0.15	40.86-115.27	14.16-29.22
6	19	19	18	18	7.17 (0.12)	0.01 (0.04)	117.01 (92.34)	47.71 (74.86)	7.11-7.23	0.00-.04	71.08-162.93	23.90-71.51

ANOVA p values for pH, *eosinophil count, C-reactive protein (CRP), and Urea levels were 0.001, 0.041, 0.004, and 0.001, respectively.

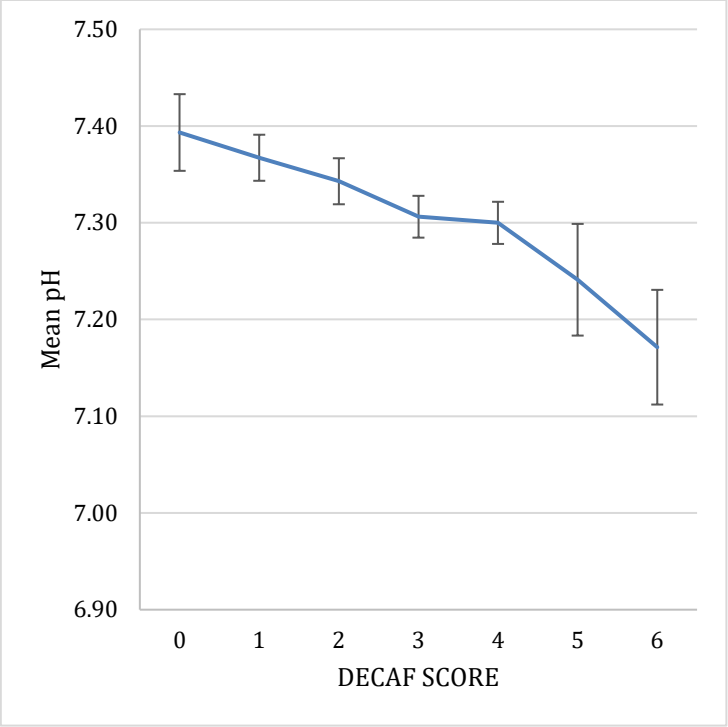

Fig 21a.

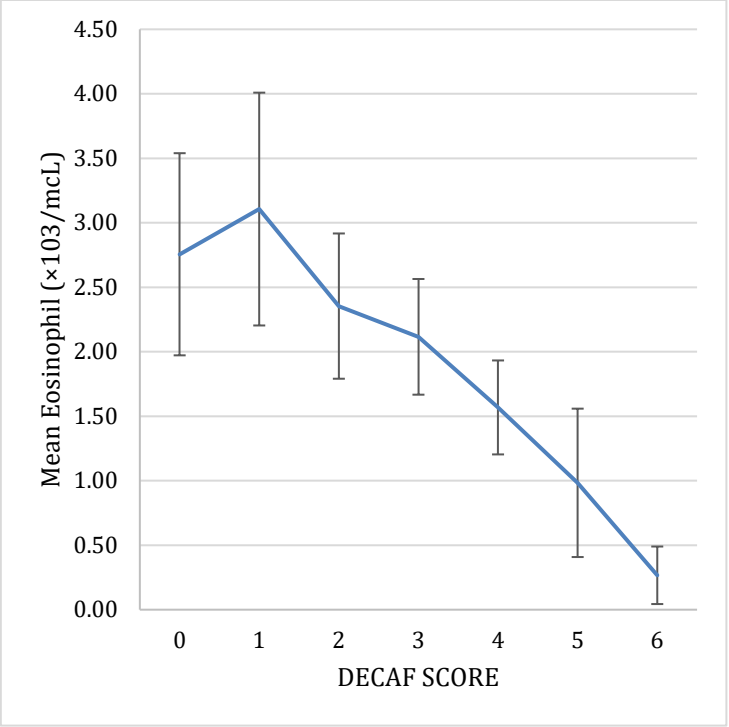

Fig 21b.

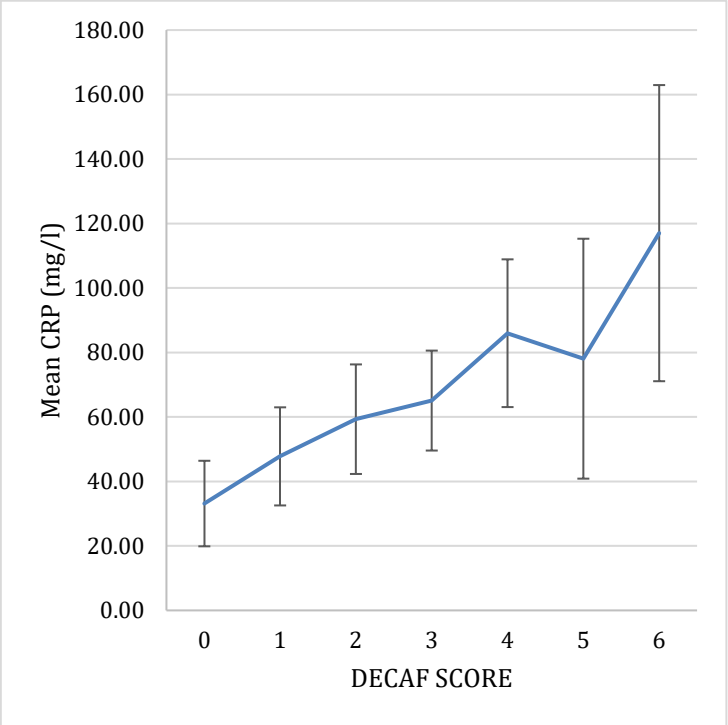

Figure 21c.

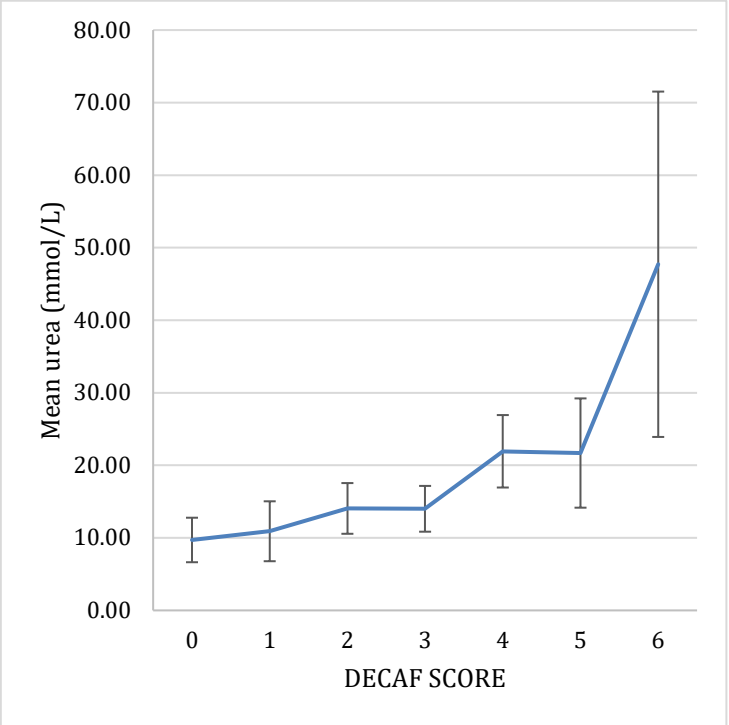

Figure 21d.

Figure 21. DECAF Score versus Means of Laboratory Findings. (CRP: c-reactive protein).

5.6. Association of Atrial Fibrillation with DECAF Score.

We analysed the proportions of patients with atrial fibrillation across DECAF scores using error bars (**Figure 22).** Overall, the proportions of patients having atrial fibrillation increases with the increase in DECAF score. Furthermore, we noticed that the proportions having atrial fibrillation were statistically similar across consecutive DECAF scores. The proportions of patients having atrial fibrillation across patients with DECAF scores of 6 and 0 were 90.0% versus 8.3% ($p<0.05$), respectively. The proportions of patients having atrial fibrillation across patients with DECAF scores of 6 and 5 were 90.0% versus 78.4% ($p>0.05$), respectively.

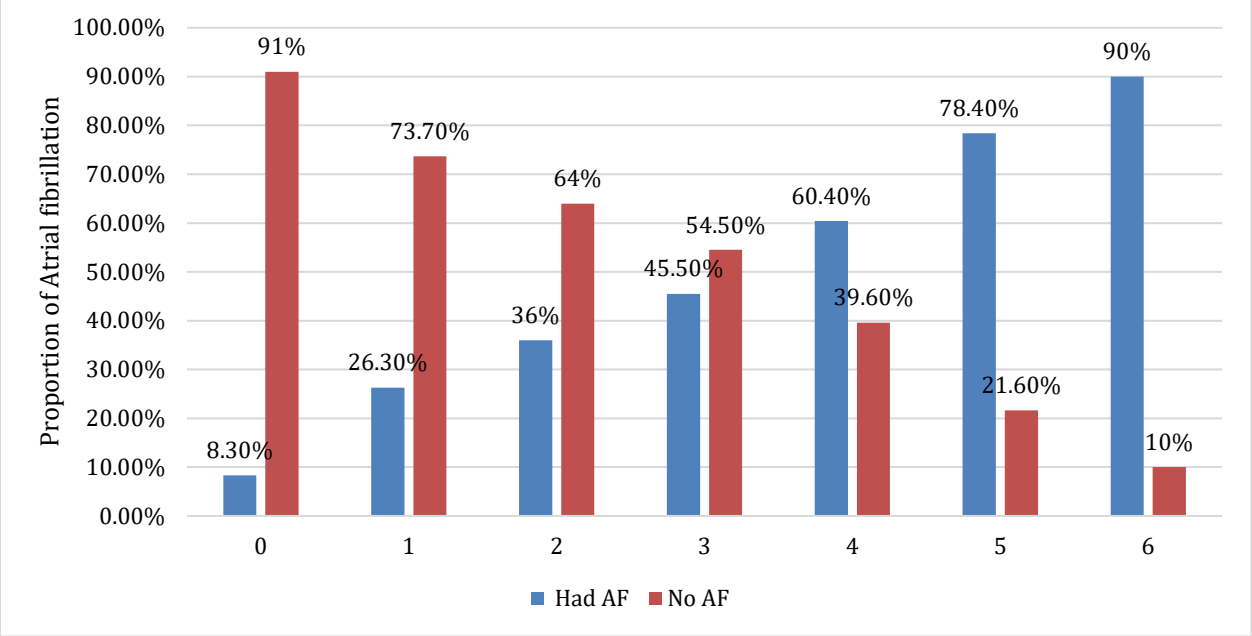

Figure 22. DECAF Score versus the Proportion of Patients Who Had Atrial Fibrillation. ***This figure shows the proportion of atrial fibrillation (AF) across the DECAF score. As the DECAF score increases, the percentage of the AF increases. The highest proportion of the AF was found in patients with 6 DECAF score.***

5.7. Patients Needing Assistance with Activity versus DECAF Score.

We measured the differences in patients needing assistance for doing daily activities across DECAF score **(Figure 23a-c**). The proportion of patients needing assistance for washing was increased with the increase in DECAF score. The threshold for this increase is estimated to be between DECAF scores of 1 and 2. In detail, the proportions of patients needing assistance for

washing was statistically similar across DECAF scores 6, 5, 4, and 3($p>0.005$). This finding can be generalized into needing assistance for dressing and feeding. The proportions of patients needing assistance for washing, dressing, and feeding were significantly lower in patients with DECAF scores 0 and 1 compared to other scores ($p<0.005$).

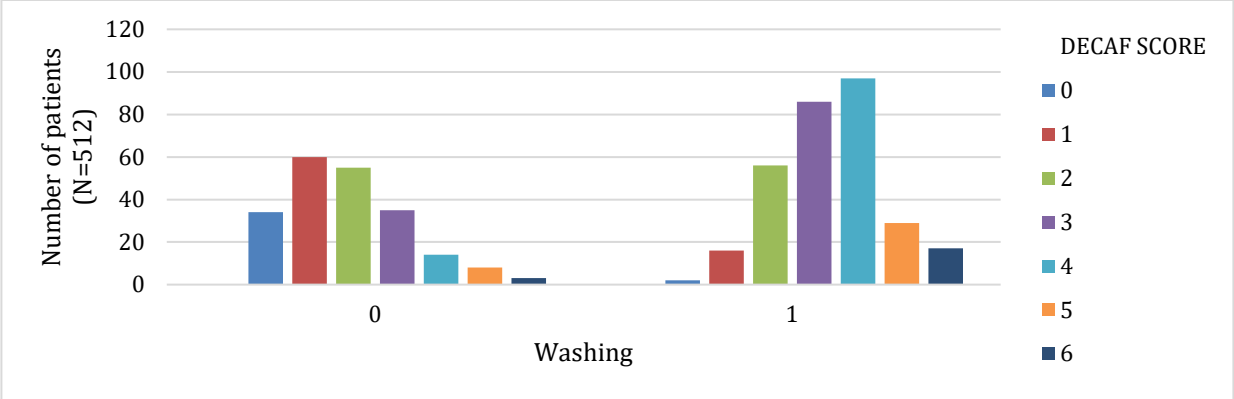

Figure 23a.

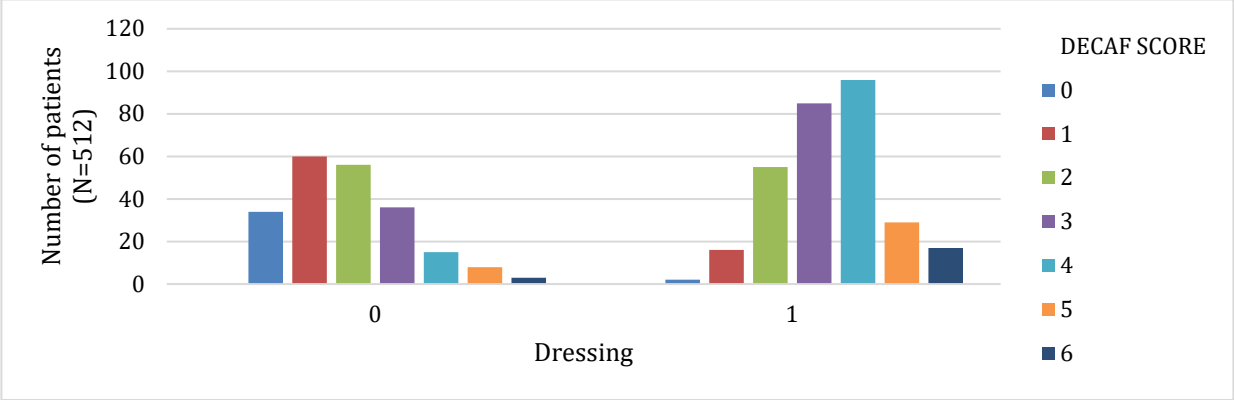

Figure 23b.

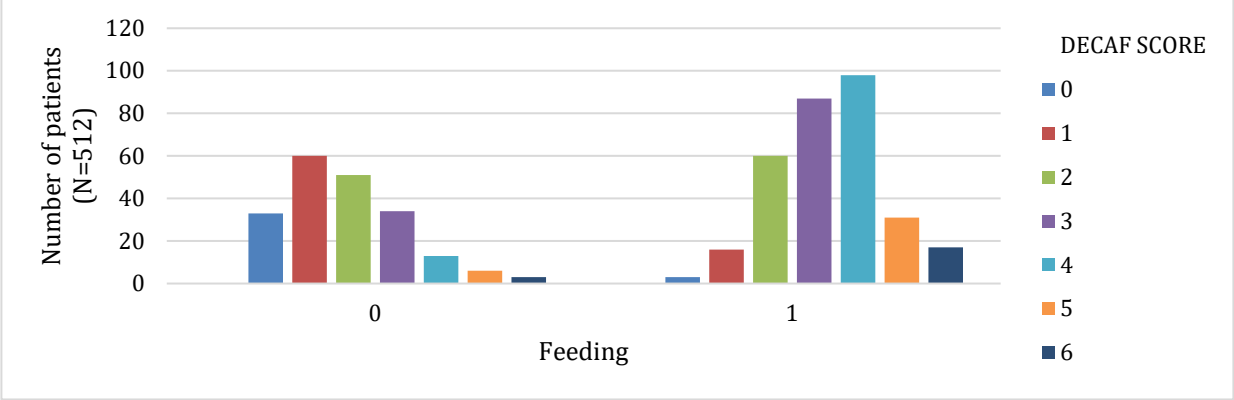

Figure 23c.

Figure 23. DECAF Score by Needing Assistance in Daily Activities(0: No, 1: Yes).

(This figure shows the distribution of patient needing assistance in daily activity (assistance for washing, assistance for dressing, and assistance for feeding) across DECAF score. The highest proportions of patient needing assistance in daily activities were found in patients with 4 DECAF score.

5.8. Body Mass Index versus Inpatient Death

There was no significant difference in mean BMI across patients who died as inpatients; the mean BMI for patients who died versus patients who did not were 31.05 versus 30.62 (p=0.758) **Table 10.**

Table 10. Body Mass Index (BMI) versus Inpatient Death

Inpatient death	Mean BMI (kg/m^2)	N	Std. Deviation	P value
No	30.6	387	11.5	0.758
Yes	31.1	125	19.0	

5.9. Inpatient Death versus Length of Stay

There was a significant difference in mean length of stay across patients who died during admission and those who were alive; the mean LOS for dead patients versus alive patients were 21.9 versus 15.97 ($p<0.05$) **Table 11.**

Table 11. Inpatient Death versus Length of Stay

Inpatient death	Mean LOS (days)	N	Std. Deviation	P value
No	16.0	387	28.7	0.04
Yes	21.9	125	35.1	
Total	17.4	512	30.5	

5.10. Admission Pulse Rate versus Length of Stay (more than 30 days versus less than 30 days).

The findings of this study indicated a potential association between length of stay and admission pulse rate **Table 12.** In detail, the means pulse rate for patients who stayed more than 30 days in hospital versus those who stayed less than 30 days were 96.4 bpm versus 108.4 bpm (p=0.01).

Table 12. Pulse Rate (PR) versus Length of Stay

Stayed more than 30 days in hospital	Mean PR (bpm)	N	Std. Deviation	P value
No	108.5	423	32.5	0.01
Yes	96.4	89	29.1	
Total	106.4	512	32.2	

5.13. Inpatient Death across DECAF Scores

The findings of this comparison showed that when the DECAF score increases, the probability of inpatient death increases **Table 13**. Specifically, the proportions of inpatient death between patients who had DECAF scores of 1 versus 6 were 5.30% versus 95.00% ($p<0.05$).

Table 13. Inpatient Death versus DECAF Score

In patient Death	DECAF							P value
	0	1	2	3	4	5	6	
Yes	1 (2.8%)	4 (5.3%)	9 (8.1%)	22 (18.2%)	39 (35.1%)	31 (83.8%)	19 (95.0%)	0.001
No	35 (97.2%)	72 (94.7%)	102 (91.9%)	99 (81.8%)	72 (64.9%)	6 (16.2%)	1 (5.0%)	

5.14 AECOPD Mortality and High Provision of Oxygen Therapy

There was a significant difference in mortality across patients with different oxygen dose. Specifically, the findings of this comparison showed that 69 patients out of 512 received high doses of oxygen ($PaO_2 \geq 13$). When the oxygen supplementation increases, the inpatient death increases **Table 14**.

Table 14. Patients with Oxygen Dose (PaO2 Kpa)

		Number of patients	Percent
	None	1	0.2
	PaO2 ≥13	69	13.5
	PaO2≤ 13	442	86.3
	Total	512	100.0

Table 15. Mortality/ PaO2 ≥13 KPa

Inpatient death	PaO_2 (KPa), mean (SD)	P value
Yes	8.4 (8.1)	0.03
No	6.2 (7.1)	

5.15. Serum Albumin Level versus Inpatient Death

There was no significant association between mean serum albumin and inpatient death **Table 16**. In detail, the mean serum albumin across deceased patients was 31.9 (SD: 17.4).

Table 16. Albumin versus Inpatient Death

Inpatient death	Mean	SD	P value
Yes	31.9	17.4	0.974
No	32.0	25.2	

5.16. BMI Categories versus Inpatient Death

There were no significant differences in the proportions of BMI categories across patient death **Table 17**. Overall, 468 (91.4%) of the study sample were obese patients and 44 (8.6%) were underweight patients. Among patients who died, 112 (92.0%) were obese and 13 (8.0%) were underweight. Among survivors, 356 (89.6%) were obese, and 31 (10.4%) were underweight. BMI is a measure of body fat based on height and weight, calculated as weight in kilograms divided by height in meters squared. BMI categories are defined based on the following ranges: underweight: BMI less than 18.5 kg/m2, healthy weight: BMI between 18.5 and 24.9 kg/m2, overweight: BMI between 25 and 29.9 kg/m2, and obese: BMI 30 kg/m2 or greater.

Table 17. Body Mass Index (BMI) Categories versus Inpatient Death

Inpatient Death	BMI categories				P value
	Underweight	Healthy	Overweight	Obese	0.407
Yes	13 (8.0%)	0 (0.0%)	0 (0.0%)	112 (92.0%)	
No	31 (10.4%)	0 (0.0%)	0 (0.0%)	356 (89.6%)	

5.17. DECAF Score versus Other Parameters

There was no association between sex and DECAF score ($p>0.05$) (**Figure 25**). On the other hand, there was a significant association between geographic locations of patients and the DECAF score ($p<0.05$). The proportions of patients who were from Dubai and had a DECAF score of 4, 5, and 6 were 32.9%, 6.8%, and 11%, respectively (**Figure 26**). The proportions of patients who were from Sharjah and had a DECAF score of 4, 5, and 6 were 19.3%, 9.9%, and 3.9%, respectively. The proportions of patients who were from Ras Al-Khaimah and had a DECAF score of 4, 5, and 6 were 26.0%, 4.5%, and 1.3%, respectively. The proportions of patients who were from Fujairah and had a DECAF score of 4, 5, and 6 were 12.8%, 7.4%, and 3.2%, respectively. The proportions of patients who were from Umm Al Quwain and had a DECAF score of 4, 5, and 6 were 0.0%, 0.0%, and 0.0%, respectively. The findings of this study showed a significant association between smoking status and the DECAF score (p=. 0.038). The proportions of patients who were smokers and had a DECAF score of 4, 5, and 6 were 19.2%, 8.2%, and 4.6% respectively (**Figure 27**). The proportions of patients who were former smokers and had a DECAF score of 4, 5, and 6 were 28.6%, 6.8%, and 0.8%, respectively. The proportions of patients who were never smokers and had a DECAF score of 4, 5, and 6 were 19.4%, 5.1%, and 6.1%, respectively.

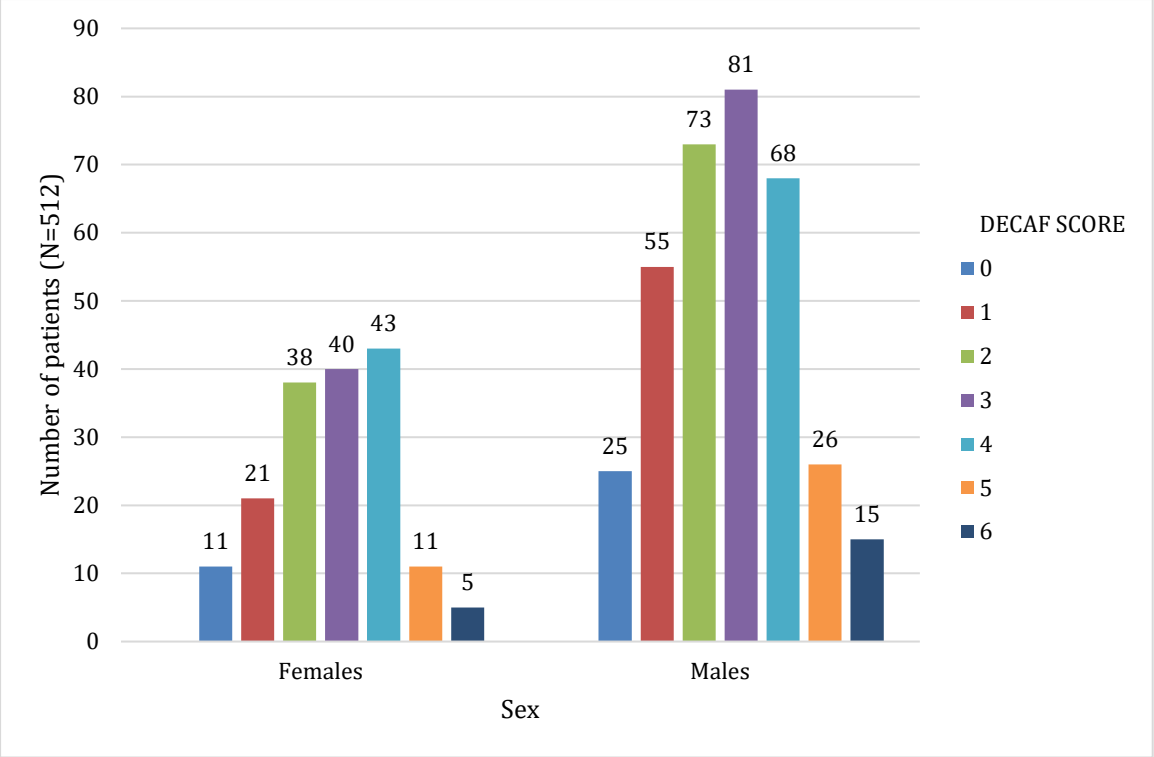

Figure 24. DECAF Score Clustered by Sex

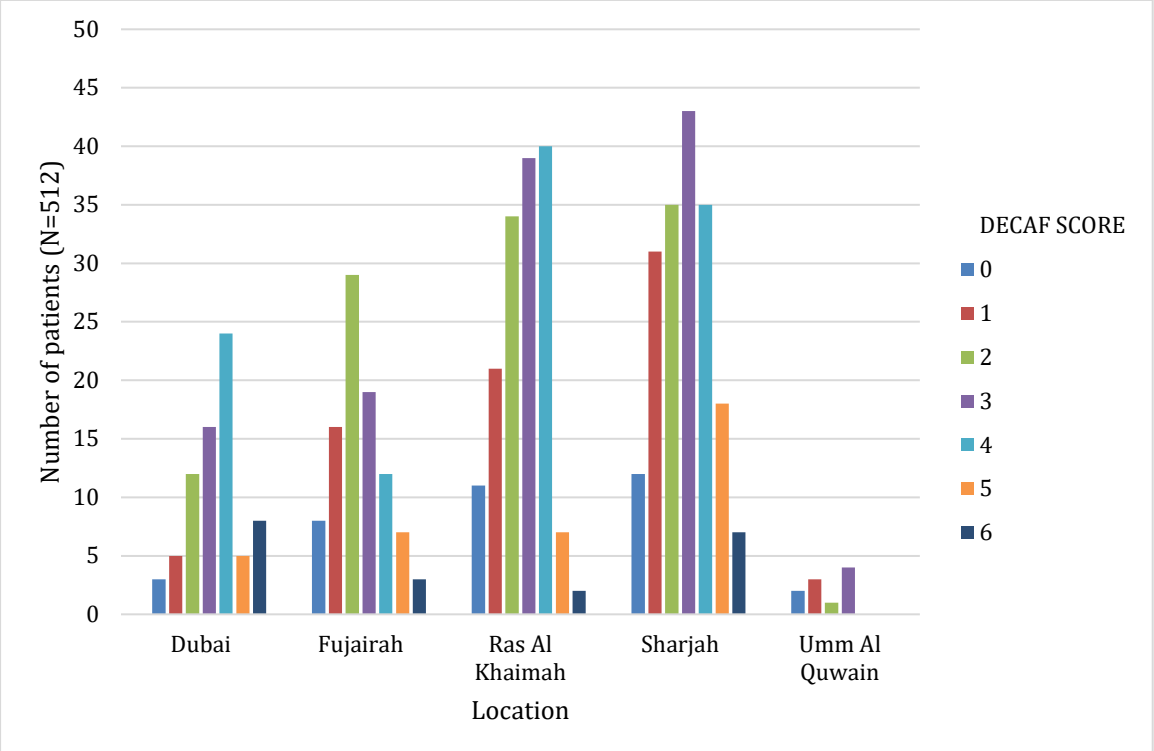

Figure 25. DECAF Score Clustered by Location

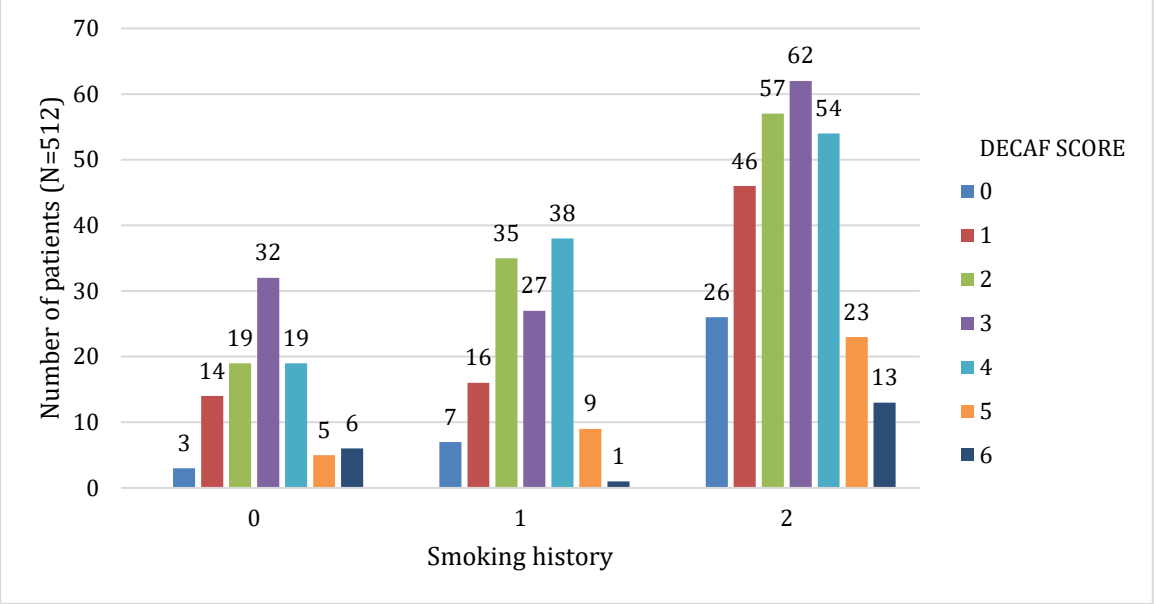

Figure 26. DECAF Score Clustered by Smoking History (0: Never smoker, 1: Former smoker, 2: Current smoker

5.19. Association of Age with the Study Outcomes

The DECAF score is more likely to be higher in older patients than in younger patients ($p<0.05$) **(Figure 28)**. Patients with 0, 1, 2, 3, 5, and 6 DECAF scores had similar age means ($p>0.05$). The highest age mean was observed in patients with a DECAF score of 4 (77.71 years), while the highest age mean in patients with a DECAF score of 1 was 69.96 years.

Figure 29 indicates that there was no statistically significant difference in the mean BMI between patients aged above 65 years (30.2) and those aged below 65 years (32.4) ($p>0.05$).

Moreover, **Figure 30** reveals that the mean BMI was similar among patients aged above and below 65 years for different DECAF scores ($p>0.05$).

Figure 31 indicates that patients aged 65 years or above had a mean length of hospital stay of 18.4 days versus 14.3 for patients under 65, however this difference wasn't statistically significant ($p>0.05$). There was no significant difference in the DECAF score across patients who were aged above 65 years and those below 65 years ($p>0.05$).

Figure 32 outlines the distribution of DECAF scores among participants aged 65 or younger (in brackets). DECAF scores range from 0-6; higher DECAF scores reflect more severe disease conditions. Analysis was completed with 390 participants over 65 years of age, who all held DECAF scores between 4 (94, 24.1%) and 3 (87, 22.3%), The number of individuals scoring zero (25 6.4%) as well as 5/6 (18 4,6% respectively) being relatively small numbers. At 65 or

under years old, there were 124 participants included in this analysis of DECAF scores for participants below 65 years. As with those above 65, however, DECAF score distribution differed drastically with most having either no DECAF score (11/8%) or just 1 score (17/17%). Overall, the **figure 32** indicates that DECAF scores tend to be higher among participants aged 65 years or above compared with younger patients; older participants also tend to occupy more high score categories than their counterparts.

Figure 33 depicts the relationship between age categories and inpatient mortality rates. The sample was split into two age categories, above 65 years old (n=391) and below 65 years old (121) to evaluate patient survival in hospital stays; of those above 65 years, 289 (73.9%) survived their hospital stay while 102 (26.1%) perished whereas among the latter group only 23 (19%) died. Therefore, the findings demonstrate a higher rate of mortality among patients above 65 years old. However, according to the findings of the Chi-square test, the difference was not statistically significant ($p=0.113$).

Figure 34 indicates that among participants aged over 65 years, 60.4% (236) did not experience readmission within 90 days, compared to 39.6% (155) who did. For participants under 65 years however, 76.0% (92) experienced no readmission at all while 24.0% (29) did. Overall the 90-day readmission rate among younger age groups was higher, with 35.9% (184) of participants experiencing readmission versus 64.1% (328), making their difference statistically significant ($p<0.05$).

Figure 35 displays the results of smoking history and age distribution among the study sample (N=512). Smokers were divided into three groups based on current smokers (2), former smokers (1), and never smokers (0). Among the participants above 65 years old, 193 (49.4%) were current smokers, 114 (29.2%) were former smokers, and 84 (21.5%) were never smokers. In contrast, among participants below 65 years old, 88 (72.7%) were current smokers, 19 (15.7%) were former smokers, and 14 (11.6%) were never smokers. Differences were statistically significant ($p<0.001$) across categories in this regard.

Figure 36 shows the relationship between diabetes and age categories. Of the patients above 65 years old, 45% had diabetes while 55% did not; 24.5% of patients below 65 years old had diabetes while 23.2% did not. The findings suggest that the prevalence of diabetes was higher in the older age group than in the younger age group. However, the difference in diabetes across age categories was not statistically significant ($p>0.05$).

Figure 37 displays the distribution of renal disease by age category. Among participants above the age of 65, 68.8% did not have renal disease and 31.2% did have renal disease. In the below 65 age category, 85.1% of participants did not have renal disease, while 14.9% of participants did have renal disease. The difference in the distribution of renal disease by age category was statistically significant ($p<0.05$).

The findings indicate that there is a significant difference in DECAF score of patients above 65 years old across locations ($p<0.05$) **(Figure 38a**). No significant difference was found in patients below 65 years old ($p>0.05$) (**Figure 38b**). As shown in **Figure 38**, for patients above 65 years of age, 33.3% had a DECAF score of 4 and 1.3% had a DECAF score of 6.The proportion of patients with DECAF score 4 was highest in Sharjah (29.8%), while the highest proportion of patients with DECAF score 6 was observed in Fujairah (16.7%). Of the patients below 65 years old, 38.2% had a DECAF score of 4 and 2.9% had a DECAF score of 3.The proportion of patients with DECAF score 4 was highest in Ras Al Khaimah (41.2%), while the highest proportion of patients with DECAF score 6 was observed in Fujairah (28.6%).

Among patients above 65 years old, longer stay at hospital are significantly linked with higher DECAF score ($p<0.05$) (**Figure 39a**). Among patients below 65 years old, no significant difference in DECAF score across length of stay (**Figure 39b**). As shown in **Figure 39**, patients above 65 years old who had a stay longer than 30 days had a higher proportion of patients with a DECAF score of 4 or 5 compared to those with a shorter stay (23.1% vs 7.7% and 28.4% vs 7.5%, respectively). For patients below 65 years old, those with a stay longer than 30 days had a higher proportion of patients with a DECAF score of 3 or 4 compared to those with a shorter stay (28.1% vs 18.2% and 23.1% vs 14.8%, respectively)

As shown in **Figure 40**, among patients above 65 years old, the proportion of inpatient death ranged from 8.3% for a DECAF score of 0 to 100% for a DECAF score of 6 (**Figure 40a**). Among those below 65 years of age (**Figure 40b**), the proportion of inpatient death ranged from 11.2% for a DECAF score of 0 to 100% for a DECAF score of 6. The chi-square test was used to compare the distribution of the DECAF scores of patients who died and those who lived for both age categories. The test results suggest that the DECAF score is significantly associated with inpatient death for both age categories ($p < 0.05$).

As shown in **Figure 41**, among patients above 65 years of age, a total of 236 patients were readmitted and 155 patients were not. Of those who were readmitted, the majority had a DECAF score of 0, 1, or 2 (60.4%), while those who were not readmitted had a higher

percentage of patients with a DECAF score of 3 or higher (39.6%) (**Figure 41a**). Among patients below 65 years old, a total of 92 patients were readmitted and 121 patients were not. Of those who were readmitted, the majority had a DECAF score of 3 or higher (76.0%), while those who were not readmitted had a higher proportion of patients with a DECAF score of 0, 1, or 2 (24.0%) (**Figure 41b**).

Figure 42 shows the percentages of DECAF score clustered by age categories and diabetes. There was no significant differences in DECAF score across patients who had diabetes and those who did not in both age categories (P>0.05) (**Figure 42a and Figure 42b**).

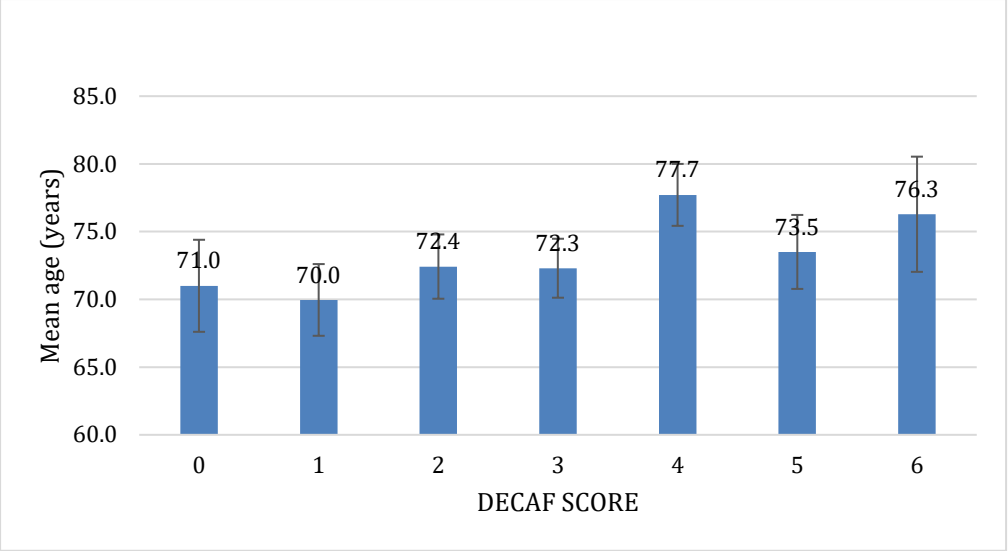

Figure 27. DECAF Score versus Age of Patients

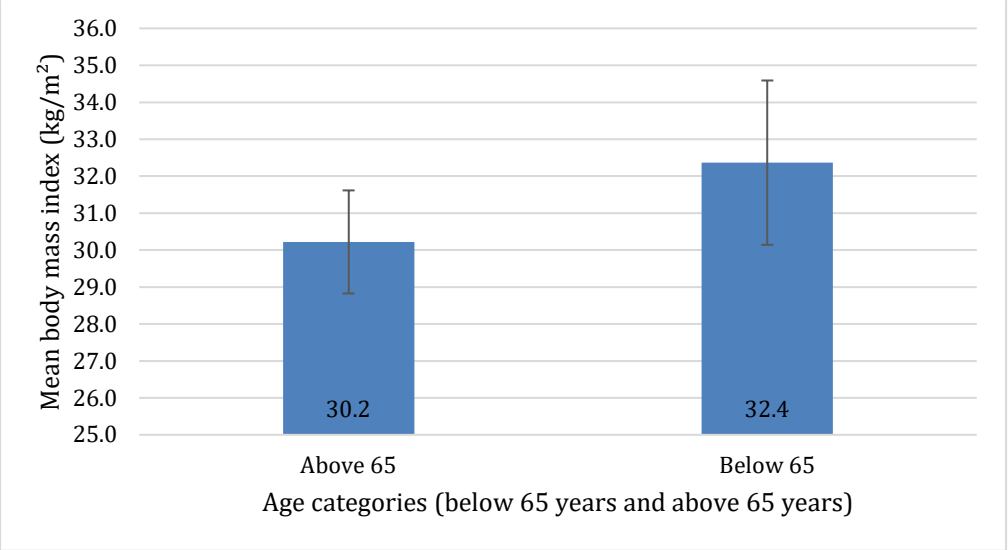

Figure 28. Body Mass Index (BMI) by Age Categories.

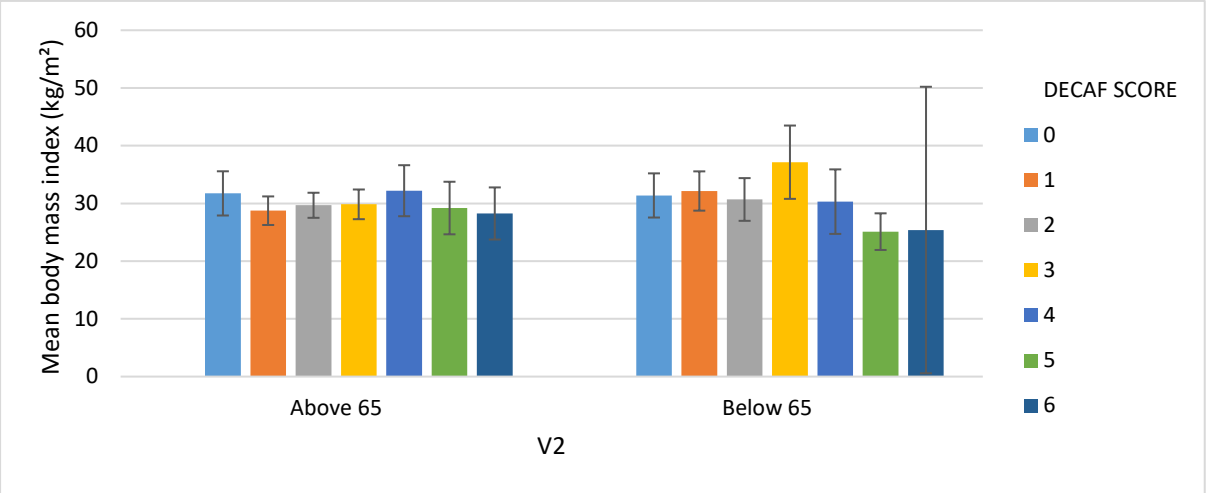

Figure 29. Mean Body Mass Index by Age Categories by DECAF Score

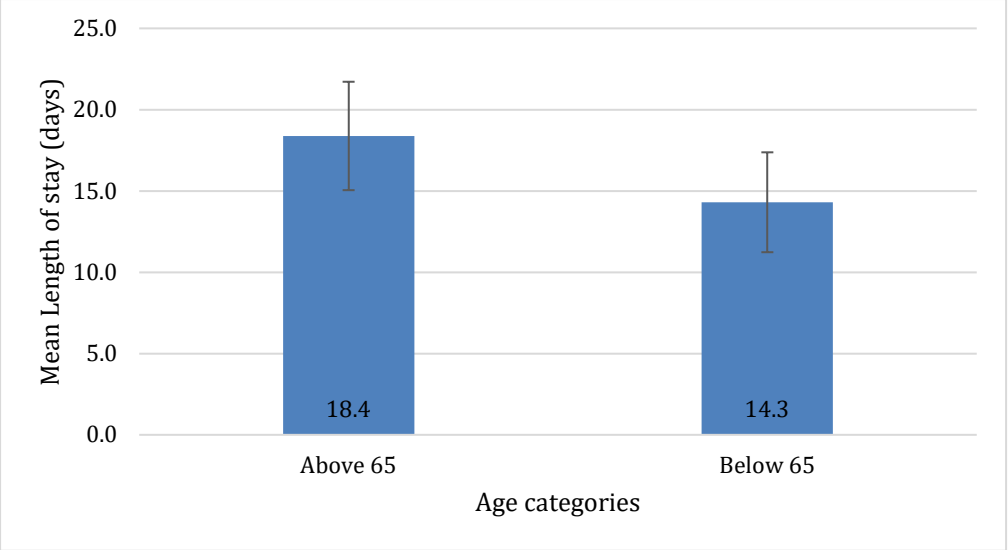

Figure 30. Distribution of DECAF Scores by Age Group ***(this figure displays the distribution of mean length of stay across age categories using error bars with 95% confidence interval)***

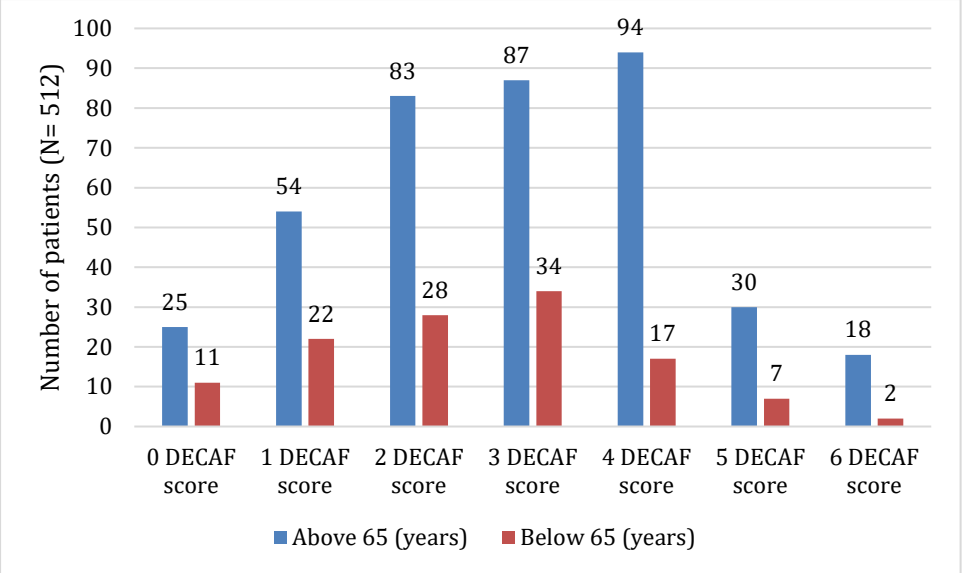

Figure 31. Age Categories versus DECAF Score. ***(This figure shows the distribution of DECAF scores among study participants, grouped by age (above or below 65 years old). The DECAF score ranges from 0 to 6, with higher scores indicating more severe disease.)***

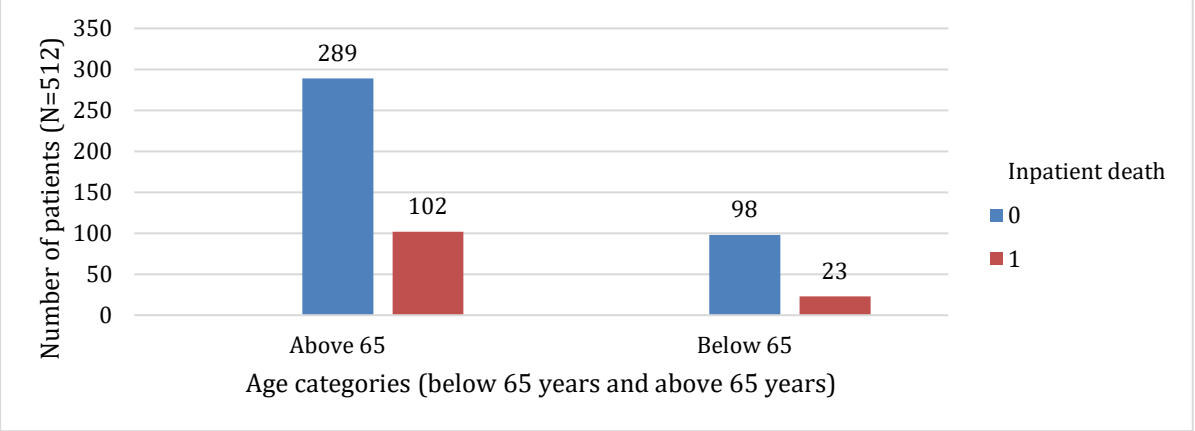

Figure 32. Mortality versus Age Categories ***(0: No, 1: Yes)***

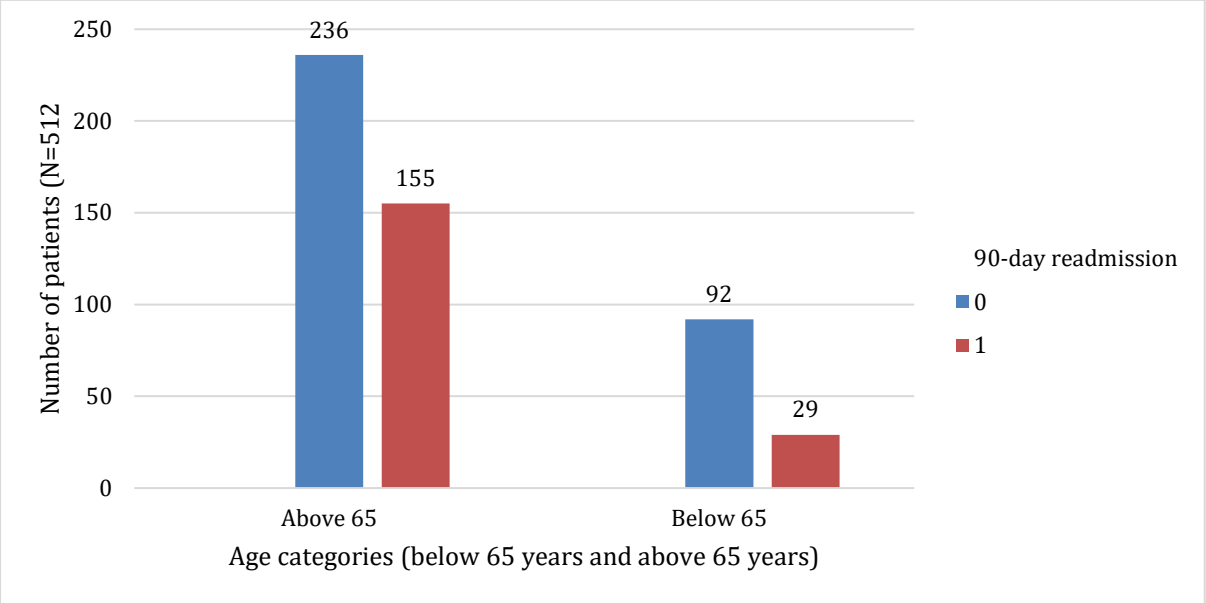

Figure 33. The Distribution of 90-Day Readmission across Age Groups ***(0: No, 1: Yes)***

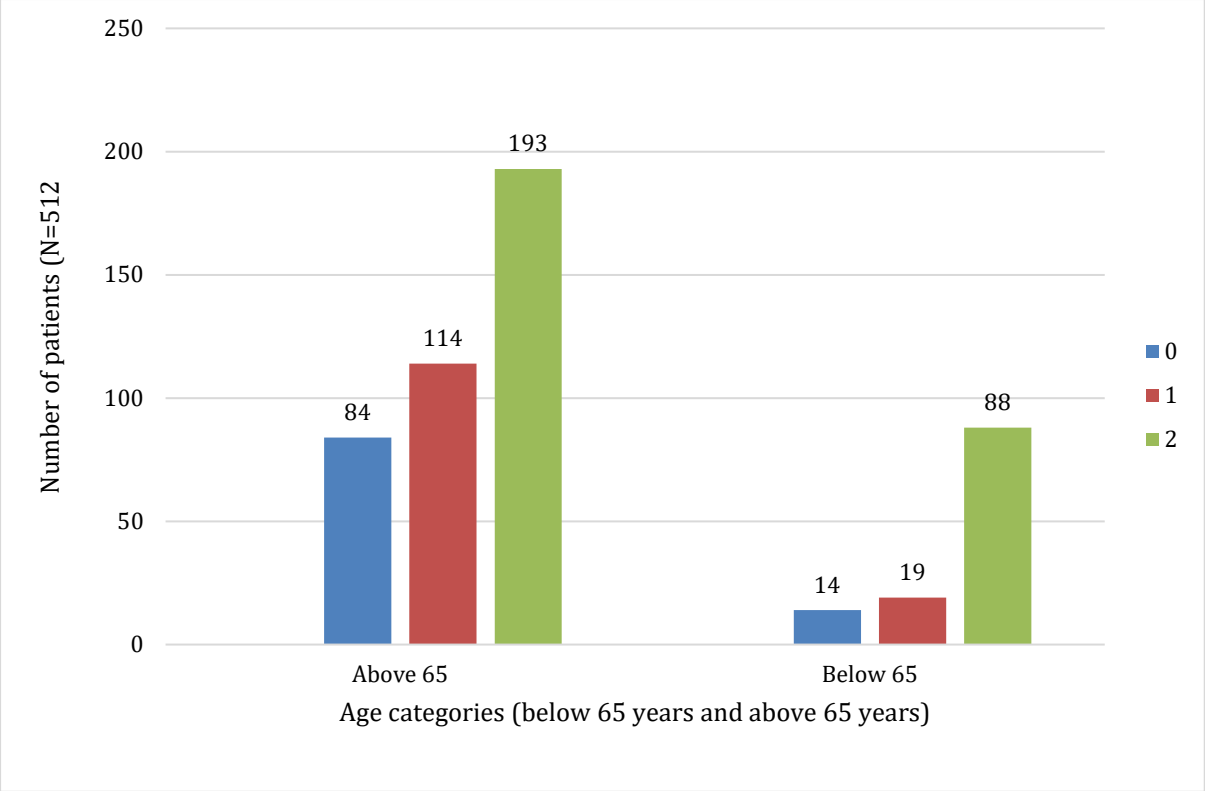

Figure 34. Smoking History across Age Categories ***(0: never smoker, 1: former smoker, 2: current smoker)***

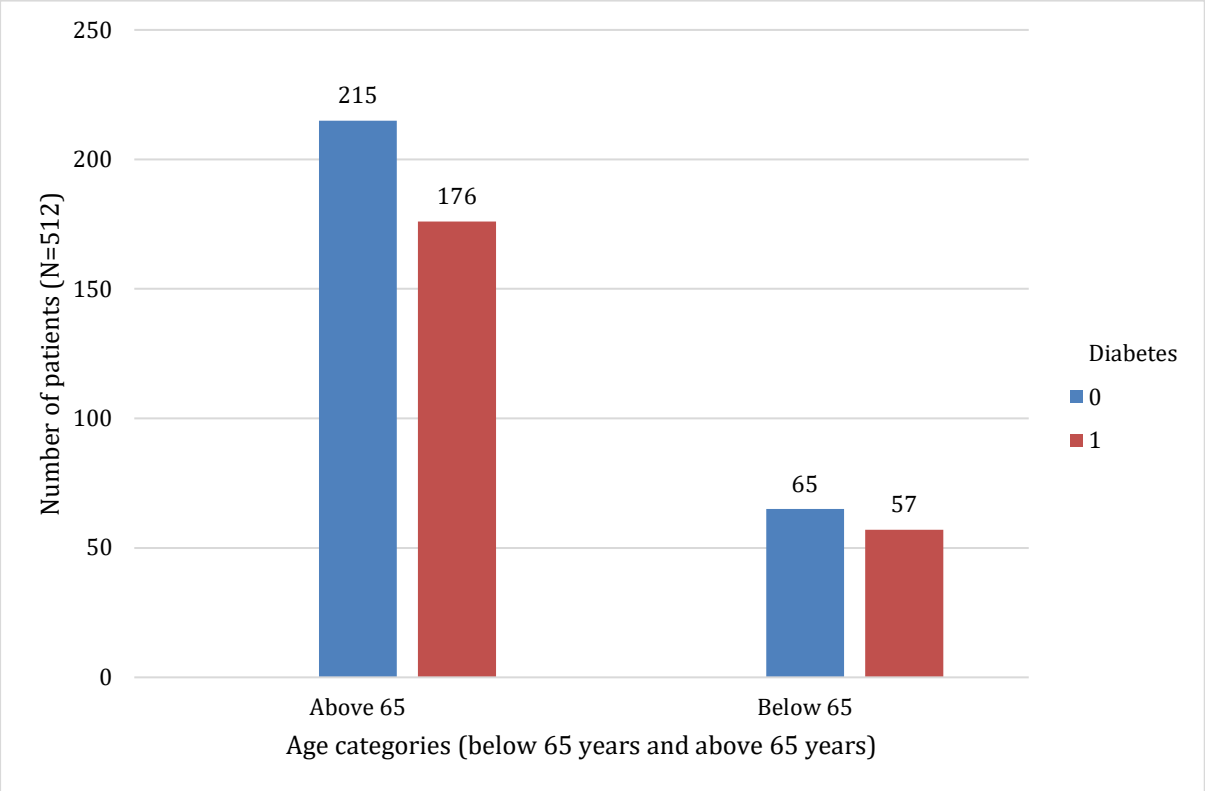

Figure 35. Presence of Diabetes across Age Categories ***(0: No, 1: Yes).***

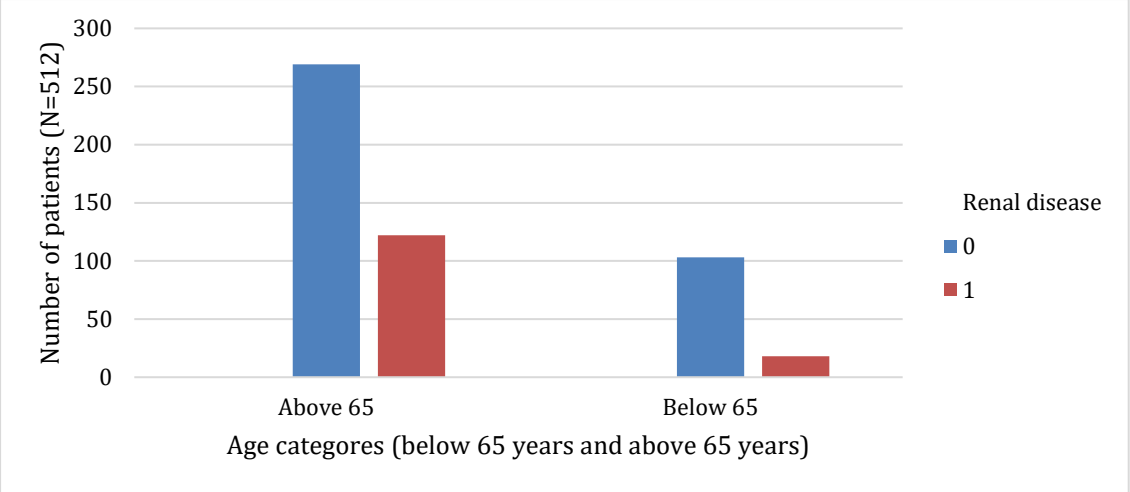

Figure 36 Presence of Renal Disease across Age Groups ***(0: No, 1: Yes)***

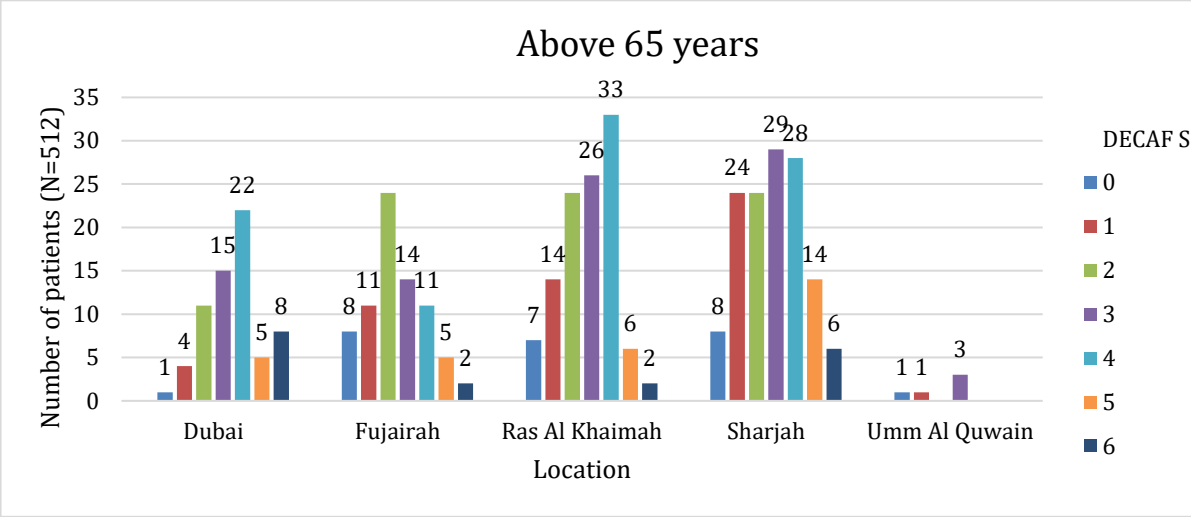

Figure 38a.

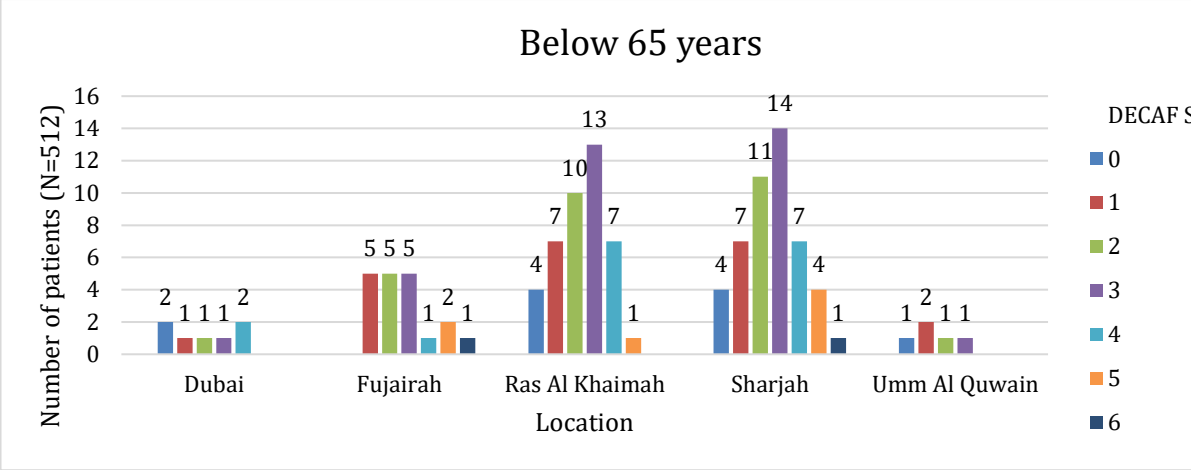

Figure 38b.

Figure 37. Decaf Score by Age Categories by Location

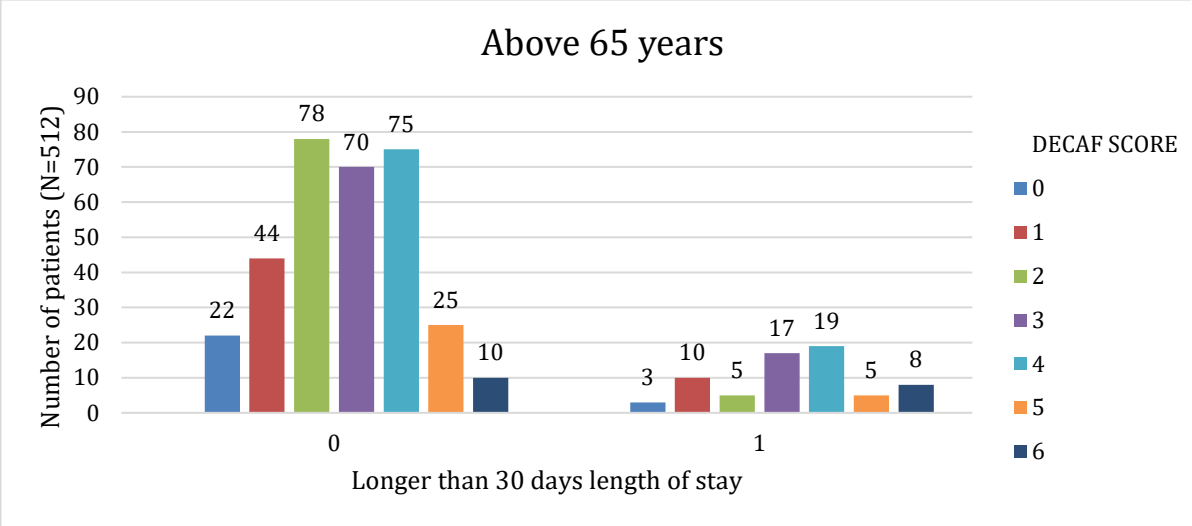

Figure 39a.

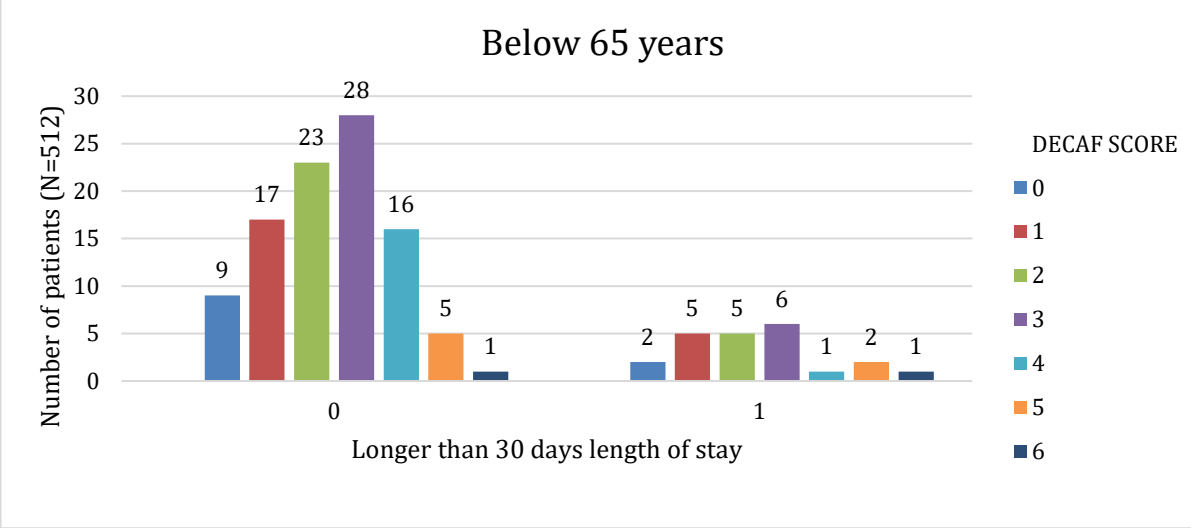

Figure 39b.

Figure 38. DECAF Score by Age Categories by Length of Stay (0: No, 1 Yes).

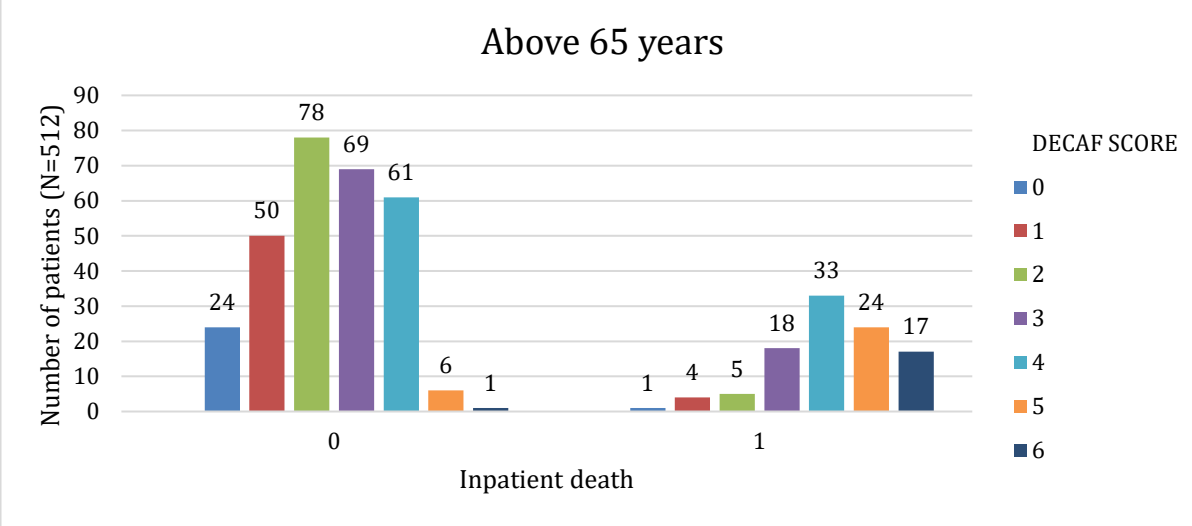

Figure 40a.

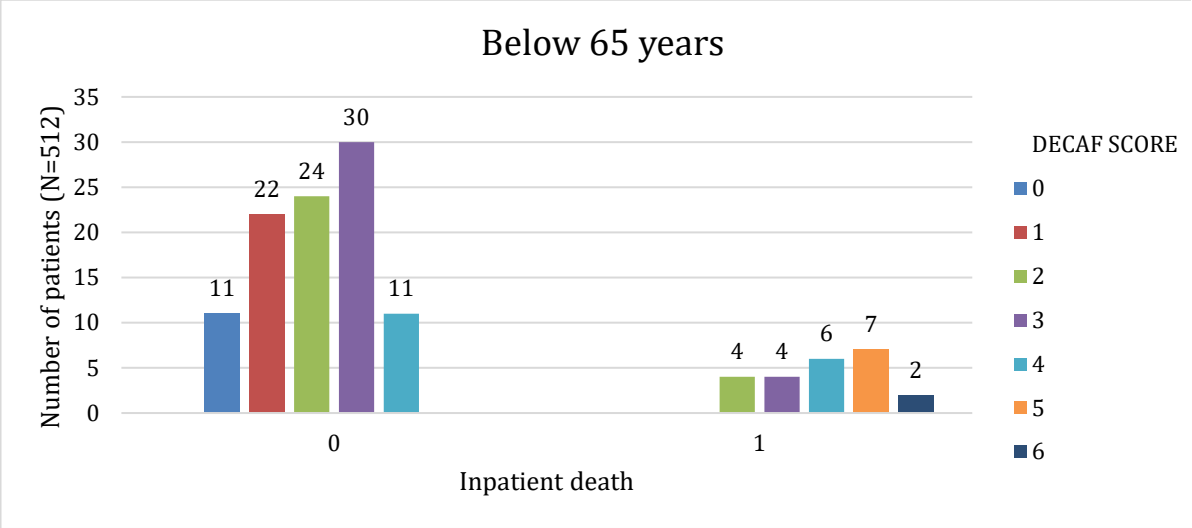

Figure 40b.

Figure 39. DECAF Score by Age Categories by Patient Death(0 No, 1 Yes)

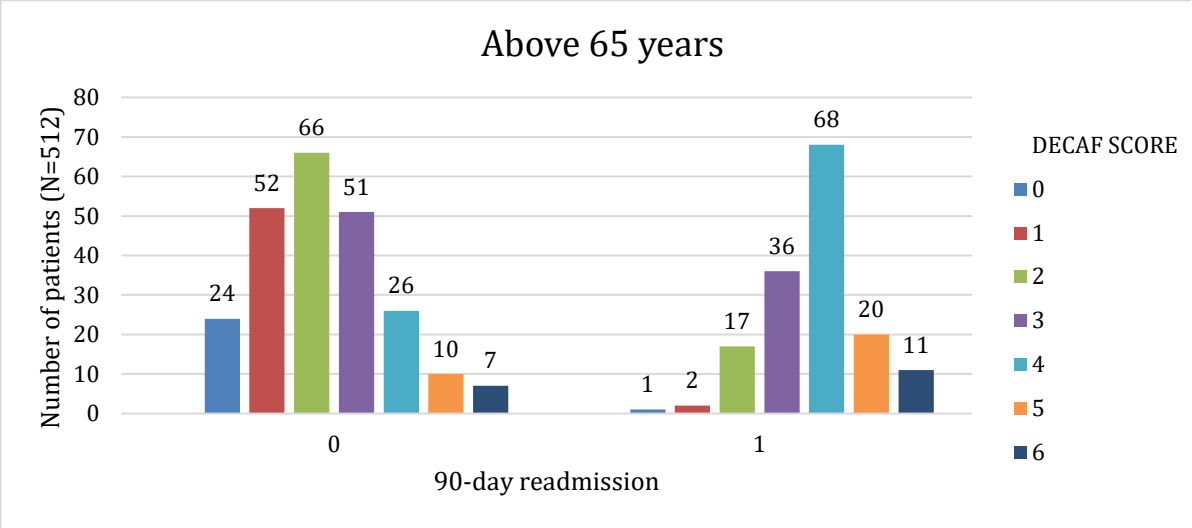

Figure 41a.

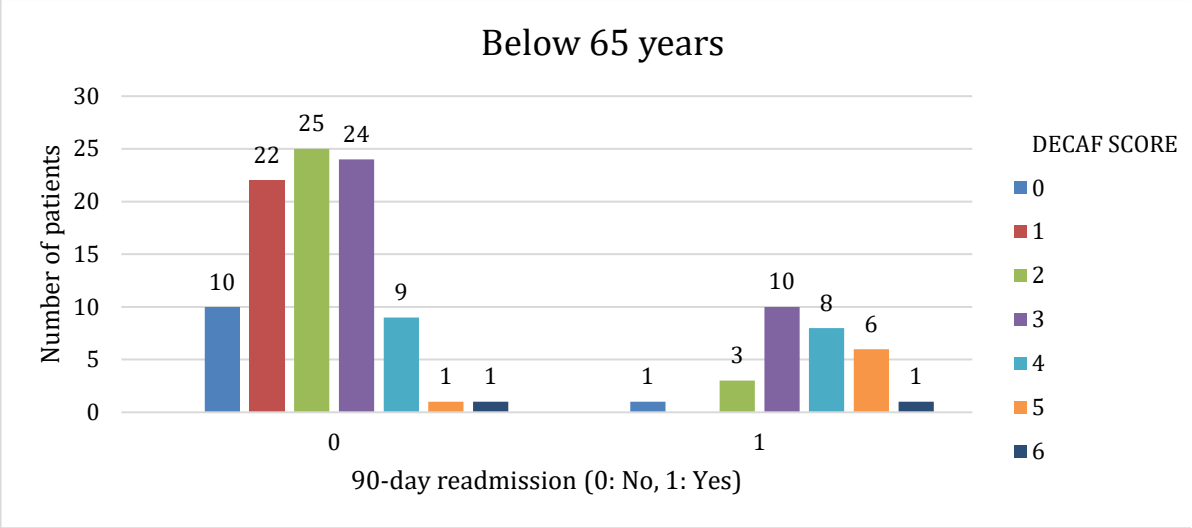

Figure 41b.

Figure 40. DECAF Score by Patient Age Categories by 90-Day Readmission(0: No, 1: Yes).

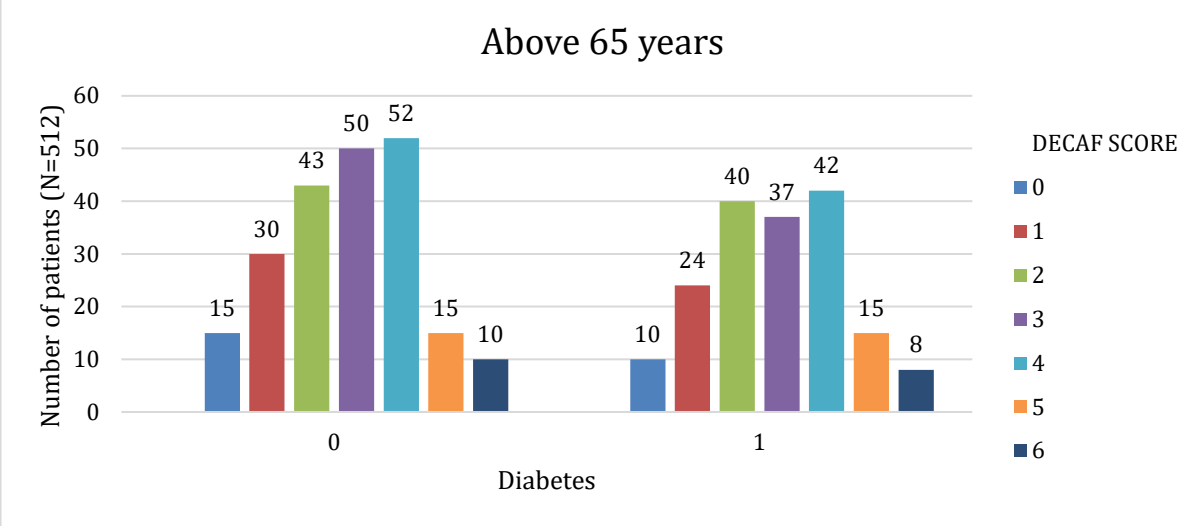

Figure 42a.

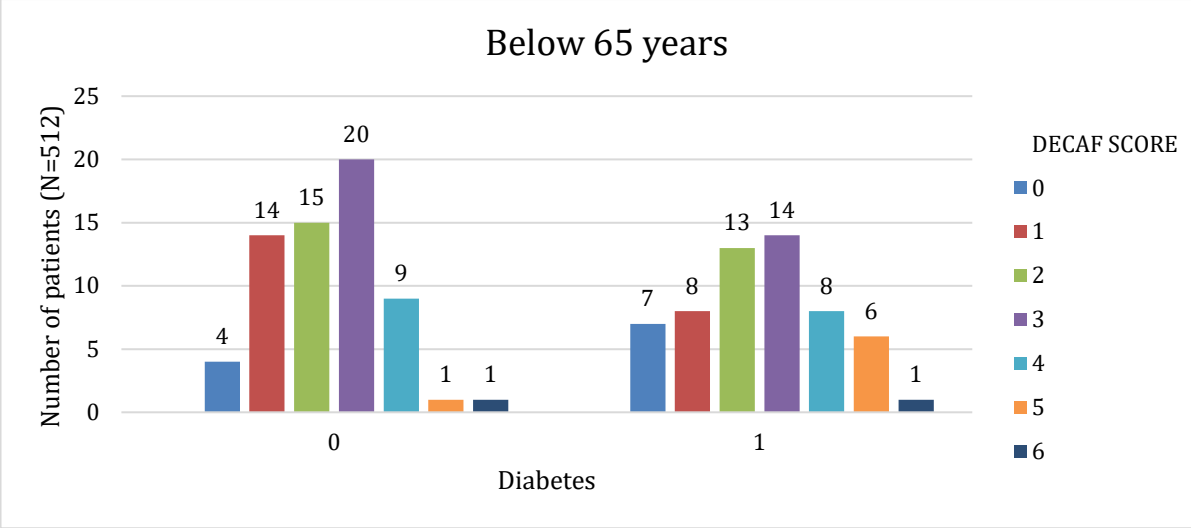

Figure 42b.

Figure 41. The Percentages of DECAF Score Clustered By Age Categories and Diabetes(0: No, 1: Yes)

5.20. Association of Sex with the Study Outcomes

Among both sexes, there were no significant differences in mean LOS across patients with different DECAF score, except for females with DECAF score of 2 and 3 (P<0.05) (**Figure 43)**. As shown in **Figure 44**, BMI was similar across different DECAF scores in both sexes (p>0.05).

The majority of both female (**Figure 45a**) and male (**Figure 45b**) patients who died had a DECAF score of 2 or higher (77.5% and 74.6%, respectively) **(Figure 45**). Additionally, a higher proportion of male patients had a DECAF score of 0 compared to female patients (97.2% versus 90.9%). As shown in **Figure 46**, the mean length of stay for males was 19.6 days, whereas it was 13.1 days for females (p>0.05).

Figure 47 shows that out of the 512 participants, 169 (33.0%) died upon admission. Of these deaths, 38 (30.4%) were females and 87 (69.6%) were males. No significant difference in inpatient death across males and females were found (p>0.05).

The distribution of readmission status was similar between genders (p>0.05). Among females, 62 (36.7%) were readmitted within 90 days, while 107 (63.3%) were not. For males, 122 (35.6%) were readmitted within 90 days, while 221 (64.4%) were not (**Figure 48).**

Figure 49 shows that 65.3%, 44.4%, and 16.4% of females were never smokers, former smokers, and current smokers, respectively. Among males, 34.7%, 55.6%, and 83.6% were

never smokers, former smokers, and current smokers, respectively. This difference in smoking history was statistically significant ($p<0.05$)

As shown in **Figure 50** (27.2%) of female patients had renal disease compared to 94 (27.4%) of males. These results suggest that there is no significant gender difference in the prevalence of renal disease among the participants in this study ($p>0.05$).

Figure 51 shows that among the female participants, 29 (17.2%) had dyslipidaemia, while among males, only 32 (9.3%) had dyslipidaemia. The findings indicate that there is a significant difference in the prevalence of dyslipidaemia between females and males ($p<0.05$).

Figure 52 shows that the prevalence of diabetes was higher in females (93, 55%) compared to males (140, 40.8%). This difference was statistically significant ($p<0.05$).

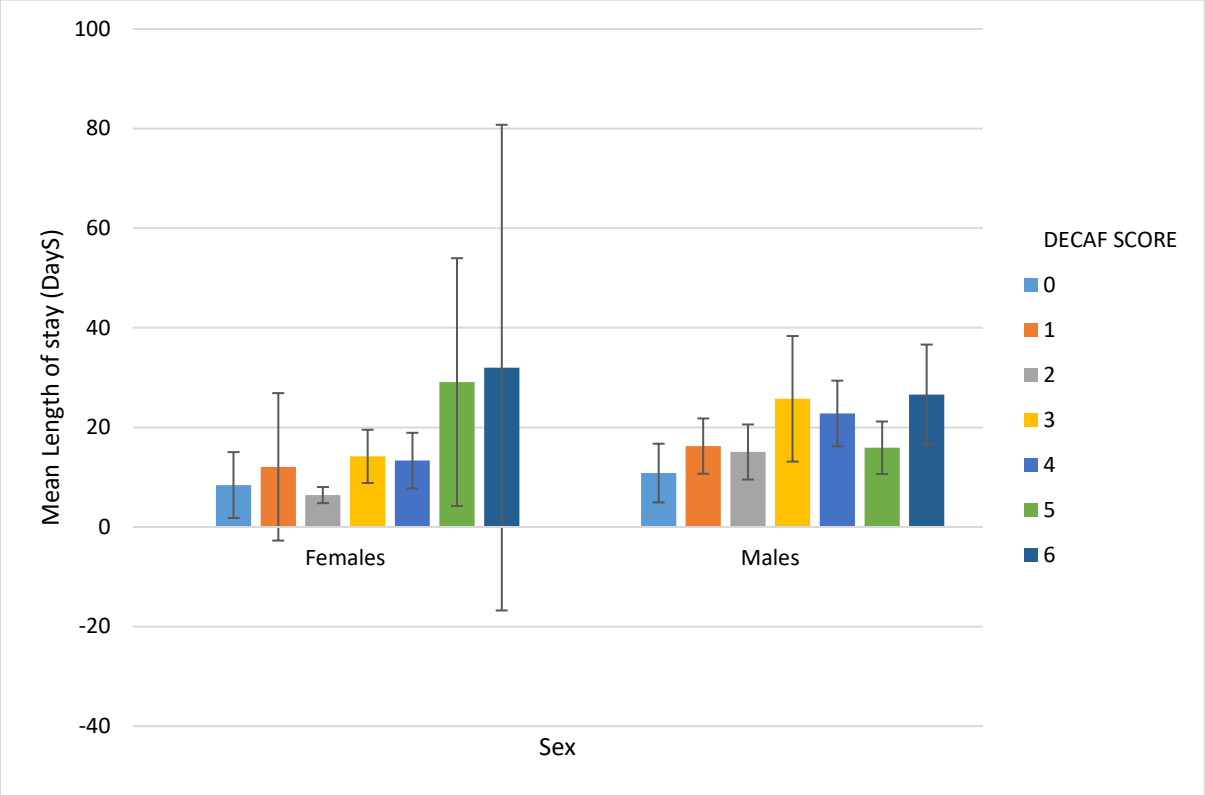

Figure 42. Mean Length of Stay Clustered by Sex and DECAF Score.

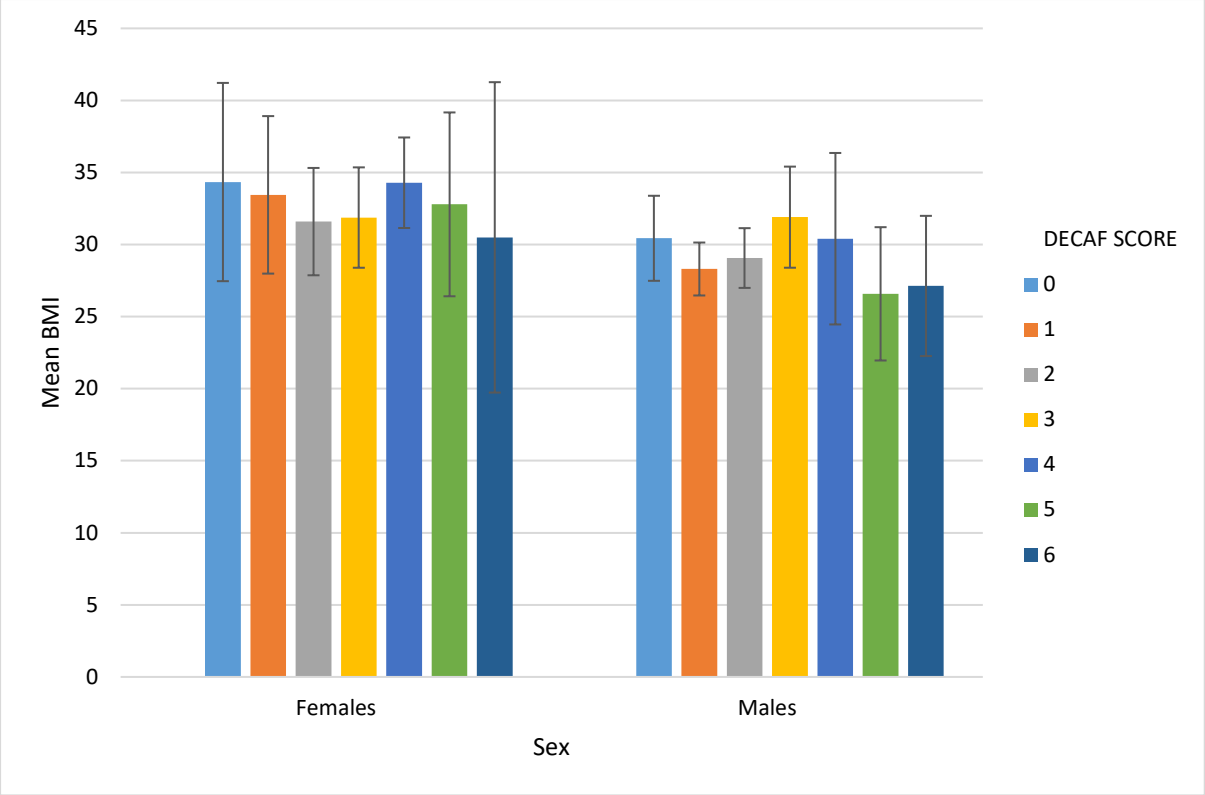

Figure 43. Mean Body Mass Index of Patients Clustered by Sex and DECAF Score

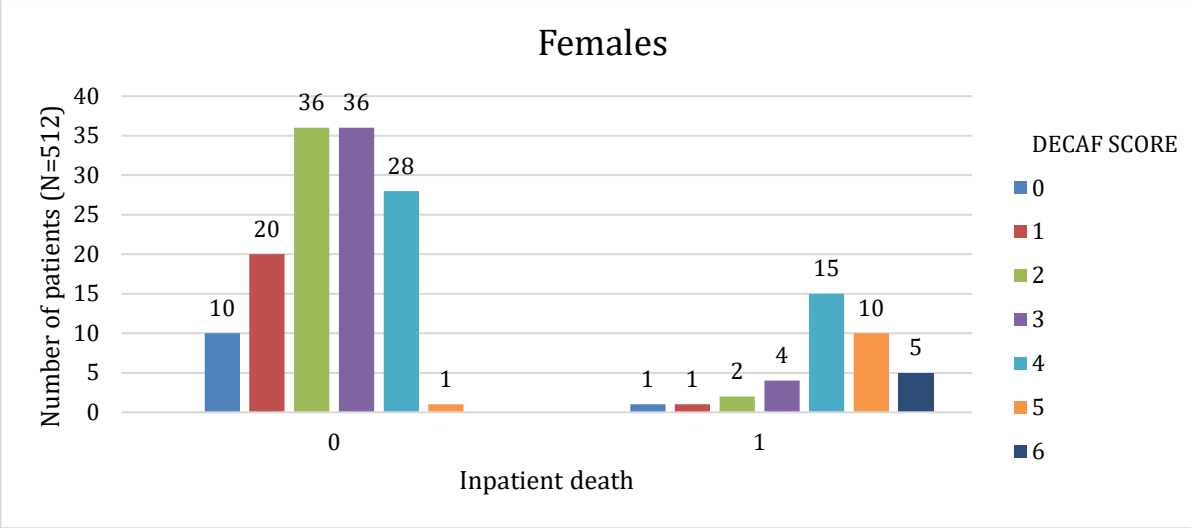

Figure 45a.

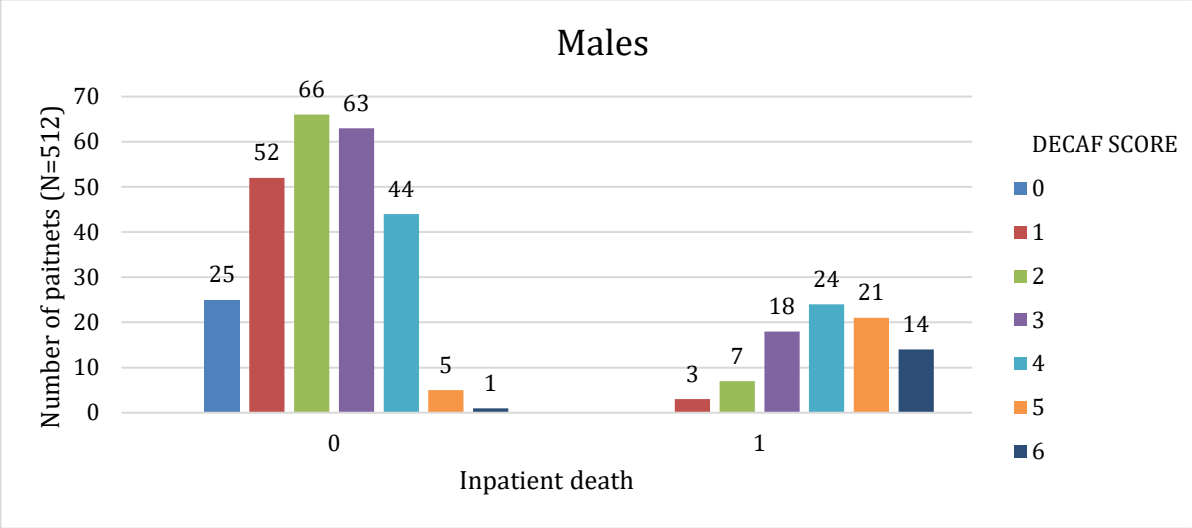

Figure 45b.

Figure 44. DECAF Score Clustered by Inpatient Death in both Sexes (0: No, 1: Yes).

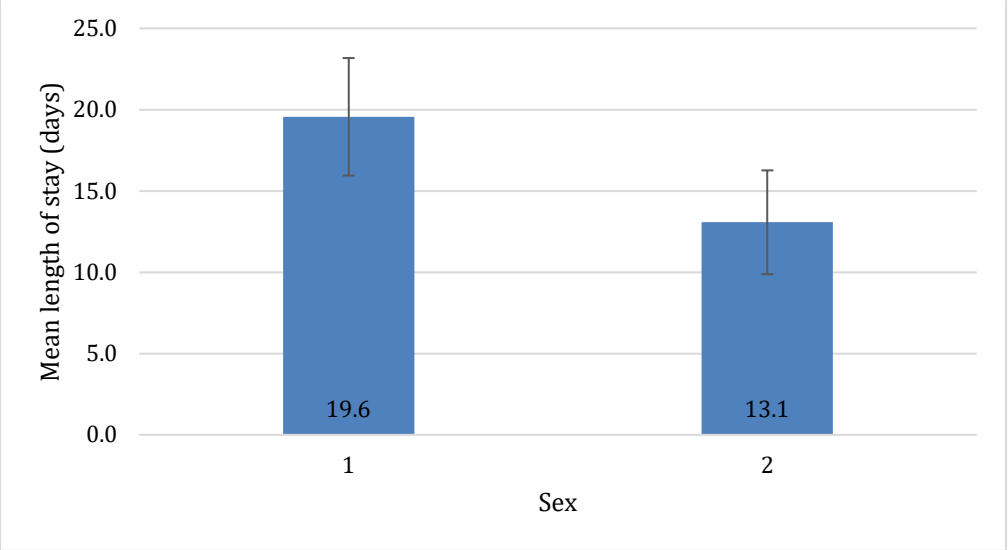

Figure 45. . Mean Length of Stay versus Sex ***(1: Male, 2: Female)***

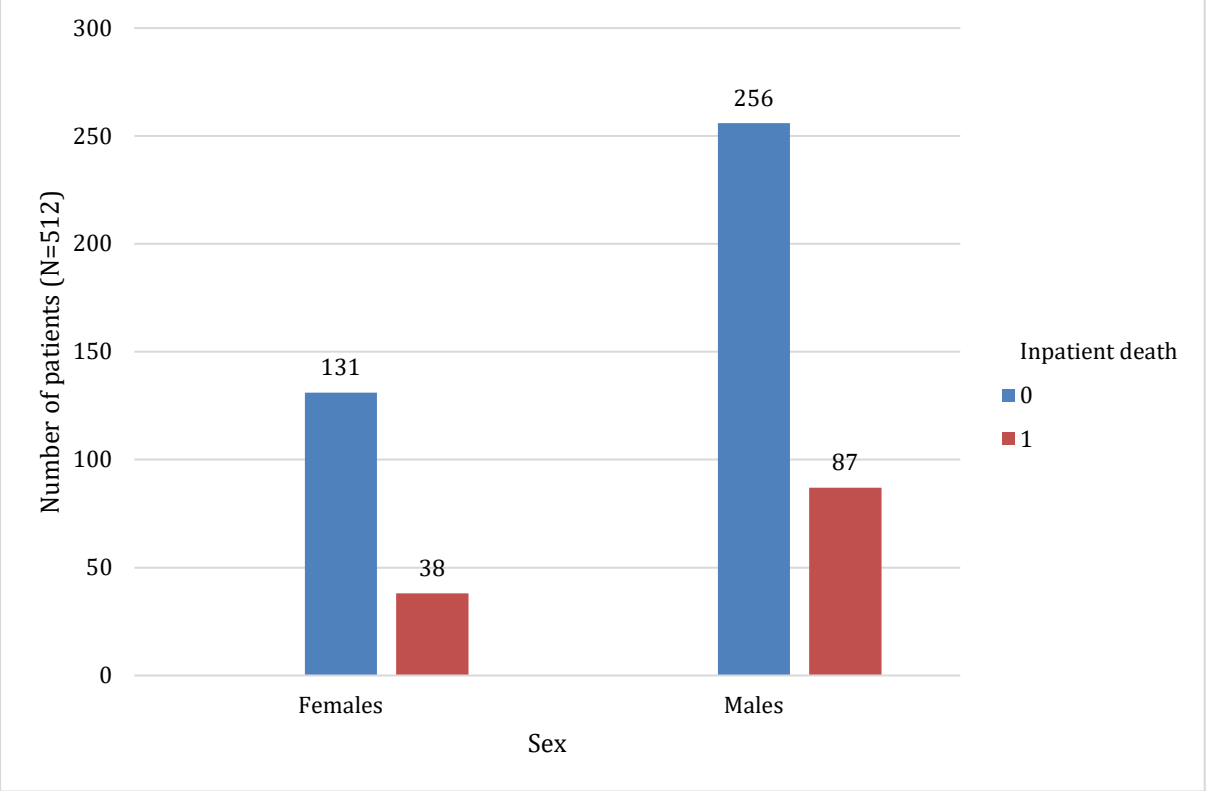

Figure 46. Inpatient Death across Sex Categories ***(0: No, 1: Yes)***

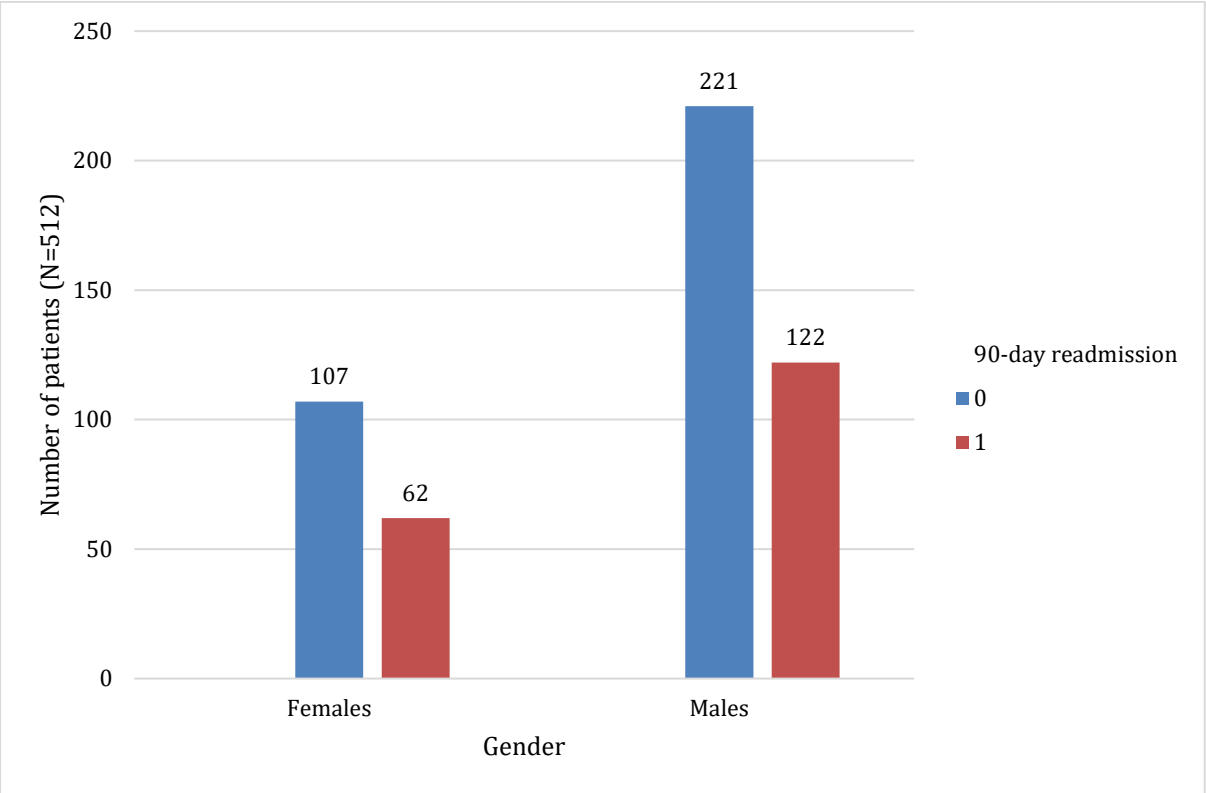

Figure 47. The Frequency of 90-Day Readmission by Sex ***(0: No, 1: Yes).***

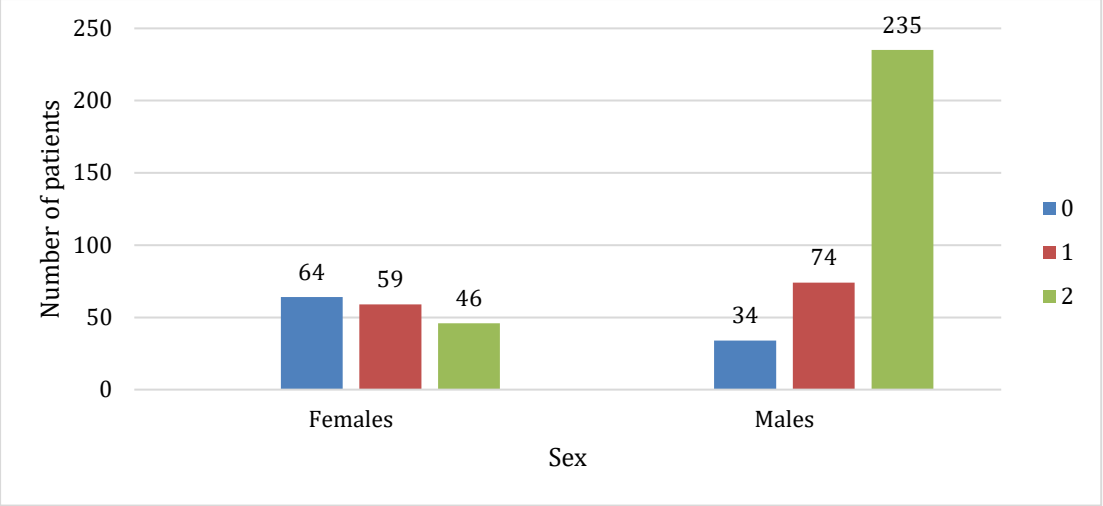

Figure 48. Distribution of Smoking History by Sex. ***(0 Never Smoker, 1 Former Smoker, 2 Current Smoker).***

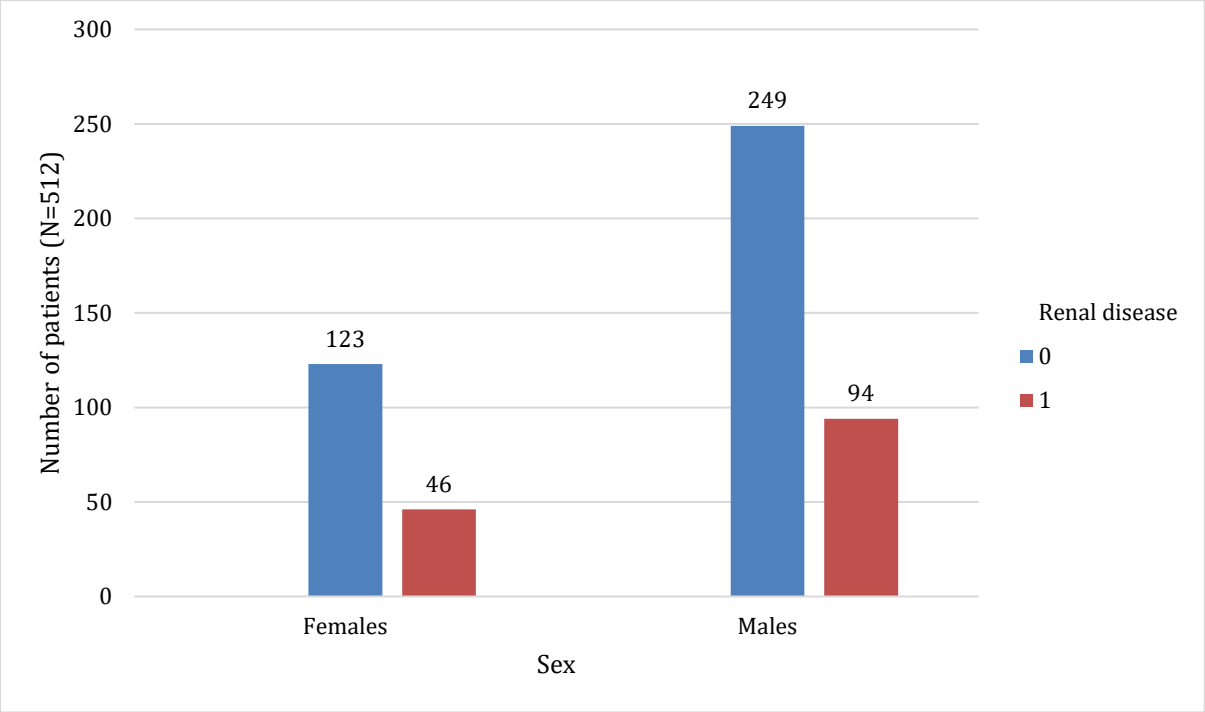

Figure 49. Distribution of Renal Disease by Sex. ***(0 No, 1 Yes)***

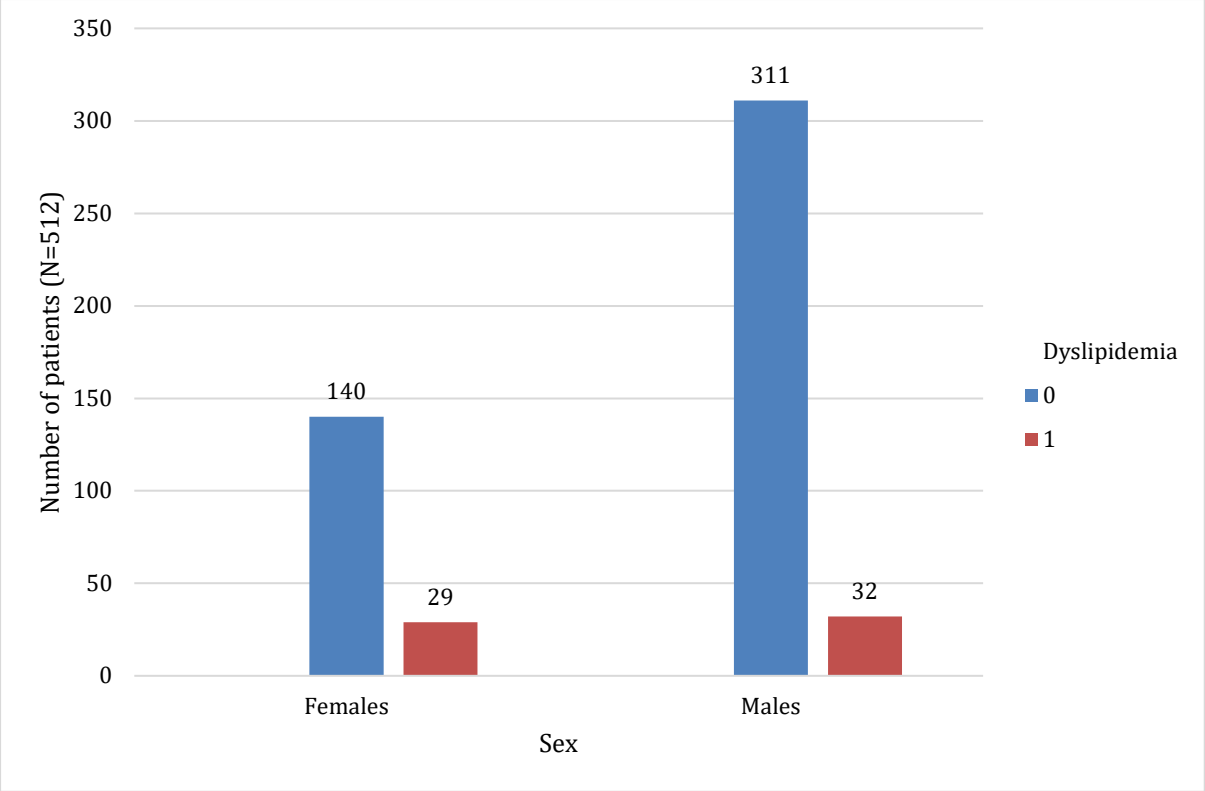

Figure 50. Distribution of Dyslipidaemia by Sex ***(0 No, 1 Yes)***

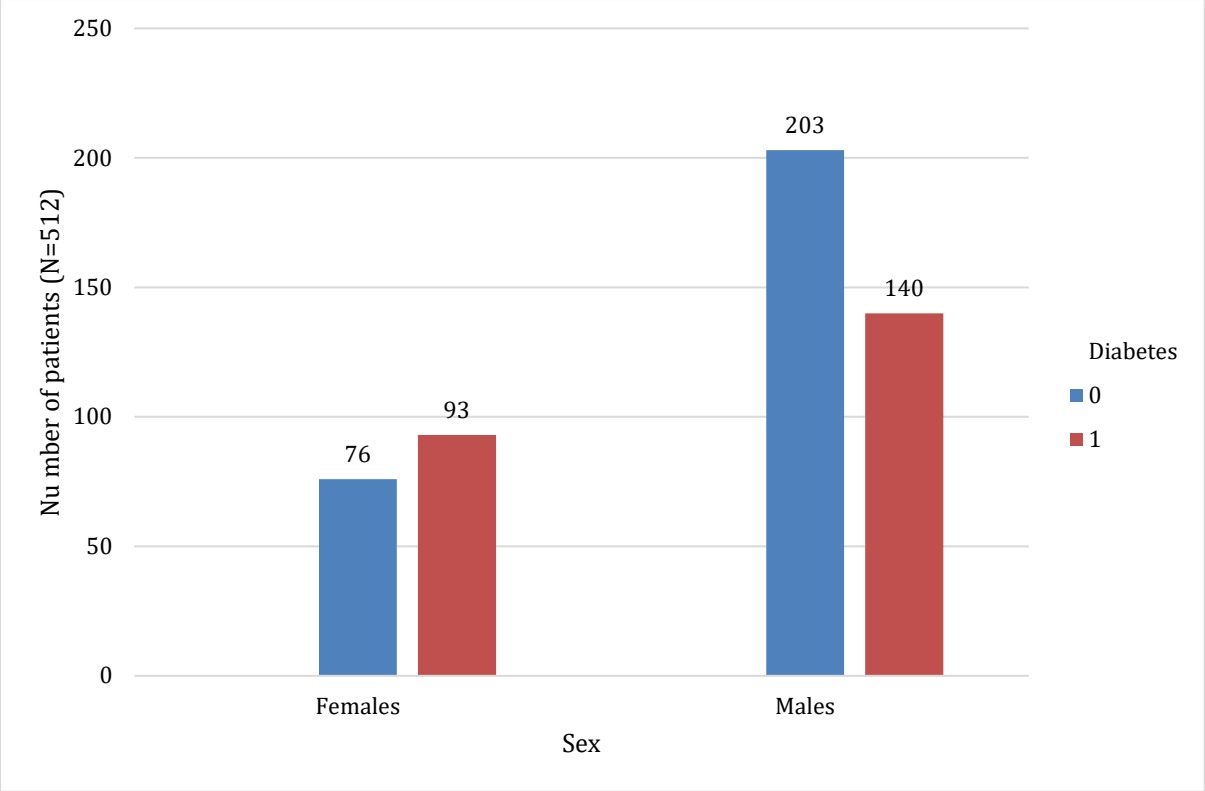

Figure 51. Distribution of Diabetes by Sex. ***(0 No, 1 Yes)***

5.21. Analysis of Outcomes by Location of Patients

As shown in **Figure 53**, the mean length of stay was similar across patients from different locations. The proportion of inpatient deaths was similar across patients from different locations ($p>0.05$). As shown in **Figure 54**, the highest proportion of inpatient deaths occurred in Sharjah (41.6%) followed by Ras Al Khaimah (32.0%). In contrast, the lowest proportion of inpatient deaths occurred in Umm Al Quwain (1.6%). The percentage of inpatient deaths in Dubai and Fujairah were 10.4% and 14.4%, respectively.

Figure 55 shows the proportions of 90-day readmission across locations. Among the cities, Ras Al Khaimah had the highest percentage of 90-day readmissions at 30.1%, followed by Sharjah with 35.4%. The difference in 90-day readmission across locations was statistically significant ($p<0.05$)

As shown in **Figure 56**, the highest proportion of current smokers was observed in Sharjah (113, 62.4%) and the lowest in Dubai (16, 21.9%). Fujairah had the highest percentage of former smokers (27, 28.7%) while Ras Al Khaimah had the highest percentage of never

smokers (21, 13.6%). The differences in smoking across locations were statistically significant ($p<0.05$).

As illustrated in **Figure 57**, the proportion of diabetes in Sharjah 35.4% was higher than that of Ras Al Khaimah (30.1%), Dubai (14.3%), Fujairah (18.4%) and Umm Al Quwain (2.0%). Nonetheless, the difference in the prevalence of diabetes across location was not statistically significant ($p>0.05$)

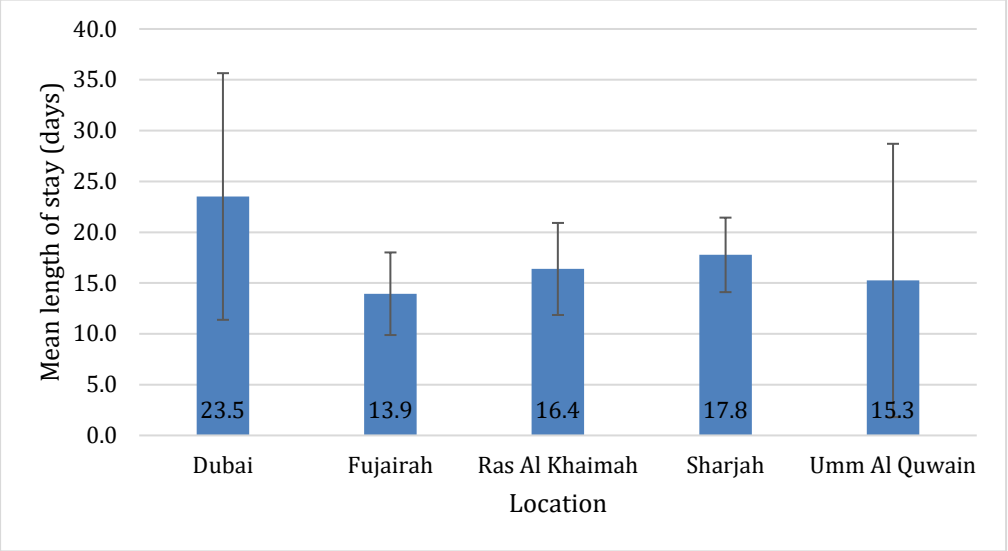

Figure 52. Mean Length of Stay by Location of Patients.

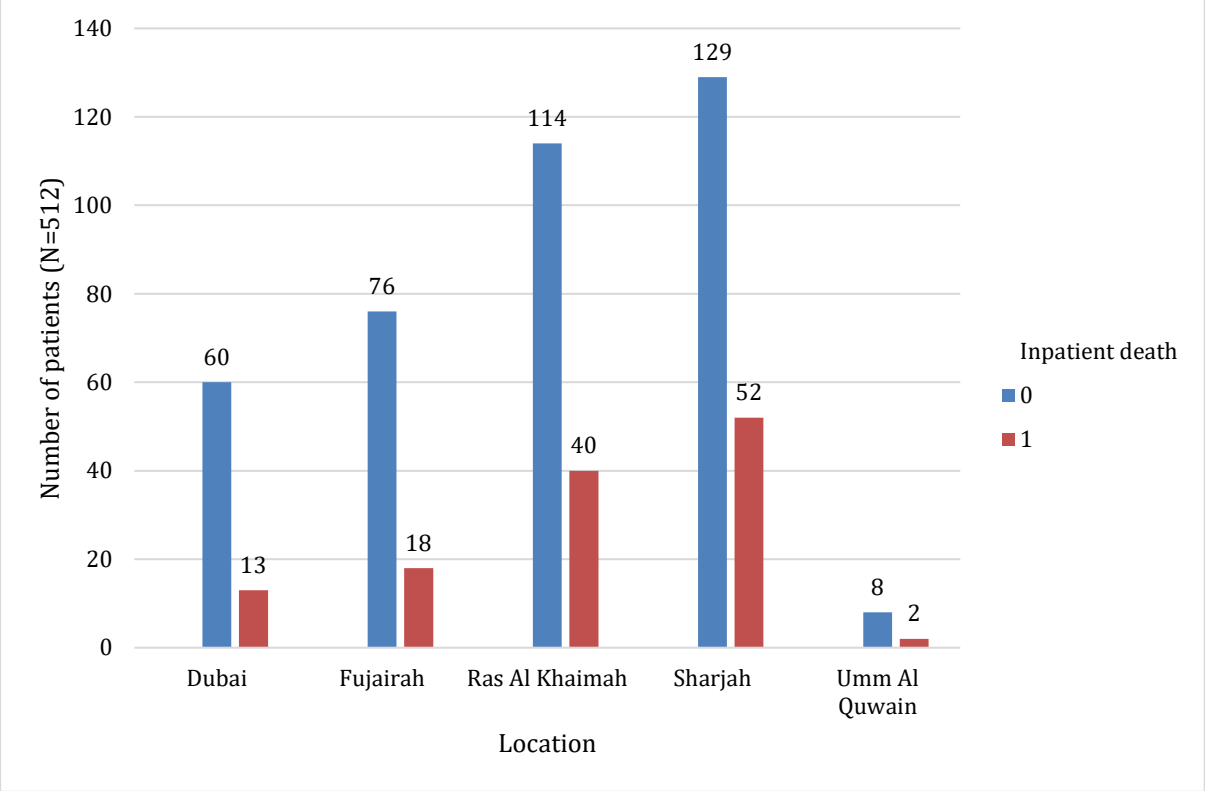

Figure 53. Distribution of Patient Death by Location. ***(0 No, 1 Yes)***

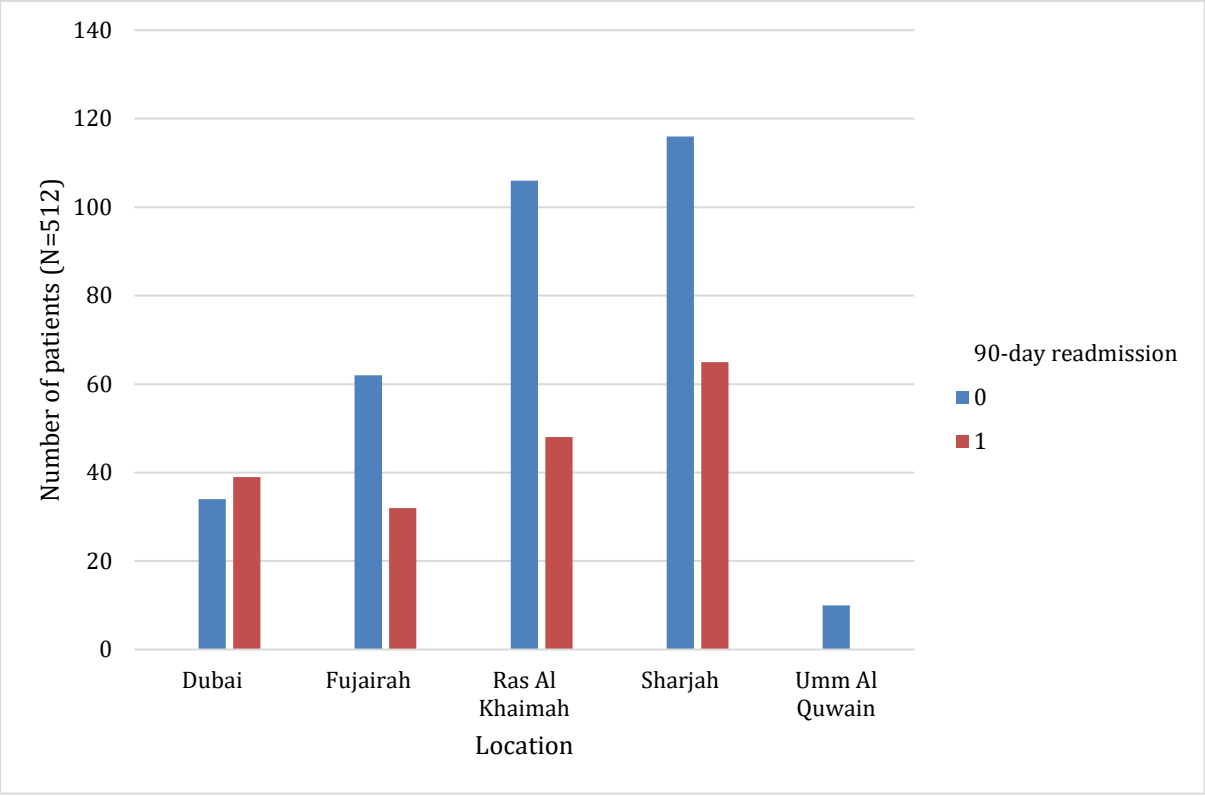

Figure 54. The Frequency of 90-Day Readmission by Location. ***(0 No, 1 Yes)***

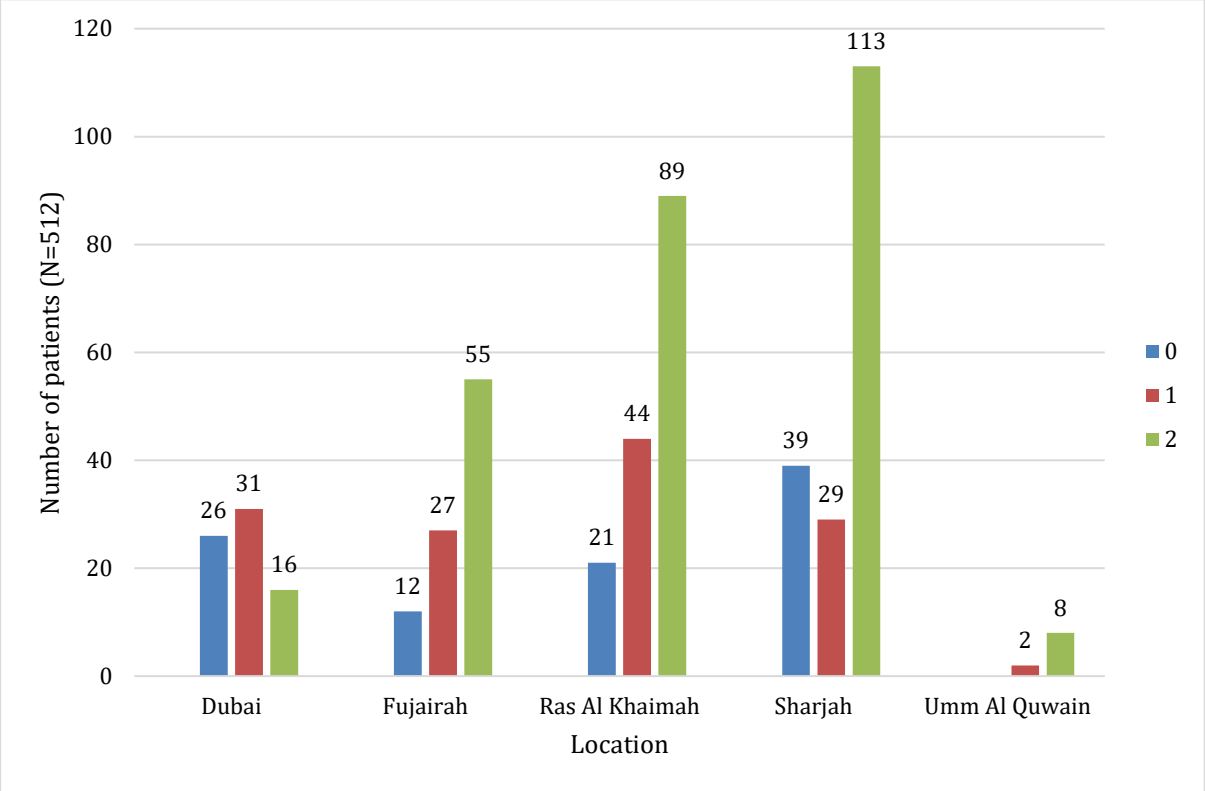

Figure 55. The Proportion of Smoking History by Location ***(0: Never Smoker, 1: Former Smoker, 2: Current Smoker)***

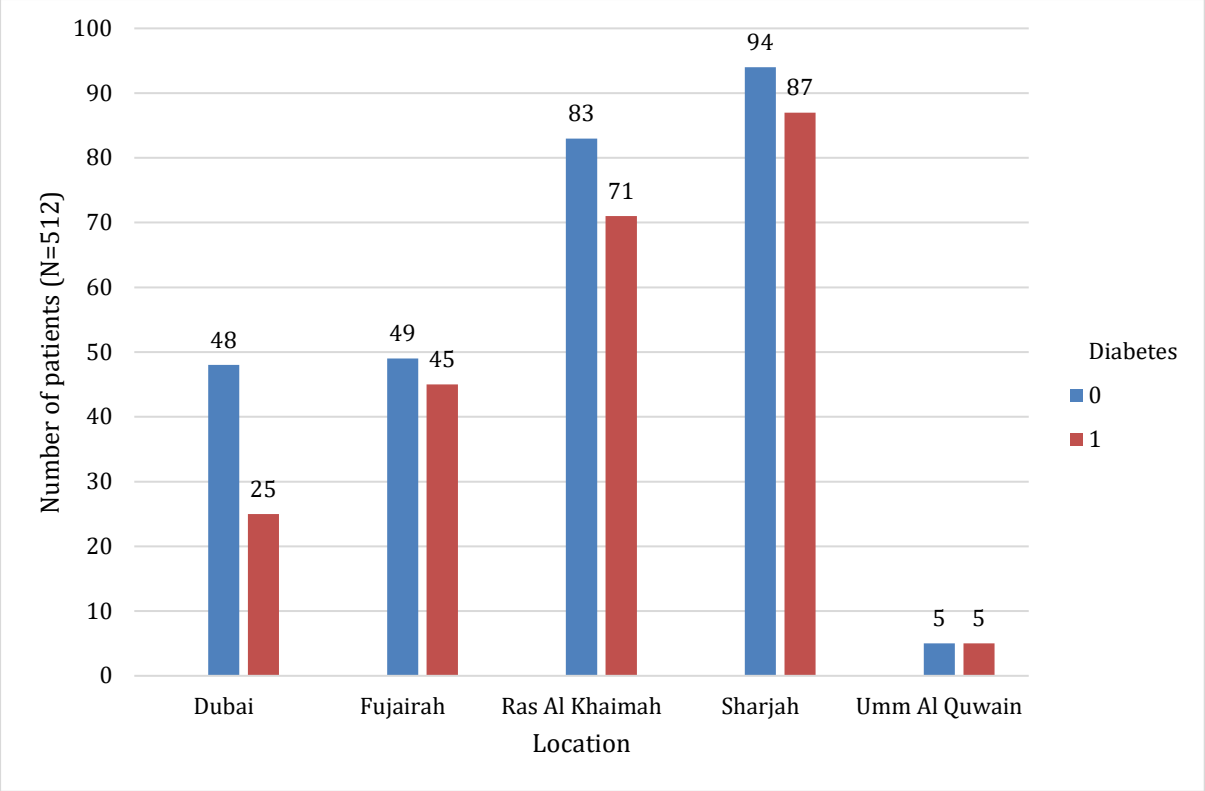

Figure 56. The Prevalence of Diabetes by Location. ***(0 No, 1 Yes)***

5.22. The Association of Diabetes with the Study Outcomes

No significant difference in mean length of stay across patients who had diabetes and those who did not (p>0.05) (**Figure 58**). As reported in **Figure 59**, the overall proportions of inpatient deaths among patients with diabetes and those with no diabetes were 28.3% vs 21.1% respectively. No significant difference was found (p>0.05).

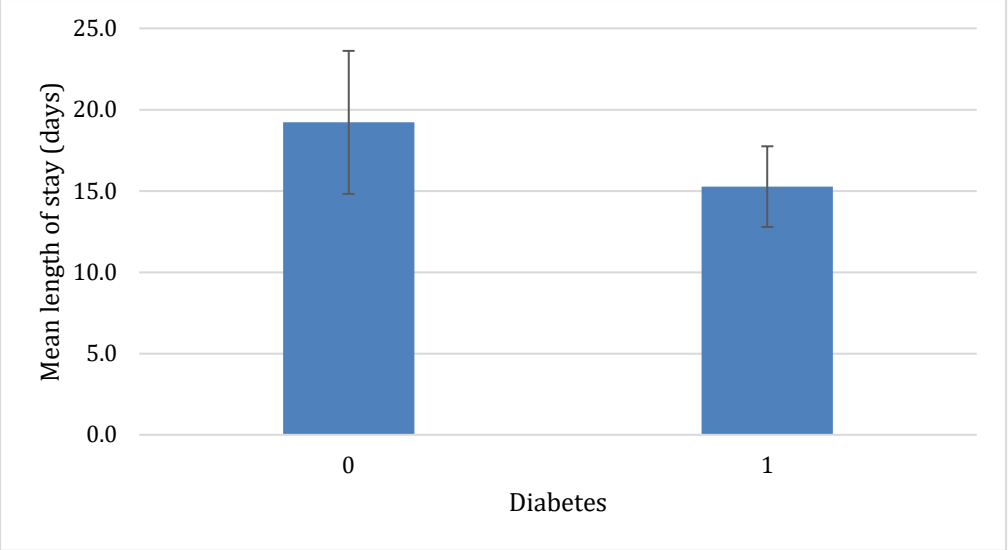

Figure 57. The Relationship between Diabetes and Length of Stay ***(0: No, 1: Yes). (This figure uses error bar technique to show differences in length of stay across patients who had diabetes and those who did not)***

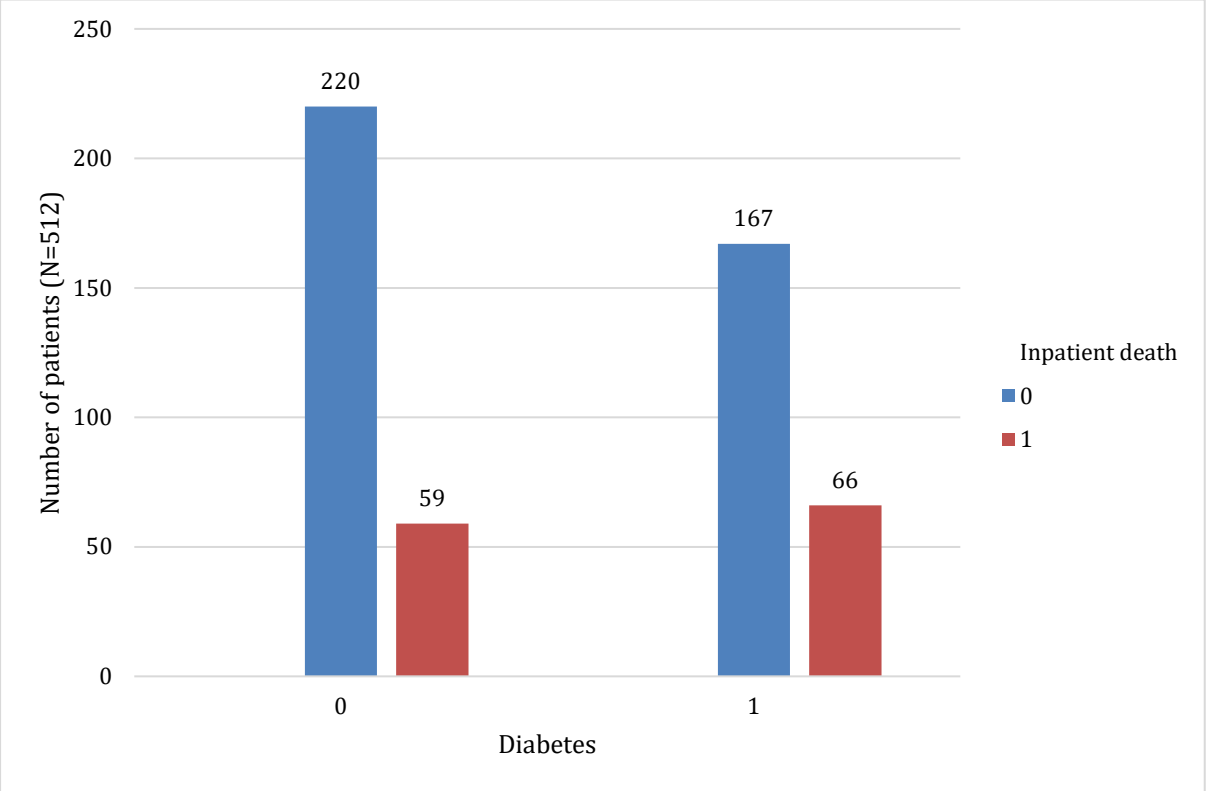

Figure 58. The Relationship between Diabetes and Patient Death ***(0: No, 1: Yes). (This figure shows differences in patient death across patients who had diabetes and those who did not)***

5.23. DECAF Score versus Other Approaches

Numerous scoring systems have been developed to predict outcomes during COPD exacerbations episodes such as the DECAF score, BAP-65 score, ADO score, APACHE II score and BODE index. This section provides a concise comparison between the DECAF score and other approaches based on evidence from published papers.

Steer et al. (2009) created the DECAF score as a comprehensive scoring system to evaluate COPD exacerbations. It incorporates five variables: dyspnoea, eosinopenia, consolidation, acidaemia, and atrial fibrillation, specifically tailored for COPD exacerbations. Numerous studies have proven its ability to accurately predict mortality rates, length of hospital stays and need for ventilator support (Steer et al. 2009; Echevarria et al. 2016), as well as having high discriminatory power and clinical utility (Steer et al. 2009; Echevarria et al. 2016). It has shown exceptional discriminatory power and clinical utility and discriminatory power and clinical utility when applied appropriately in COPD exacerbations situations.

BAP-65 Score: Chandra et al.'s (2012) BAP-65 score was developed with the purpose of predicting mortality during COPD exacerbations. It takes into account four variables: blood urea nitrogen (BUN), altered mental status (AMS), pulse rate and age. A comparative study by Steer et al (2012) indicated that DECAF scored outperformed the BAP-65 in terms of mortality prediction accuracy, its AUC being 0.81 as opposed to 0.68 for BAP-65 which suggests more accurate mortality prediction results overall.

Puhan et al. (2012) introduced the ADO score, which measures mortality risk during COPD exacerbations by considering three variables: age, dyspnoea, and forced expiratory volume in 1 second (FEV1) percentage predicted. A study by Echevarria et al. (2016) demonstrated superior predictive ability compared to ADO score with an AUC value of 0.81 for DECAF score vs 0.68 - which indicates more accurate prognostic information in DECAF score than ADO score.

The Acute Physiology and Chronic Health Evaluation II (APACHE II) score is an extensively utilized, complex scoring system used in intensive care units to assess disease severity and predict outcomes. It takes into account various physiological parameters like temperature, blood pressure, respiratory rate, laboratory values etc. Though not specific to COPD exacerbations specifically, the APACHE II score can still be used as an evaluation tool when dealing with critically ill patients; although its impact has yet to be demonstrated directly versus that of DECAF score in terms of COPD exacerbations prediction outcomes prediction outcomes prediction in COPD exacerbations situations.

The BODE index is a multidimensional scoring system which incorporates four variables: body mass index, degree of airflow obstruction, dyspnoea and exercise capacity - into one score that predicts mortality, healthcare utilization and quality of life for COPD patients. Studies have demonstrated its predictive power when used alongside DECAF score for measuring exacerbations. While BODE provides a comprehensive assessment of COPD severity, further comparative research must take place specifically with DECAF score in regard to exacerbations events.

Chapter 6. Discussion

6.1. Discussion of Findings

6.1.1. Key Findings

The evaluation of the DECAF score in the United Arab Emirates AECOPD population has achieved the primary aim of the study; confirming the DECAF score's validity and performance among the UAE population. The results showed a satisfactory fit of the DECAF score concerning UAE data on inpatient death, 30-day death, and 90-day readmission. This study's novel finding is the 90-day readmission rate. Investigating the DECAF score's benefit and effectiveness is crucial, and demonstrating AECOPD severity and its related in-hospital mortality and readmissions were the first steps in the analysis.

In a whole-case analysis (without imputation), the in-hospital death rates were 7.7% and 22.4% in the UK and UAE populations, respectively. An important finding of this work was that overall mortality is considerably higher in the UAE AECOPD population than in the UK study. Therefore, it is essential to study the DECAF score to estimate its significance as a clinical prediction measure that precisely stratifies AECOPD patients with risk (Hajian-Tilaki, 2013). Several reasons could explain the wide variation in inpatient death rates across the UAE and the UK. First, there could be different admission thresholds across the two countries. Second, staff experience could be different. Third, there could be differences in diagnostic procedures. For example, patients with AECOPD could be misdiagnosed, and their deaths could be attributed to other conditions. Finally, there could be different levels of data reporting. Specifically, the numbers in the UK could be underreported (Wedzicha and Wilkinson, 2006).

Although there is a slight difference in life expectancy estimates across the UK (81 years) and the UAE (79 years), we believe that inpatient death rates are more likely to be associated with healthcare-related issues (Wedzicha and Wilkinson, 2006). The higher risk of death in the elderly with AECOPD in the UAE could be related to late diagnosis of COPD patients and associated under treatment due to healthcare provider-associated factors. These include scarcity in knowledge and equipment in previous decades, possibly causing missed and/or late diagnoses in the United Arab Emirates setting (e.g., spirometry). Achieving the objective of earlier COPD diagnosis requires a significant knowledge transformation in primary care settings and an education initiative. Prolonged respiratory symptoms untreated for years may lead to cardiovascular disease and spirometric signs (Morgan, Zakeri and Quint, 2018). On this basis, enhancing the awareness of risk factors related to AECOPD is an important first step to

promote wellness and achieving overall better community health, along with appropriately resourced smoking cessation support in the UAE (Office of National Statstics, 2020).

It has previously been shown that the DECAF score has an advantage over other conventional scores like APACHE II, BAP-65, CAPS and CURB-65 in the UK DECAF study (Echevarria et al., 2016). This supports the idea that the area under the Curve (AUROC) could be used for stratification. Therefore, we used the AUROC to study or determine the performance of the predictive and diagnostic tools. The AUROC curve is performed by plotting sensitivity on the y-axis as a function of specificity on the x-axis for deciding the outcome measure. Thus, the ROC curve is a quick graphic examination of sensitivity and specificity.

In the UAE DECAF study, the AUROC DECAF curve analyses were applied in three outcomes: inpatient death, 30-day death, and 90-day readmission. The AUROC test helps us picture how well the DECAF score risk stratifying is performing. The AUROC of 30-day death in the UAE DECAF study is 0.776 (95% CI: 0.717-0.834), and is similar to the UK DECAF study, which was 0.83 (95% CI 0.78 to 0.87) and indicates a substantial predictive value for this DECAF score in both populations. The accuracy analysis of the study showed that DECAF scores were significant for in-hospital and 30-day mortality 0.83(0.79-0.86) and 0.79(0.76-0.83), respectively (Huang et al., 2020).

Based on previously published studies, we can generally interpret the AUROC values as follows: the AUROC value of 0.5 is considered the worst, and the AUROC value of 1.0 is perfect. In more detail, AUROC of 0.5 showed that the studied model was useless, AUROC less than 0.7 is below the required level, AUROC of 0.70 – 0.80 is a satisfactory level, AUROC greater than 0.8 is an excellent level, and AUROC of 1.0 reaches an ideal point (Narkhede, 2018). The research emphasizes the validity of our DECAF score in our region and indicates that it will be a good score in the future.

The level of prediction provided by the DECAF score can support the clinical decision-making in two major ways. First, categorizing the severity of cases, which could help in deciding whether patients can be discharged or admitted (Echevarria et al., 2015). Additionally, the DECAF score will ensure the clinical decision-making process to be swift and prioritized. Hence, avoiding negative complications and improving recovery rates. Second, the DECAF score could facilitate safe and efficient therapy management for patients with AECOPD. This is noteworthy as this similar good performance for DECAF was in a UAE population who were generally sicker as evidenced by the higher rates of death documented in this study. As stated

before, the higher death rates compared to other countries can be explained not only in the context of the sickness level, but also in the context of quality of care and diagnostic procedures (Collier et al., 2015). This means that DECAF is robust across different international healthcare settings. Moreover, we are confident that this research will serve as a base for future studies on disease predictive scoring systems, due to the increasing importance and scale of COPD in the personal, health, and economic sectors in the UAE and the Middle Eastern countries.

The pulse rate was more controlled for those with extended hospital stays than for others. This finding may be explained by healthcare providers' attempts to provide life-saving care to extend the life expectancy of patients with AECOPD. Vasopressor and inotropic drugs were used more frequently to maintain the pulse rate in AECOPD patients in the UAE. This result supports the previous finding of Yamamoto et al. (2019), who concluded that a higher pulse rate is associated with a higher chance of mortality in non-severe cases. The high pulse rate alerts healthcare providers to intensify hospital care to prevent potential complications, even in less severe conditions. The result of Crimmins' study (2015) supports a focused effort to improve health policies and practices by employing new science dedicated to extending the lives of those suffering from severe conditions.

The final key finding was that blood urea levels were associated with the DECAF score, which is a novel finding. The association between urea levels and DECAF was not analysed in previous studies. However, some studies indirectly examined this association. For example, these studies investigated the urea levels in AECOPD patients, such as the previous study by Groenewegen, Schols, and Wouters (2003) and Seneff et al. (1995). This finding was contrary to the study of Nafae, Embarak, and Gad (2015), which illustrated that the urea levels were lower in patients who died compared to those who survived, indicating that the urea level is an independent predictor of mortality in this study. This study has identified some statistically significant associations in predicting the inpatient mortality of patients presenting with AECOPD. However, there are some methodological limitations in obtaining the laboratory variables necessary for this type of work, including differences in reporting urea levels using blood urea nitrogen (BUN) and blood nitrogen between the Emirates Health Services and the Dubai Health Authority medical records. We strongly feel that consistent data entry must be undertaken to allow a definitive guideline for triage and the appropriateness of acute care.

6.1.2. Inpatient Death Key Findings

Inpatient death was significantly associated with several indices: aging, DECAF score, PO2 supplementation, and admission pulse rate versus length of stay (more than 30 days versus less than 30 days) in AECOPD admitted patients. The first index, where age correlated with inpatient death, is essentially the same finding as that noted by García-Sanz et al. (2017) that older ages and baseline disease severity were significantly correlated with a higher risk of death within one year after hospital admission. Age was addressed as a risk factor for inpatient death in our study; older patients with AECOPD died during admission. Previous studies contended that many risk factors related to inpatient death of AECOPD patients, including demographics and comorbidities, and an important demographic is the age factor (Bustamante-Fermosel et al., 2007; Roche et al., 2008). The mean age in this study was the same as the UK study population, 73 (Echevarria et al., 2016). Interestingly, the second considered inpatient death-related index is the DECAF score. The higher DECAF score readings in the UAE are related to higher death incidence, despite the absolute numbers being lower in those who scored DECAF 5 and 6. Indeed, patients who scored higher had a higher chance of death; this is consistent with the study by Echevarria et al. (2016), which stated that mortality correlates directly to the DECAF high-risk group. Therefore, the DECAF score has important implications for identifying high-risk AECOPD admitted patients in the United Arab Emirates setting, where robust inpatient mortality-risk predictive scores are currently lacking. Importantly, this study shows that DECAF can be used in the UAE setting in real-world patients.

The third index related to inpatient death was high PO2 supplementation. It was observed that 69 (13.5%) patients had high doses of oxygen (Pa PO2 >13 Kpa/ 97.5 mm Hg). Among this group, 22 (31.8%) died. As previous studies have shown, high oxygen supplementation increases the risk of in-hospital death. This finding is consistent with a study conducted in the United Kingdom, which showed that patients with oxygen saturation above normal levels died during the study period (Echevarria et al., 2021).

Oxygen therapy is given for respiratory failure conditions when the oxygenation levels (low partial pressure of oxygen [PaO2]) are accompanied by an average level of carbon dioxide (type 1 respiratory failure) or a high level of carbon dioxide (type 2 respiratory failure). Oxygen-induced hypercapnia in COPD exacerbation patients is not fully understood. However, recent studies have focused on patients who received ambulatory oxygen on the way to the

hospital. For example, in a UK retrospective study, around 20% of 1000 patients experienced respiratory acidosis at their hospital arrival, increasing the risk of tracheal intubation. More than 50% of COPD cases that received an overdose of oxygen (Pao2>13.3 kPa) reported respiratory acidosis, which was associated with mortality (Brill and Wedzicha, 2014).

Another concern is rebound hypoxia, which may occur during the withdrawal of oxygen. Rebound hypoxia occurs because oxygen and carbon dioxide displace each other in the alveolar space when administering high doses of oxygenation. The oxygenation compensation will occur directly to fix the displacement. However, the level of carbon dioxide increases simultaneously, so the body maintains a high concentration of carbon dioxide. In the case of sudden oxygen withdrawal with increased carbon dioxide, alveolar PaO2 collapse occurs (Brill and Wedzicha, 2014). The sudden withdrawal can lead to abrupt death by acute arterial hypoxemia, regardless of whether the level of carbon dioxide is improved or stable (Kane et al., 2011). Therefore, oxygen therapy must be tapered down slowly (O'Driscoll, Howard and Davison, 2008).

The authors advise enhancing oxygen delivery, which may significantly impact the decline in mortality rate. Moreover, European and British guidelines recommend a target saturation of 88%–92%, altered to 94%–98% if carbon dioxide is normal. Encouraging pulmonologists to stay updated on AECOPD disease management is a key finding in this study. Communication between pulmonologists and general practitioners, emphasising training in dealing with AECOPD cases, is of key importance. Since the general practitioner is the first contact for the AECOPD patient, proper management from this initial step is a preventive practice to implement in the future, as suggested by this study. The establishment of a strict and consistent international practice in delivering oxygen within a recommended range is also required. It can be predicted that this will reduce the incidence of death in AECOPD in our setting.

The final inpatient death-related index is the correlation between the length of stay and inpatient death, which is intriguing. For longer-term deaths, the length of stay showed a longer time to inpatient death. This result is worth mentioning because an extended hospital stay may be considered as a sign to identify patients at a higher risk of long-term mortality. This result is essentially the same as that found by Zhang and Lin (2019), who affirmed that a longer length of hospital stay is one of the risk factors for the mortality of AECOPD patients. The DECAF score has an advantage over previous predictive scores in predicting short- and medium-term mortality in a multicentre cohort of patients admitted with AECOPD (Echevarria et al., 2016).

Overall, these data indicate that the DECAF score could be a useful tool in the UAE to identify which patients may be eligible for earlier escalation in treatment, palliative care, or home management.

6.1.3 Discussion of the DECAF Score Effectiveness

COPD is increasingly recognized to have a profound effect on overall health and the economy in the GCC region, as it does globally. In 2021, the WHO declared that COPD is the third leading cause of death and the seventh leading cause of morbidity worldwide, mainly in low- and middle-income nations. Acute exacerbation of the disease affects health status and leads to a faster deterioration in lung function, which eventually influences post-admission emotional, social, and professional life. Additionally, exacerbations are associated with a decline in daily physical activity and the overall quality of life. The occurrence of AECOPD mortality is associated with the severity of the disease status. Studies have confirmed that AECOPD is associated with mortality after either short- or long-term severity, particularly for those needing hospital admission to an intensive care unit (Suissa, Dell'Aniello and Ernst, 2012). The prevalence of AECOPD is growing worldwide (Lopez and Murray, 1998). It consequently correlates with the abundance of risk factors in the environment and patient-associated risk factors, some of which may be avoidable or modifiable. High AECOPD prevalence in COPD is related to noteworthy economic costs (May and Li, 2015). The published literature estimates that around 3 million deaths were associated with COPD in 2019. Furthermore, the WHO projects an increase in mortality until the upcoming decade at the very least. The growing rates of AECOPD trigger severe consequences not only on public health but also on healthcare capabilities, particularly in nations where healthcare facilities suffer from profound shortages in staff, equipment, and resources. This has brought attention to the importance of preventive measure strategies. Some organizations like the WHO have suggested focusing on preventive measures, such as early diagnosis and good disease management, to reduce the burden of disease severity and premature death. Strategies to mitigate disease severity and exacerbation episodes should be evaluated, optimized, and implemented.

The GOLD initiative (Halpin et al., 2021) has led to standardized worldwide approaches in COPD management, for example in staging disease severity according to degrees of airflow limitation. Despite the importance of AECOPD, however, practically, no scale to stratify the risk, severity, and mortality in AECOPD has been adopted consistently. Such a scale could provide optimal disease management in the admission and even after admission (Alameda,

Carlos Matía, and Casado, 2016). The scale should be based on information from a history and routine examination and be augmented with information from laboratory investigations, chest radiography, blood gases, and ECG to determine the severity. Furthermore, the predictive score would be required to be set up and help reduce mortality, morbidity, pressure on healthcare workers, and finally support decision-makers.

Currently, calculating a predictive score in AECOPD patients in the United Arab Emirates settings is limited; conventional scores with different indices and risk-stratifying are achievable but are not widely used in the UAE and have modest accuracy. The lack of effective predictive scores in hospitals will lead to improper risk stratification in AECOPD patients. This situation will confuse decision-making regarding treatment escalation, early discharge, and severity prediction.

In the United Kingdom, the DECAF score has been shown to be a robust tool that has been implemented in the AECOPD care pathway. DECAF consists of indices that aid healthcare providers in detecting a patient's health status and allows for accurate forecasting of their mortality in the hospital. This score is simple and can be easily calculated at the time of admission. Accurate score calculation has been shown to guide healthcare providers to good disease management and avoid the burden of unnecessary interventions.

In several published studies of admitted patients with AECOPD, the DECAF score has been shown to have advantages over other routine scores (Diamantea et al., 2014, Echevarria et al., 2017). Reviewing the patients admitted with AECOPD, the DECAF score is shown to be simple in predicting the severity and mortality of individuals using regular recorded readings on admission. The United Kingdom DECAF study showed that DECAF was superior to other conventional scores (BAP-65, CAPS, APACHE-II, CURB-65) in predicting immediate death incidence after the previous in-hospital admission (Echevarria et al., 2016).

In our region, no appreciable DECAF score validation studies have taken place, and in general, further international investigations are needed to validate the original UK DECAF score. Therefore, this study aimed to validate the DECAF score in the United Arab Emirates (UAE). We initiated a DECAF study among AECOPD admitted patients in the UAE setting. This study is considered the first of its kind in the region to stratify AECOPD patients into risk groups by DECAF score. DECAF studies in the Middle East are limited. A study was conducted by Egyptian scientists (Zidan, Gharraf and Wahdan, 2020). Most DECAF studies have been carried out in Europe (Shen et al., 2021). Therefore, this study validated the DECAF score and

predicted inpatient mortality and severity in AECOPD patients in the UAE population. Another important objective is investigating factors associated with the inpatient death of AECOPD patients. Finally, we aim to describe the clinical characteristics of AECOPD patients in the UAE hospital setting.

The ultimate goal of this research programme is to strengthen the evidence regarding the predictive performance of the DECAF score and its role in improving the clinical management of AECOPD cases in the UAE. This research programme could eventually bring the attention of healthcare managers and policymakers to the importance of this index in clinical settings. Given the high inpatient death rates and numbers of hospital admissions due to AECOPD, documenting the clinical and financial benefits of the DECAF score could expedite the process of adopting this tool.

This observational study began in September 2018 in the United Arab Emirates; 438 and 74 AECOPD admitted patients were included from 11 hospitals in the Emirates Health Services (EHS) and 4 hospitals in the Dubai Health Authority (DHA), respectively. The data were retrieved using existing electronic systems. In this research, the number of recruited patients was significantly high at both sites (the Emirates Health Services and the Dubai Health Authority). The UAE cohort size of 512 patients is comparable to the external validation group used in the original UK study, which validated the DECAF score to predict hospital mortality in AE COPD (845 patients) (Echevarria et al., 2016). In order to calculate the DECAF score, electronic records for patients were used. This showed that in the real-world setting, much of the information on COPD patient records was missing or not recorded

Of 132 variables from CERNER electronic records obtained via the EHS and SALAMA system from the DHA missing data was found in more than 50% of patients. The data for calculation of DECAF was available in most patients. However, the DECAF score could not be calculated in 40 (7.8%) patients in the study group. It reveals the situation where a patient's observations or details for a parameter of interest were not recorded by the designated employee. For example, this may be due to the employees working in governmental hospitals.

The data obtained in this study are sufficient to obtain satisfactory answers to the main research questions of the thesis however and are the first such data in the UAE. In general, the 512 patients with an AECOPD studied were elderly, with significant levels of breathlessness and disability evidenced by the fact that 303 (59.6%) needed assistance in washing, 300 (58.5%) needed assistance in dressing, 312 (60.8%) needed assistance in feeding, and only 39 (7.6%)

tolerated exercise. The exercise intolerance indicates the breathlessness due to the deterioration to the lungs from the COPD exacerbation disease. This will impact the daily activity, and it is a fundamental contributor to cardiovascular disease, recurrent hospital admissions related to exacerbations, disease advancement and reduced health-related quality of life (Albarrati *et al.*, 2020).

In the United Kingdom, the social fund designated for people with social deprivation has declined. Though, the attempts from the NHS and a good and serviceable funding system are required to solve this issue (Thorlby *et al.*, 2018). Moreover, the designated social care is only for those whose families are far, unattached females, elderly people whose families cannot sustain them financially, and those who suffer from diseases. In the Middle East region, including the UAE, the families have a strong bond, and the patients' relatives take care of them. Thus, it will mitigate a social burden in the middle east region (Abyad, 2006). Five hundred twelve AECOPD patients were involved in the study as per the inclusion and exclusion criteria. The average age of our participants was 73.3 years. This finding matches with a previous result of the UK DECAF validation score, where the average age 73.1 years old. Increasing age is considered a risk factor in managing AECOPD and in-hospital admission. This confirmed that we had an elderly patient more than other younger age groups. Also, it has been confirmed that age is one of the risk factors recorded in ACOPD disease (Al Ghobain, Al-Hajjaj and Wali, 2011) (Al Ghobain *et al.*, 2015). Aging may indicate an accumulated exposure to irritants or pollutants throughout their lives. Furthermore, the delay in treatment after years of symptoms of an acute exacerbation of chronic obstructive pulmonary disease (AECOPD) increases the risk of disease severity and hence recurrent in-hospital admission (Chandra, Tsai and Camargo Jr, 2009).

While the mean age of our UAE study was similar to previous work on DECAF in the UK the in-hospital death rates were 7.7% and 22.4% in the UK and UAE populations, respectively. An important finding of this work therefore was that overall mortality is considerably higher in the UAE AECOPD population compared to the UK study. This is despite the similar mean ages. COPD management practice in the UAE settings is still questionable and not well-grounded with unified standards in all locations. For example, some general practitioners see some COPD exacerbation cases and may suffer from a lack of information and experience. The importance of rising rates of chronic health problems poses a significant burden in societies. Therefore, consistent systematic approaches are needed to ensure a robust background of the assigned healthcare professional to manage disease and tackle problems beyond it.

Furthermore, enacting policies to ensure consistency of disease management is crucial in improving clinical management of AECOPD cases (Koornneef, Robben and Blair, 2017). This includes educating healthcare professionals about the disease, benchmarking and policymaking on health policy updates. Additionally, appropriate regulations, infrastructure and practices need to be in place. The UAE government has implemented various health reform plans in recent years to build a world-class health system, as documented in the study by Al Katheeri et al. (2021). This has led to significant improvements in healthcare delivery and outcomes, as demonstrated by the efficient healthcare response to the COVID-19 pandemic in the UAE (Al Hosany *et al.*, 2021)

Among the 512 patients included in the study 169 (33.0%) were females and 64 (12.5%) were smokers in the whole group. Females recruited in this study therefore represented a smaller group in the AECOPD population than males. Due to the cumulative and gradual injury caused by smoking patients being admitted for AECOPD broadly represent smoking exposures-initiated decades previously and it may be that in recent years smoking and environmental smoke and irritant exposures have been increasing in women in the UAE, indicating a future 'time bomb' of COPD burden increasing in women (Razzak *et al.*, 2020). There are currently a large population of women and men seen in the public restaurants practising shisha smoking (Razzak, 2020). Also, women, spend more indoors time for cooking than men and are more exposed to biomass fuel and combustible products, and are likely to develop COPD as a result (Rothnie *et al.*, 2018). The trend of smoking is prone to increase and was shown to double from 1.4% to 2.9% throughout 2005-2010 (Goel *et al.*, 2014) in females, for self-reported smoking. The tobacco consumption international survey among the adolescent group showed that 14.2% were girls (Spyratos *et al.*, 2012). This study reflects the magnitude of smokers' habits by sex. A survey was used to study the patterns of tobacco use in the United Arab Emirates Healthy Future (UAEHFS) study in 2018; it was a pilot study of 517 participants, including 157 females. The striking findings indicates high levels of tobacco use and exposure in the Emirate of Abu Dhabi, with 36% of men reporting tobacco use and 3% of women reporting tobacco use. In the UAE, smoking consumption among the UAE nationals is 24% in men, whereas 0.8% of females. The female smokers were from non-Arab expatriates and were 10.7%. Smoke exposure reported in the same study was nearly 30% of female of UAE nationals, and classified as second-hand smokers and exposed to tobacco at home (Al-Houqani *et al.*, 2018). If we extrapolate these findings for female population smokers in the UAE, then it would be expected that a considerable number of female smokers will exist in the upcoming years. COPD develops

after decades of smoking and it is likely that women will have a high burden of COPD and AECOPD by the middle of the 21st century (Tageldin *et al.*, 2012). However, most smokers are males and have been in this habit for more than 20 pack years in both current and ex-smokers. The COPD causing exposures are different in the UAE population compared to the UK population. In the UAE population smokers consume a variety of forms of smoking such as pipe, shisha, tobacco, and cigar. Bukhoor is a unique form of tobacco and is typical in GCC Gulf countries: Saudi Arabia, Kuwait, the United Arab Emirates, Qatar, Bahrain, and Oman. It has been shown in the UAE that smokers can be exposed to multiple forms of tobacco e.g. smoking cigarettes and taking part in Shisha. This means that the often used "pack year" quantification of smoking exposure may need revision in the UAE and Gulf countries, because it may underestimate exposure.

This study showed that AECOPD occurred in the never-smoked population and this finding requires discussion. The Bukhoor-tradition involves a daily practice for burning incense in a closed room, which can end up in severe lung disease including AECOPD. Some studies have shown that Bukhoor smoke consists of nitrogen dioxide, carbon monoxide, volatile organic compounds, and biological allergens (Lin, Krishnaswamy and Chi, 2008). Environmental tobacco smoke and biomass smoke exposure are associated with COPD development (Rothnie *et al.*, 2018). Additionally, Biomass, including different forms (harvest debris, wood, and animal wastage), are burnt in rural areas and are used in cheap stoves, in inadequately ventilated indoor area. To reduce the risk of these hazardous factors, by place setting-up effective awareness campaigns to raise audience interest and educate your community about the risk of smoke and the associated -future dire consequences on the health and economy may be indicated by the findings of this study.

DECAF stratified the UAE populations into risk groups stratified as low=DECAF 0–1 in 85 patients (16%); intermediate=DECAF 2 in 39 (7.6%) patients; high=DECAF 3–6 in 261 patients (60 %). Apparently, the high-risk group was dominant over other groups. We found a much higher number of high-risk participants compared with previous reports in the UK (Steer, Gibson and Bourke, 2012). In the UK the low-risk group represented 53.5% of the study population, and the intermediate-risk group represented 24.5% of the study population, the high-risk group represented 22% of the study population. There are several possible explanations for this result, that most cases in the UAE population were severe, and this is consistent with the higher rates of mortality associated with the AECOPD population in UAE compared to the UK discussed previously. These data may indicate that compared to the UK

healthcare setting UAE patients are receiving health care later in the disease process or at a more severe stage. An excellent way to avoid COPD exacerbation is to have a better diagnosis and proper care at the right time in the early stage of the disease. Unfortunately, despite the danger of the disease, some patients do not observe or report the symptoms to their healthcare provider in the right way at the right time. The reasons because of facing obstacles in accessing the healthcare providers, Reporting any progression and existence of new symptoms. Thus, patients' training on the self-observing and managing of the abnormal symptoms and how to contact their healthcare providers in a new-created system ease the access to out-patient for exacerbations (Locke *et al.*, 2022).

Although the inpatient death rates for AECOPD were different to the experience documented in the UK discovery and validation studies of DECAF (Shen *et al.*, 2021). The DECAF score indeed had a substantial predictive performance for inpatient mortality in general, 30-day inpatient mortality, and for 90-day readmission in the UAE setting, as previously shown in the UK DECAF studies. The incidence of inpatient death was calculated among the studied population, with a novel finding of the 90-day readmission in our population. The rate of death and readmission in the UAE AECOPD patients is relatively high. The concurrent morbidities may increase the chance of death and the AECOPD severity for a long time. Comorbidities along with COPD Exacerbation can impact the overall severity in patients. The main three comorbidities observed in the UAE AECOPD population studied were hypertension (48.3%), diabetes (45.4%), and atrial fibrillation (45.2%). This result confirms the previous result of the study of (Hoogendoorn *et al.*, 2011) that death in COPD is prevalent and severe exacerbations of COPD are one of the death causes. The co-morbid conditions may contribute to poor clinical outcomes in AECOPD patients (O'Driscoll, Howard and Davison, 2008). Also, it was reported that COPD is strongly associated with cardiovascular disease and hospitalization. For example, hypertension and atrial fibrillation are reported to be twice the percentage of non-COPD patients, and cardiac disorders lead to reduced quality of life, increased frequency of admission, and death (Milne and Sin, 2020). The prevalence of diabetes was 25.8%. During the following year of observation, 18.2% of patients with COPD and diabetes were admitted for exacerbation cases, compared to 8.9% of healthy individuals. Uncontrolled diabetes can worsen the disease condition and lead to death, according to (Castañ-Abad *et al.*, 2020). The high levels of AECOPD comorbidities, including diabetes, found in this study are an essential finding and issue that will lead to a striking economic burden on AECOPD. Action to correct comorbidities in COPD is possible and clearly necessary. Otherwise, this is expected to have severe

consequences in the future. And the raising awareness of this crisis among the UAE public in an early stage is crucial to optimizing the AECOPD disease management among the United Arab Emirates (UAE) AECOPD population.

On screening the practice, some AECOPD patients were not adequately treated with the standard triple therapy Long-Acting Beta Agonists (LABAs), long-acting muscarinic antagonist (LAMA) and inhaled corticosteroid (ICS). Meanwhile, not all medication options are available in UAE settings for the groups above. Therefore, good practice should be fully compliant with international standards. According to the NICE guideline, the typical three LAMA/LABA/ICS therapy is essential for following up on patients' health status improvement in daily activity, exercise tolerance, and symptoms alleviation.

The length of hospital stays steadily increased with the increase in the DECAF score. This result supports previous findings (Yadavilli *et al.*, 2016) that the most extended length of stay occurred for those scored with high-risk DECAF score, and the lowest length of stay for that scored with low-risk DECAF score. This concurred with the finding of the original UK DECAF validation score, as well (Echevarria *et al.*, 2016). The clinical judgments possible through other conventional prognostic scores have not been accurate, but this study and previous publications have shown the significant robustness of the DECAF score. The DECAF score is destined to become an essential score in stratifying the high-risk AECOPD patients within the next few years. It could be applied to aid a final decision; the results of this study show that UAE clinicians can select this excellent service for the low-risk patients like ESD and HAH services according to the mortality risk recommended by the National Institute for Health and Care Excellence (NICE). Implementing this kind of service could be a very positive addition to healthcare practice in the UAE, since we lack these services in the country and these have been shown to be cost effective and appreciated by patients and carers (Snell *et al.*, 2016). DECAF scores allow clinicians to use risk stratification tools like hospital admission and close monitoring as tools to detect patients at higher risks, providing intensive management to ensure better patient outcomes while simultaneously cutting healthcare costs by avoiding hospitalizations for low-risk individuals.

Therefore, using DECAF score can be seen as an outstanding service; as it gives clinicians a reliable means of stratifying patients and allocating resources accordingly, leading to improved patient outcomes and reduced healthcare costs. DECAF could even become essential when managing AECOPD patients; which further highlights its quality.

Body mass index -BMI- is one of the factors associated with AECOPD in previous studies. A meta-analysis conducted outlined that being overweight is related to general mortality in a population compared to normal-weight individuals; it confirmed however that the obese patients with COPD had a less in all-cause mortality (Cao *et al.*, 2012). Similarly, in this research, there was no significant association between BMI and inpatient death. This risk factor, obesity, fits the obesity paradox and is described as a reverse correlation between survival and severe diseases such as diabetes, kidney disease, and cardiovascular diseases in previous studies (Guo *et al.*, 2016). Our results support that BMI is not a strong mortality risk factor in the acute exacerbation of COPD, among the UAE population.

In summary, the present study reveals that the studied DECAF score for the AECOPD inpatient admission is highly associated with important consequences for patients. The score showed a strong performance to predict the AECOPD severity and mortality risk represented by 30-days mortality risk and 90-days readmission. Further, some vital factors were shown to be important in this patient group including age, length of stay, comorbidities, and the healthcare routine practice that change the disease severity and mortality outcome. The COPD prevalence in Gulf Cooperation Council (GCC) countries is high, and thus we believe that this DECAF score could also assist researchers in establishing similar research in their settings in nearby GCC countries; United Arab Emirates, Saudi Arabia, Qatar, Oman, Kuwait and Bahrain. This would be useful as COPD and AECOPD are leading to an increasing burden in patients and healthcare systems of the GCC.

The findings of this research showed significant differences in the DECAF score across patients from different cities. The proportion of patients with higher DECAF scores (4, 5, and 6) is higher in Dubai and lower in Umm Al Quwain. Specifically, the proportions for each emirate are as follows: Dubai (32.9%, 6.8%, and 11%), Sharjah (19.3%, 9.9%, and 3.9%), Ras Al-Khaimah (26.0%, 4.5%, and 1.3%), Fujairah (12.8%, 7.4%, and 3.2%), and Umm Al Quwain (0.0%, 0.0%, and 0.0%). As this study shows, variations in case severity among different cities could be attributable to different diagnostic procedures and clinical practices. Accessing healthcare services and medical facilities could have an enormously positive effect on diagnosis and treatment quality, leading to better results and ultimately leading to lower DECAF scores in cities with excellent healthcare infrastructure. Advance diagnostic tools such as CT scans and MRI machines could aid early identification and prompt management of complications, leading to lower DECAF scores overall. Treatment protocols used in various cities for respiratory disease could have an impactful influence on severity of cases and, consequently,

DECAF scores across cities. Finally, variations among patient populations (age, sex status smoking status and any coexisting disorders) could contribute to differences between severities of cases across cities as measured by DECAF score.

Patients who were smokers were more likely to have higher DECAF scores. The fact that smoking is a leading cause of COPD might have contributed to this finding (Laborín, 2009). Findings also reported that older people are more likely to have higher DECAF scores. However, Holm et al, (Holm, 2015) found that patients who develop a chronic illness at a young age may be more likely to have worse psychological and clinical outcomes.

The study results revealed a statistically significant variation in DECAF scores between patients over 65 and those under the age of 65, as measured by DECAF score comparison. Furthermore, age was found to play an influential role when it comes to disease severity as those aged over 65 had significantly older mean ages than their younger counterparts; further highlighting its possible impact in terms of predicted severity levels as evidenced by more severe DECAF scores among elderly participants reflecting more serious health conditions.

Study results also revealed that patients over 65 tended to stay longer at hospitals compared with younger ones, although statistical significance wasn't achieved. This may be because older individuals tend to need longer to recover and respond slowly to treatments; additionally, longer hospital stays could also be due to higher DECAF scores indicating more serious diseases conditions.

Although not reaching statistical significance, older patients' higher mortality rate suggests age may be an independent risk factor in terms of acute exacerbations of COPD mortality, supporting previous research which identified age as one such significant risk factor for mortality in COPD patients. Unfortunately, however, due to small sample size or needing longer follow up time frames this finding did not reach statistical significance; but nevertheless is in line with previous findings and research in other fields.

Overall, these findings demonstrate the significance of age as an indicator for predicting COPD exacerbations severity and its outcomes. They further imply that older patients may require longer hospital stays and face greater mortality risks when experiencing exacerbation episodes, potentially impacting care management strategies accordingly.

6.2. Limitations of the Study

Despite that this study provides substantial theoretical and practical contributions to the current research efforts for COPD, this study should be considered in light of its limitations. First, the study had a problem with missing data, defined as the data that is not well recorded or saved during the study. This issue is expected in the field of hospital-based research and can have a notable impact on research (Graham, 2009). In this study, the electronic records of people with AECOPD had a considerable amount of missing information with 19 variables having more than 50% missing information.

DECAF scores were calculated from the electronic records, and for the DECAF score, the five component indices were not possible to calculate in a minority of patients. For example, forty (7.8%) DECAF scores were missing. The missing data were in three indices; radiographic consolidation, eosinophil count, and eMRCD record, describing that radiographic consolidation represented 37 (7.2%) of the missing data, and most of the missing due to "no examination" happened throughout the admission. At the same time, eosinophil counts and eMRCD in 34 (6.6%) patients and 20 (3.9%) patients, respectively. In the UK DECAF score, there was no missing data that inform the five indices of DECAF (Echevarria *et al.*, 2016). The missing data in the UAE setting are due to unrecorded readings by clinicians or nurse staff at the time of admission. Interestingly, there were no missing inpatient mortality data in both UAE and UK DECAF research, indicating that important data can be collected given appropriate prioritisation. The findings of this study indicate that we need to establish a well-structured and informed health workforce to improve the healthcare practice, which is eventually reflected in robust and comprehensive health sector services in the UAE. To mitigate this, the researcher may impute the missing data and enhance the statistical power by using a statistical test such as the Markov method to impute the missing data.

Although this study covers most hospitals in Dubai and the Northern areas of the UAE, most AECOPD admitted patients are located in the studies two health authorities; the Emirates Health Services and the Dubai Health Authority hospitals. AECOPD patients in Abu Dhabi hospitals, the capital of the UAE, were not included in this study due to difficulties in obtaining ethical approvals despite many attempts. Thus, the findings of this study may not be generalizable to all UAE hospitals. Nevertheless, variations in the prevalence of the AECOPD or response to DECAF score implementation are not anticipated to be observed given that most hospitals in the UAE run similar medical practice and guidelines in clinical settings. An important challenging factor in this study was the time between submitting the first ethics

application and receiving ethical approval, which took several months, depending on the committee meetings. Also, the validity of the license is just for one year with an annual renewal, which also delays the submission of the renewal ethical approval certificate. All this time is deducted from the time of the research period, ultimately consuming a large proportion of the time in the study. So, the decision beyond this issue is to cover the nearby and easily accessed hospitals with good proportions of annual AECOPD admission. But, again, the geographic distance poses access difficulties, worsened by transportation problems across a wider geographic region. However, it needs many efforts to conduct this research in distant regions – from northern UAE to Abu Dhabi for a small proportion of AECOPD admitted patients. In the end, realising that there are similarities in in-hospital processing among UAE hospitals with the same clinical process and practices, the health organisations and authorities in the UAE have a firm ground that follows the capital of health authorities in the UAE is the EHS.

Another possible limitation of the research is that the study was conducted retrospectively via the electronic medical record. Therefore, the study may be more likely to have repeatedly missing data (Camm and Fox, 2018). Moreover, the investigator could not contact healthcare providers for erroneous and missing data at the research time, along with the loss of data management. Consequently, the above issues noted led to an unintended outcome that cannot be ruled out; generally, retrieving the recorded data in the past could bias retrospective studies (Euser *et al.*, 2009). Nevertheless, the investigator must trust others for proper recordkeeping. There may be a possible advantage also; the retrospective study can assist in identifying feasibility issues and developing a forthcoming prospective study and this yield “real world” data.

The ideal solution for the collection of data might could be the implementation of the "six Sigma approach". The Six Sigma approach is "a disciplined and highly quantitative approach to improving product or process quality" (Hahn, Doganaksoy and Hoerl, 2000). It was invented by the Motorola Corporation in 1986 and sought to enhance quality by determining and rectifying the triggers of errors (Mason, Nicolay and Darzi, 2015). Six Sigma is an approach developed in the 1980s by Motorola Corporation that seeks to increase product and process quality by eliminating defects or errors and variance. It employs highly disciplined data-driven processes aimed at finding and eliminating root causes of errors or variability within processes; since then it has become widely adopted throughout organizations globally. Six Sigma refers to a statistical goal of producing no more than 3.4 defects for every million opportunities for defects - equivalent to having an extremely high defect-free rate (99.99966% defect-free rate

in manufacturing or service industries). Six Sigma typically involves five stages: Define, Measure, Analyse, Improve and Control (DMAIC). During this initial step of DMAIC projects, goals and objectives for improvement of processes will be established, along with possible improvement options being identified as part of Define stage activities. Measure Phase Data Collection In this step, data is gathered in order to assess current process performance. Analyse Phase Identify Root Causes of Errors/Defectivities Through various statistical tools and techniques at this phase, potential solutions to address root cause are proposed and experiments conducted to verify them. At last, during the Control phase, an improved process is monitored and managed so it remains stable while meeting quality levels expected of it. By adopting the Six Sigma methodology for data collection, organizations can increase both its quality and accuracy. By tailoring DMAIC process to individual needs of data gathering, process maps, control charts and statistical process control tools such as process maps can help monitor quality control resulting in substantial increases in efficiency, productivity and cost-savings to organizations.

Therefore, identifying the biases can be crucial, and defining their results by modifying ways can enhance clinical evaluation and health care practice. Adopting this approach by the healthcare system in the UAE will ensure consistent, systematic, and efficient data collection and reporting in clinical settings. The first step towards adopting the six sigma approach is to identify the research questions and then determine the type of data that could be needed for the project. Next, estimating how much data could be needed. This is associated with the sample size and statistical power of the project. The fourth step in this data collection plan is to determine the most applicable techniques for data collection. In research, the most appropriate method was reviewing patient medical records. Surveys and interviews are incapable of answering o research questions. The final step will be identifying the source of the data. In project, it e and electronic health database.

This project made several observations that would seem to possibly impact the time taken for the research and associated efforts. First, is the method of collecting data; this differs from one health authority to another health authority, as for the Emirates Health Services during the research time. Second, the administrative process renews their instructions in the research domain by requesting the investigators to get assistance from the statistics centre and asking the statistical team the type of data. This process will consume time as several amendments have been asked in case of misunderstanding between the investigators and the statistical unit. Third, the delay in data submission is definite if the investigator could not follow the data

retrieval due to the system being down on some occasions. Also, awaited data may not be expected and needs some drops or modification and new data according to what has been observed from the existing data. Regarding the, the difficulty was when the investigator was not an employee in the same authority. And a particular workstation needs necessary managerial approval, and this also took time for selecting a suitable place to investigate the files. That resulted in delays in approval submission and administrative agreement, which took months for research ethics, self-attend, and smooth access approvals. In addition, dealing with an unfamiliar medical system requires special training for the assigned employee, which affects her/his work; volunteers may feel confused coping with extra work and eventually affecting his productivity. However, it is worthwhile noting that all these obstacles were minimized by extending the time of research submission to efficiently deal with these postponements.

Chapter 7. Conclusion

7.1. Summary

This study shows that the DECAF score has efficient predictive performance for inpatient mortality and readmission in AECOPD management in the UAE. Thus, it has promising utility in the UAE and could be used throughout the UAE and may help COPD research in the Middle East that is relevant to males and the increasing number of females who smoke or are exposed to environmental smoke. Calculation of DECAF scores can easily stratify the patients into groups and guide them to appropriate decisions like 1- Early prediction of the disease severity 2- Deciding the type of care, ordinary or intensive care 3-earlier escalation of the treatment ESD/HAH Early supported discharge/hospital-at-home services, 4- decide the life-saving and/or life-ending treatment.

7.2. Academic Recommendations

The research program indicates a need for further investigations in order to produce more reliable evidence regarding the DECAF score's efficacy and generalizability, particularly across different populations. As its current limitations limit its efficacy and generalizability. An Abu Dhabi region-focused observational study is advised in order to produce generalizable findings regarding its predictive performance as supported by similar analyses in which DECAF score performance in COPD patients mortality prediction was examined (similar). However, Multicentred investigations should validate findings as well as assess its generalizability across populations (Khalid et al. 2020). Additionally, longitudinal research should also be undertaken in order to measure the predictive ability of DECAF score on longer-term patient outcomes such as mortality and hospital readmission rates. One such longitudinal study evaluated its performance by looking at its ability to accurately predict hospital readmission risk among COPD patients; its conclusions found that DECAF could reliably identify high risk COPD patients and thus identify additional care for these high-risk cases (Samp et al, 2018). Last, another research objective should include creating and validating a modified DECAF score that includes more variables, including age and length of stay, for AECOPD patients in UAE. A study that evaluated this approach concluded that its modified form performed better in predicting COPD mortality risk predictions than its original predecessor (Samp et al. 2019). In summary, the research program detailed in this thesis is well supported by existing literature; however, additional studies to substantiate its efficacy is warranted to produce more robust evidence about DECAF scores effectiveness are warranted in UAE AECOPD patients. A larger prospective study, longitudinal investigation or modified DECAF score development might serve as avenues of future investigation to assess its predictive ability among UAE AECOPD patients.

.7.3. Professional Practice Recommendations

Effective data reporting and staff training are fundamental aspects of clinical practice in the UAE, as highlighted by its research program. According to studies, inconsistent reporting can result in inaccurate predictions that compromise patient care (Chen et al. 2016; Nilsson et al. 2018). Therefore, healthcare professionals must report all readings and documents into electronic systems to validate DECAF predictions accurately while simultaneously adhering to data recording standards set out by WHO (World Health Organization 2013) to maintain consistency and reliability when recording information (WHO 2013).

Simplifying information collected, with particular focus on key details, can enhance data reporting and ensure improved patient outcomes. Studies have proven the efficacy of this strategy in terms of both error reduction and quality care (Chen et al. 2016; Pablos-Mendez et al. 2013). To enhance data reporting skills among healthcare providers further, workshops covering both techniques for reporting as well as awareness should also be given on its importance (WHO 2013).

Utilizing the DECAF score in daily clinical practice to predict patient outcomes can also significantly enhance quality care provided. Studies have illustrated how using this measure has shown its efficacy by helping identify high risk mortality or hospital readmission patients and lead to improved treatment decisions and outcomes (Echevarria et al, 2016; Steer et al 2016). Therefore, adopting DECAF into UAE clinical practices would ensure better patient care results. Overall, effective data reporting and staff training, in addition to incorporating DECAF scores into clinical practice are integral steps toward elevating quality care delivered in the UAE.

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Appendices

Appendix1. Data Collection form

Form 1, Data collection tool DECAF. External validation.

Code No: .....

Date of birth: .....

Hospital No:

M / F Hospital ..... **Admitted Date**..... **Time** .....

Inclusion criteria: (√= Yes)

Primary diagnosis of AECOPD (nonpneumonic or pneumonic) ☐ Age ≥ to 35 years ☐

Smoking history ≥ to 10 pack years ☐ Obstructive spirometry (FEV1 / VC < 70%) ☐

Exclusion criteria: (X= No. Please note, "no" is needed to meet these criteria)

Home ☐ Home+carers ☐ Sheltered ☐ Sheltered+carers ☐ Res care ☐ Nursing ☐ Community hospital ☐

No. of admissions:		Number of exacerbations:	**No. of A&E visits in past**	
12 months:	**6 months:**	(patient reported)	**6 months:**	12 months:
Resp ……	Resp……	past 12 months ……	Resp ……	Resp ……
Other ……	Other ……		Other ……	Other ……

Independent: Washing ☐ Dressing ☐ Feeding ☐ **eMRCD** ..... Exercise tolerance .....

Admission: **Pedal oedema?** ☐ Pulse rate ..... BP ..... RR .....

T ..... Sats ..... Oxygen ..... GCS ..... Acute confusion? Y ☐ N ☐

Height (m)..... **Admission weight (kg).....** Weight 3 to 6 months ago.....

Unintentional weight loss 5-10% .....kg (past 3 to 6 months)☐

Unintentional weight loss > 10% .....kg (past 3-6 months) ☐ There has been or is likely to be no nutritional intake for >5 days ☐

CXR consolidation

Y ☐ **N** ☐

Cough:

Effective ☐ Partially effective ☐ Ineffective ☐

Comorbidities		**Cerebrovascular disease** ☐	AIDS ☐	connective tissue disease ☐
Dementia ☐	Hemiplegia ☐	**Cor-pulmonale☐ (clinical☐echo☐)**	Leukaemia ☐	malignant lymphoma☐
IHD ☐	**Myocardial infarction** ☐	Congestive heart failure ☐	PVD ☐	Ulcer disease☐
Asthma☐	Cognitive impairment ☐	LV dysfunction ☐	**AF** ☐	Depression ☐
Diabetes ☐ end organ damage Yes/ No		Liver disease ☐ (Mild ☐ Moderate ☐ Severe ☐)		Anxiety ☐
Renal disease ☐ (Mild ☐ Moderate ☐ Severe ☐)		Malignant solid tumour ☐ (metastatic ☐ Non metastatic ☐)		

Medication	

LTOT □	Na^+ …… K^+ …… **Urea ……** Creat …… baseline Cr…… **Alb ……** Bicarb …… **Glucose (serum…… BM……**) bilirubin …… Troponin…… CRP …… Hb …… WCC …… Hct …… plt…… Neut …… **<u>Eosin</u> ……** **ABG**: FiO_2 …… **<u>pH</u> ……** pCO_2 …… pO_2 …… HCO_3 …… BE……
□-blocker □	
Longterm Pred. □……mg	
Maintenance Diuretics □	
Statin □	
ACE-i □ ARB □	
	ABG deemed unnecessary and sats >92% on room air? Y□ N□

<u>NIV</u> Respiratory acidosis (any time during admission) Y □ N □ **Treated with NIV?** Y □ N □ **IPPV***? Y □ N □

Resus Status IPPV* Y □ N □ NIV Y □ N □ CPR Y □ N □ *invasive positive pressure ventilation

IDENTIFICATION CODE

Notes

Discharge **Survived to discharge? Y / N** **Date of d/c …… ?delay for social care yes/ no**

Spirometry **FEV_1 …… % pred ……** **Follow-up clinic spirometry** **FEV_1 …… % pred …… Date…… FVC…… Ratio ……** **Date…… FVC …… Ratio ……**

Death **Y ☐ N ☐** **Cause of death** **post-mortem? Y N**

Date of death …… Ia

Place of death **Ib**

- **In-hospital ☐** **Ic**
- **Home ☐☐II**
- **Hospice ☐**
- **Care home (e.g.Residential/ nursing home) ☐**

Readmissions in 90 days

Admission date	Discharge date	Reason
		Resp/ NonResp
		Resp/ NonResp
		Resp/ NonResp
		Resp/ NonResp

5. Extended MRC Dyspnoea (eMRCD) Score (instructions overleaf)

"In the **past 3 months**, when you were **feeling at your best**, which of the following statements best describes your level of breathlessness?" (please circle)

Breathless only with strenuous exertion	1
Breathless when hurrying on the level or walking up a slight hill	2
Walks slower than peers, or stops when walking on the flat at own pace	3
Stops after 100m, or for a few minutes, on the level	4
Unable to leave the house unaided but independent in washing and/ or dressing	5a
Unable to leave the house unaided and requires assistance in both washing and dressing	5b

eMRCD Scale

Remember that you are asking the patient for their level of dyspnoea **on a good day** in the preceding 3 months, **not** their **breathlessness at admission**.

Explanatory notes:

- A patient only achieves a higher grade if their symptoms are as bad as defined in that higher grade.

- For example, if their symptoms are worse than defined in eMRCD 3, but not as bad as eMRCD 4, the grade remains eMRCD 3.

- A key distinction is between eMRCD 4 and eMRCD 5a/5b:

- only score 5a or 5b if the patient cannot leave the house without assistance:

  - For example, if a patient can only walk 30 to 40 yards but can leave the house unaided, score eMRCD 4.

  - If a patient can only walk 5 to 10 yards and requires a wheelchair to travel further outdoors, score eMRCD 5a or 5b.

  - If a patient requires assistance in personal washing **and** dressing score eMRCD 5b. If they only require assistance in washing **or** dressing score eMRCD 5a.

- Remember to ask about putting shoes and socks on as many patients require assistance with this.