Applying Statistical Models to Health Outcomes For Australian Patients with Bronchiectasis

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CERTIFICATE OF ORIGINAL AUTHORSHIP

I, [Pitchaya Kingkam] declare that this thesis, is submitted in fulfilment of the requirements for the award of doctoral degree, in the School of Mathematical and Physical Sciences at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise reference or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

This document has not been submitted for qualifications at any other academic institution.

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Finally, I would like to dedicate this thesis to my deceased father, who passed away during my study. His love gave me forces to make this project.

ABSTRACT

Bronchiectasis is a common disease caused by chronic infection in the small airways of the lungs. Patients often carry a heavy burden of symptoms. Unfortunately, little is known about the impact of bronchiectasis on Australians or on our healthcare system. For many years, bronchiectasis was considered as another Chronic Obstructive Pulmonary Disease and was bundled (for costing purposes) with COPD or other pulmonary infections, without recognition that the condition was associated with significant, particular clinical features that required longer and more complex admissions to hospital than COPD. Prior to July 2018, there was no disease specific code within the system that allocates hospital funding and consequently, episodes of care for patients with bronchiectasis were assigned into other respiratory illness in the AR-DRG system. This misallocation is likely to have affected hospital funding which is calculated based on ALOS associated with the AR-DRG group of diseases. The main purpose of this thesis was to explore the factors contributing to the length of stay and hospital readmission for patients with bronchiectasis in Australia in three parts;

i) An evaluation of the effect of a specific AR-DRG on funding of length of hospital stay for bronchiectasis patients and a comparison of the actual length of stay in hospital (LOS) with the average length of stay (ALOS) based on the assigned AR-DRG. We found that the AR-DRG system consistently underestimated the LOS and costs for acute hospital admissions due to bronchiectasis.

ii) An investigation of the effect of seasonality of presentation and patient characteristics (sex, age, smoking status, ABR registry status) on hospital LOS and ALOS. The cohort in this study included 299 patients who were diagnosed as bronchiectasis with 505 admissions of >24 hours to Concord Hospital, NSW between July 2011-June 2018. The results were showing significance (p <0.05) between the non ABR-registry and the response lnALOS. This implied that bronchiectasis patients who participated with ABR- registry tend to have length of stay in hospital shorter than patients who did not register in the ABR.

iii) An analysis of the time between episodes of care of bronchiectasis patients using longitudinal data analysis and multilevel models. Bronchiectasis patients who were smokers and hospital LOS, were statistically significant risk factors for readmission. Hospital LOS was negatively correlated with time to readmission suggesting that longer stays in hospital can reduce readmission risk. In addition, patients who were smokers had a significantly higher readmission rate than patients who were not smokers.

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KINGKAM, P., VISSER, S., BROWN, J., WOODCOCK, S., BAIRD, T., JACKSON, D. & MORGAN, L. 2017. The argument for a bronchiectasis specific AR-DRG: analysis of hospital discharge data (2012-2016) for patients registered to the Australian Bronchiectasis Registry. *Respirology,* 22**,** 206-207.

CHAPTER1
Introduction

The main purpose of this chapter is to set the scene for this thesis. This chapter introduces bronchiectasis as a model of a chronic disease where the severity and burden of disease is marked by exacerbations that sometimes require hospitalization. The motivation for this project was to explore whether traditional statistical modeling could accurately predict what might happen to a patient with bronchiectasis, how long they would stay in hospital, to predict future risk of exacerbation for an individual and to refine the disease specific expectations of cost of these admissions. This chapter closes with the thesis outline.

1.1 Project overview and motivation

Bronchiectasis is a common lung disease caused by chronic infection in small airways. Despite its relatively low profile, bronchiectasis is a common condition in Australia and remains a major cause contributing to chronic respiratory morbidity in less-affluent populations in both Indigenous and non- Indigenous populations [(Blackall et al., 2018), (Visser et al., 2019)]. Clinically significant bronchiectasis has been increasing in prevalence both in Australia and internationally (Chandrasekaran et al., 2018). This increase in prevalence has been mirrored by an increase in admissions to hospital. The hospitalization rate for bronchiectasis as a principal diagnosis increased steadily from 2007–08 to 2016–17 (from 20 to 28 per 100,000 populations respectively). In addition, bronchiectasis was the principal diagnosis for 7,719 hospitalizations and an additional diagnosis for a further 10,803 hospitalizations in Australian hospitals during 2017-18(AIHW, 2018). Although the number of patients with bronchiectasis has found a progressive increase in the healthcare system, at the commencement of this project, there was no disease specific code in the Australian Refined Diagnosis Related Group (AR-DRG) system for hospital funding purposes. The AR-DRG is a classification system which provides a clinically meaningful way of relating the number and type of patients treated in a hospital (known as hospital casemix) to the resources required by the hospital to provide benchmarked clinical care (AIHW, 2019). Each AR-DRG represents a group of patients with similar clinical conditions requiring similar hospital services. Every episode of inpatient hospital care is assigned an AR-DRG code based on the predominant diagnosis. Length of stay in hospital remains a significant factor of hospital efficiency (Clarke, 2002). This AR-DRG classification system includes the average length of stay (ALOS) for patients admitted to hospital with that specific diagnosis and uses the ALOS to calculate the amount paid to the hospital [(Antioch and Walsh, 2004), (Busse et al., 2006)]. Patients who require admission to hospital for

bronchiectasis were stay longer (6.3 days), on average, than patients with other chronic airway diseases with well- established AR-DRG codes such as asthma (3.6 days) (The AIHW National Hospital Morbidity Database 2017–18). In the absence of a disease specific AR-DRG, these prolonged episodes of care for patients who required admission to hospital for bronchiectasis were being allocated funding based on an inaccurate classification and were being automatically funding. To explore the relationship between AR- DRG classification and funding, this project is to investigate the whether or not the observed length of stay (LOS) of bronchiectasis patients is consistent with the average length of stay (ALOS) based on the AR-DRG classification system that they were assigned to the other group of diseases. This study is organized and provided the bronchiectasis the dataset by the Lung foundation Australia, the Australian Bronchiectasis Registry and Concord Hospital. Especially, Concord hospital, which is a major hospital in Sydney NSW Australia established in 1941 as the 113th Australian hospital, has conducted the bronchiectasis data for this research. There are 299 bronchiectasis patients and 505 episodes of care in Concord Hospital for the period December 2011- June 2018. The three main purposes have been presented in this research.

1.2 Project Aims and Objectives

Bronchiectasis is common, causes a significant burden of illness and contributes to a large number of hospitalizations every year. The main objective of this project was to understand more about the impact of bronchiectasis on the Australian health care system. The project was designed in three parts.

Part I:

To explore the relationship between the observed length of stay in hospital (LOS) for patients with bronchiectasis as the major contribution to the episode of care and the ALOS for the AR-DRG classification to which they were assigned.

Part II:

To describe a cohort of patients with bronchiectasis admitted to one hospital in Sydney between 2011- 17 and to explore a range of patient characteristics and environmental factors which might has an effect on their length of stay in hospital (LOS).

Part III

To predict the effect of a range of patient characteristics on the time to hospital readmission within the same cohort and a two –level model for binary outcomes with a single explanatory had been considered to analyze time to readmission into hospital.

1.3 Layout of thesis

Chapter one provides the overview of the thesis motivation and the main purposes of the project.

Chapter two represents the background information on bronchiectasis, literature review and provides an overview of studies on the disease relating to the purposes of this study. It is included a rationale for the statistical approaches used for this project.

Chapter three presents the bronchiectasis data supplied by the Australian Bronchiectasis Registry (ABR), Lung Foundation Australia and Concord Hospital with an initial analysis of the data.

Chapter four describes the relationship between the actual length of stay in hospital (LOS) and the average length of stay in hospital (ALOS) of bronchiectasis patients associated with the AR-DRG system. It is included the multilevel model for investigating the relationship between the actual length of stay in hospital (LOS) and patients' characteristic with the environmental effects resulting in the LOS.

Chapter five represents the multilevel models for the binary response to examine time to readmission in hospital since patients were last discharged.

Chapter six summarizes the project and highlights possible future work to extend the analysis.

CHAPTER 2
Literature Review

The purpose of this chapter is to provide background information related to the research. The first part of this section presents an overview of bronchiectasis and current research for those wishing to understand more about the disease, providing evidence of how the disease affects many people around the world. Included in this section are the Australian Refined Diagnosis-Related Groups (AR-DRGs) classification and the length of stay in hospital (LOS). Finally, the statistical framework is given to fulfill a clear picture of the project.

2.1 Bronchiectasis

The word bronchiectasis is derived from the Greek words "bronckos" (airway) and "ektasis" (widening). Bronchiectasis is a disease characterised morphologically by the abnormal dilatation of bronchi and bronchioles, and clinically by recurrent or persistent bronchial infection, cough and often sputum. Bronchial dilatation in bronchiectasis was traditionally thought to be permanent; however, there is emerging evidence, particularly in children, that dilatation is potentially reversible with early diagnosis and intervention. Bronchiectasis is has been long recognised as an important cause of chronic cough and recurrent chest infections (Smith and Morris, 1962). The pathogenesis of bronchiectasis is related to chronic airway infection and inflammation resulting in "*a vicious circle of transmural inflammation, infection and retained secretions"* (Barker, 2002). Bronchiectasis may be localised to one lobe or segment, or generalised in both lungs. Repeated infection over time causes the internal mucosal surfaces of the affected airways to become scarred and thickened resulting in the distortion of the shape of the airways and impaired mucociliary clearance. When the excess mucus in the airway tubes cannot be cleared, it builds up an environment for bacteria growth and chronic infection. Mucus retention and chronic inflammation of the airway wall contributes to chronic cough and breathlessness. The amount of bacteria in the airways makes the lung vulnerable to repeated infection that leads to the long term lung function disability. Bronchiectasis may be localised to one lobe or segment, or generalised in both lungs. Bronchiectasis is increasingly recognized as an important cause of chronic cough and recurrent chest infections. Bronchiectasis can be classified by underlying cause, as related to cystic fibrosis (CF) or not CF. CF bronchiectasis, is a due to a genetic defect that affects a protein for transfer of salt and water into cells, resulting in thick and sticky mucus in the airways. CF bronchiectasis is a very specific subset of the condition, is coded and funded quite differently from non CF bronchiectasis and will not be discussed further in this thesis. Bronchiectasis can develop when the bronchi become inflammed, scarred, widen and permanent enlarged. It may occur at any

age. Although the prevalence of bronchiectasis is higher in males, females are more likely to present the non-CF bronchiectasis particularly people with asthma (Vidaillac et al., 2018b). About half of patients with bronchiectasis also suffer from other chronic conditions resulting in repeated respiratory infections such as HIV, tuberculosis, inherited immune deficiency, chronic obstructive pulmonary disease (COPD) and asthma (King et al., 2006), (Redondo et al., 2016).

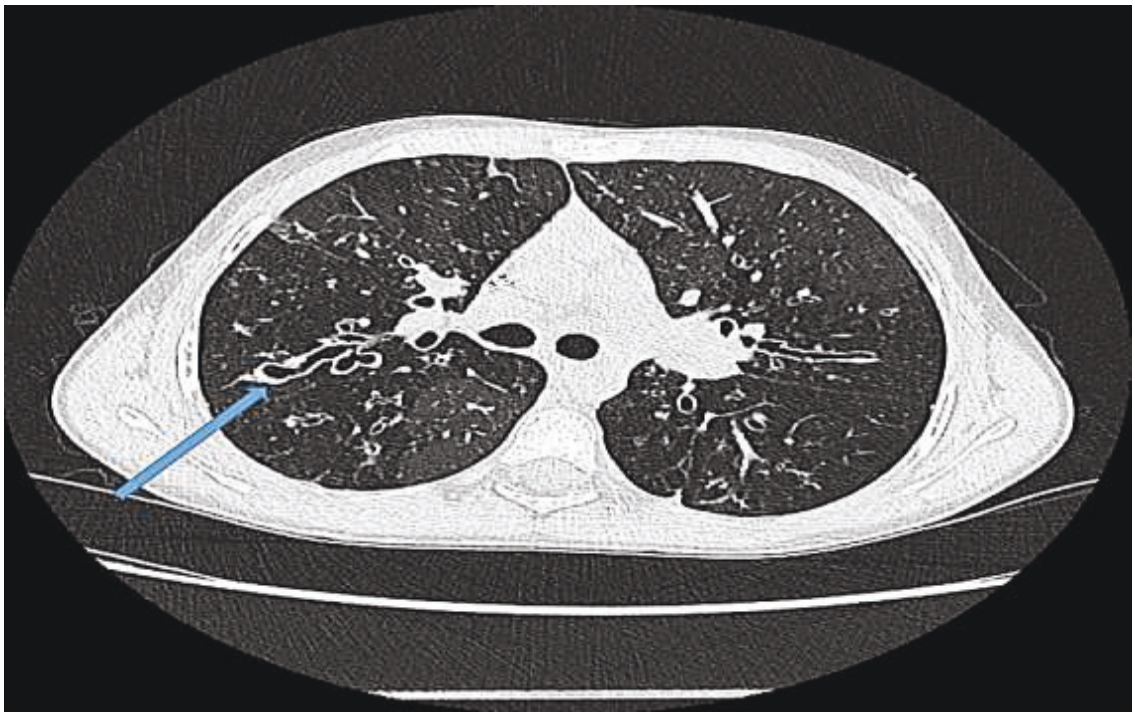

Figure 1 Computed Tomography of bronchiectasis

(Source: www. http://bronchiectasis.com.au.)

2.1.1 Causes of bronchiectasis

Bronchiectasis is the result of airway damage from a variety of mechanisms that all lead to chronic airway inflammation, altered mucus, recurrent infection (Allison, 1982, King et al., 2006). When the lungs are continually exposed to germs, the immune system will attempt to keep the lungs free from infections by creating white blood cells. These cells send chemicals against infections, which causes inflammation around the surrounding the airway tissues. The abnormal airways then become filled with excess mucus resulting in persistent coughing and allowing the lungs to become easily infected (NHS, 2018). People who have a weakened immune system are at increased risk for chronic bronchial infections, which can develop bronchiectasis. Aspiration, where small particles of food or fluids from the mouth or stomach get into lungs, could trigger lungs inflammation leading to bronchiectasis (Hu et al., 2015). Although bronchiectasis generally occurs as a result of infection, non- infectious factors that may contribute to the development of this condition include radiation therapy directed to the

chest (breast cancer treatment). Bronchiectasis can frequently occur in parallel with COPD - a progressive and disabling condition where narrow and inflamed airways cause cough and breathlessness. Most COPD is associated with tobacco smoking. Recent clinical research found that 48.70 % of participants had COPD associated bronchiectasis (Arram and Elrakhawy, 2012). Both diseases have similar symptoms of progressive shortness of breath and chronic cough and intermittent exacerbations. But the mechanisms that cause the symptoms are slightly different. COPD is mainly caused by lung irritants (e.g. dusts or tobacco smoke) which contribute to fixed airflow obstruction, gas trapping and emphysema. But bronchiectasis is a result of recurrent bacterial airway infection and dilatation. Delayed and incorrect diagnosis contributes to substandard management of people with bronchiectasis, more severe symptoms, and a greater burden of illness. The treatment may be more complicated when a patient with bronchiectasis has already received a diagnosis as another chronic respiratory disease (Maguire, 2012).

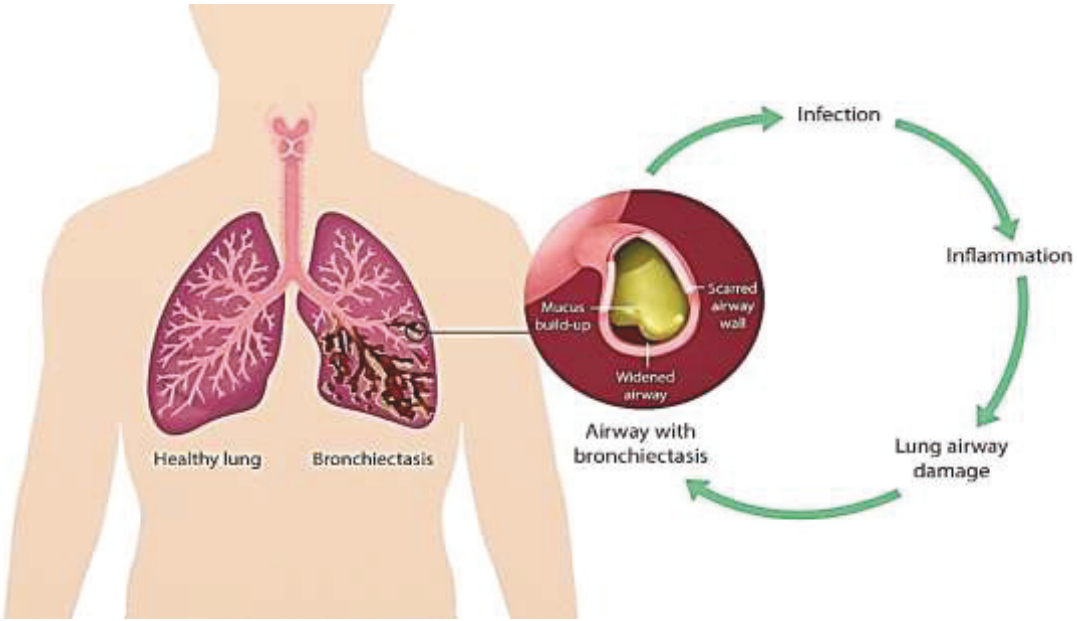

Figure 2 A cycle of infection and inflammation of bronchiectasis

(Source: www.doctorsaustralia.com.au)

2.1.2 Symptoms of bronchiectasis

The symptoms of bronchiectasis are variable but all relate to persisting bronchial infection. Some patients have no symptoms in between exacerbations while others have a high burden of day to day symptoms and infrequent exacerbations (Goeminne and Dupont, 2010). The common symptoms of bronchiectasis are a persistent and/or recurrent productive cough, breathlessness, anorexia, weight loss and fatigue. Sputum that is purulent and often blood

stained will smell and taste bad when chronically infected and contributes to poor appetite and malnutrition. Tenacious sputum that blocks the airways contributes to impaired ventilation and breathlessness. Retained secretions and nocturnal cough contribute to poor sleep quality and fatigue. Exacerbations are flare ups or worsening of symptoms from baseline (Bell et al., 2018). They contribute to impaired quality of life – patients feel sicker than usual and sometimes require hospital admission for treatment. Severe exacerbations require hospitalization. The exacerbations also increase the risk of further exacerbations, hospital readmission and mortality [(Khoo et al., 2016), (Roberts et al., 2012)]. Patients with severe bronchiectasis have more frequent exacerbations and a higher risk of mortality [(Chalmers et al., 2014), (Finch et al., 2015)]. The exacerbations are an indicator of bronchiectasis severity.

Chalmers et al. (2014) presented the bronchiectasis severity index (BSI) which consisted of HRCT score, FEV1, Medical Research Council dyspnoea score, bacterial colonisation, exacerbation and prior hospital readmission. Another study, Martínez-García et al. (2014), introduced the FACED score, which comprises FEV1, age, P. aeruginosa colonisation, radiological extension and dyspnoea. Both scores effectively predict mortality. These severity indices reflect the impact of exacerbation frequency on impaired quality of life and mortality. The severity scores were classified into BSI (0-26), FACED score (0-7) and QoL-B domain scores (0-100). In general, the typical symptoms of disease severity are presented as the table 2.1 below.

Table 2.1 Symptoms of bronchiectasis severity

Mild	Moderate	Severe
● few symptoms ● breathless on moderate Exertion ● recurrent chest infections ● little or no effect on daily activities	● breathless walking on level ground ● increasing limitation of daily activities ● increased cough and sputum Production ● exacerbations requiring oral corticosteroids and/or antibiotics	● breathless on minimal exertion ● daily activities severely curtailed ● experiencing regular sputum production and chronic cough ● exacerbations of increasing frequency and severity

(Source: Lung foundation Australia)

2.1.3 Diagnosis

The symptoms of recurrent or persistent productive cough are not specific to bronchiectasis. Chest X-ray is appropriate for the investigation of cough and breathlessness and is likely to confirm the diagnosis of pneumonia or lung mass lesions but is not sensitive enough to detect bronchiectasis and CXR may be apparently normal even in extensive bronchiectasis. High-resolution computed tomography (HRCT) is the gold standard for diagnosis of bronchiectasis. The radiological definition requires the bronchial diameter to exceed that of the adjacent vessel as imaged using HRCT (Visser et al., 2018). For the purposes of this thesis, the word "bronchiectasis" refers to a clinical syndrome of chronic cough and recurrent chest infections AND the radiological features. Bronchiectasis is sometimes but not always a chronic obstructive disease. Pulmonary function testing often reveals associated airflow limitation; however, 48% of patients with bronchiectasis will present with normal spirometry and only about 34% of patients will present with airflow obstruction (Visser et al., 2019).

2.1.4 An overview of prevalence of bronchiectasis

Bronchiectasis has been recognized for over a century (Whitwell, 1952). The prevalence, trends and risks factors of Bronchiectasis have been reported for decades. A large study of 400 subjects with bronchiectasis founded in 1940 showed a mortality rate over 30% for patients below the age of 40 (Perry and King, 1940). In recent years, there has been increased recognition of bronchiectasis as a major cause of morbidity and burden on communities and their healthcare systems internationally; this has been reflected in an increase in clinical research activity and publications regarding bronchiectasis (Chalmers et al., 2015). Organizations included the European Respiratory Society and the European Bronchiectasis Registry (EMBARC) have been established with the goal of developing the European Bronchiectasis Registry, working to support national clinical trials and gathering researchers from clinical researchers around Europe. The EMBARC expects to enroll more than 10,000 participants by March 2020. They will be followed up annually with treatment outcomes and quality of life for up to five years (Chalmers et al., 2016).

The prevalence of bronchiectasis is not the same in all parts of the world. For instance, in the UK, bronchiectasis was growing in terms of incidence, prevalence and mortality, in particular among the elderly population. Across all age groups, the incidence of bronchiectasis in women increased from 21.2 per 100,000 person-years in 2004 to 35.2 per 100,000 person-years in 2013; and in men it rose from 18.2 per 100,000 person-years in 2004 to 26.9 per 100,000 person-years in 2013 (Xu et al., 2016). A group of patients in the UK were followed up for 13 years from recruitment in 1994 and found approximately 29.7% of them died during this period

(Loebinger et al., 2009). Ringshausen et al. (2013) provided evidence of a constantly increasing prevalence of bronchiectasis in Germany after review of 61,838 records extracted from 125 million hospitalizations for the years 2005-2011. Similar to Germany, the prevalence of bronchiectasis in Spain between 2004-2013 had a significant increase as a secondary diagnosis while COPD was the most frequent disease in a primary diagnosis (Sánchez-Muñoz et al., 2016). Additionally, bronchiectasis was the underlying cause for an increased risk of mortality in patients with moderate to severe COPD (Martínez-García et al., 2013). COPD is not the only lung disease to coexist and contribute to the burden of bronchiectasis. More than one third of patients with severe asthma have bronchiectasis (García-Clemente et al., 2019). In Belgium, between May to November 2017, among 186 bronchiectasis patients enrolled by the Belgian Pulmonology Society, the majority of them were female and about 32% had at least one hospital admission per year and more than 50% had been received a long-term oral antibiotic treatment (Schoovaerts et al., 2019).

Bronchiectasis is being increasingly recognized in the US. The prevalence of bronchiectasis has increased in people in the 1980s as compared with those born in the 1940s. The number of all patients who were discharged with bronchiectasis as the principal diagnosis in 2012 was about 88,000 cases higher than in the prior year (Ford, 2015). Another study reviewed that although bronchiectasis was a rare chronic lung condition in US children, it was commonly found in native Alaskan children (Singleton et al., 2000). Subsequent series reported in Australia and New Zealand confirm that bronchiectasis is more common in those communities with high rates of poverty and indigenous communities (Basnayake et al., 2017).

The underlying cause of bronchiectasis differs in frequency in different parts of the world. In some countries in Asia such as Hong Kong, India and Thailand, pulmonary tuberculosis (MTB) infection was the most common cause of bronchiectasis [(Redondo et al., 2016), (Palwatwichai et al., 2002) and (Chan-Yeung et al., 2008)]. In contrast, in Shandong China, a study found idiopathic bronchiectasis (no clear cause identified) as the most common form in the Chinese Han population (Qi et al., 2015). The mortality rates of bronchiectasis in South Korea and Taiwan were increasing during 1995-2003. On the other hand, the mortality rate in Hong Kong dropped over the same period (Tan et al., 2009). In Iran, bronchiectasis is a common consequence of sulfur mustard gas inhalation amongst Iranian veterans (Attaran et al., 2006). In Saudi Arabia where immunization rates against common bacterial infections were previously low, bronchiectasis rates in children were high. It demonstrated that increasing vaccination rates may prevent the progression of the bronchiectasis [(Banjar, 2007), (Moeller and Kantar, 2018)].

In Australia, as in other parts of the world, bronchiectasis is increasingly recognized as a significant burden on the health system. The Australian National Hospital Morbidity Database (NHMD) for 2010-11 reported the hospitalization rate for bronchiectasis as a principal diagnosis was 21 per 100,000 of populations (an increase from 14 per 100,000 in 1998-1999). The average length of stay (ALOS) in hospital was 9 days for bronchiectasis – much longer than the ALOS for all causes of 3 days. Furthermore, there were 745 deaths associated with bronchiectasis in 2011. The prevalence of bronchiectasis in the Indigenous people in New Zealand and Australia is amongst the highest in the world [(Chang et al., 2010) (Steinfort et al., 2008)]. People in remote areas of Australia have been identified at particular risk for the non -CF bronchiectasis [(Maguire, 2012), (Barton et al., 2018)]. The cause of bronchiectasis in Australians is similar to all large series internationally [(Chotirmall and Chalmers, 2018), (Visser et al., 2018)]. In most cases, no cause is able to be identified and the process is deemed idiopathic. However, bronchiectasis is associated with other chronic airway diseases (COPD and Asthma), immunodeficiency, severe pneumonia and a range of other chronic inflammatory processes (Visser et al., 2018). The Australian National Hospital Morbidity Database (NHMD) for 2010-11 reported the hospitalization rate for bronchiectasis as a principal diagnosis was 21 per 100,000 of populations. It increased from 14 per 100,000 in 1998-99 and the average length of stay in hospital was 9 days while the overall of average length of stay in hospital (ALOS) for all hospitalizations was about 3 days. Furthermore, there were 745 deaths associated with bronchiectasis in 2011. A study has indicated that the prevalence of bronchiectasis in the Indigenous people in New Zealand and Australia was very high (Chang et al., 2010). During 1998−2000, in Auckland New Zealand, bronchiectasis was commonly found in children, however, only the most severe cases were being recognized (Edwards et al., 2003) Rates were highest in indigenous children in NZ (Munro et al., 2011). Bronchiectasis were a significant cause of morbidity and mortality in the Indigenous children who had been reported as the highest rates of bronchiectasis in the world (Steinfort et al., 2008).

People in remote areas of Australia have been identified at particular risk for the non -CF bronchiectasis [(Maguire, 2012), (Barton et al., 2018)]. Chang et al. (2008) identified that about 7.30% of patients with bronchiectasis in Australia visited the GP for coughing ended up with a diagnosis of bronchiectasis. Bronchiectasis is a chronic condition. The symptoms are often present for many years before a diagnosis is confirmed. Monash Medical Center reported a cross-sectional study of 103 adults with idiopathic bronchiectasis. A majority of them had chronic productive cough for thirty years prior to diagnosis most since childhood (King et al., 2006). The same group followed a cohort over 22 years and recorded a progression decline in the lung diffusing capacity for carbon monoxide and this decline in lung function was mirrored by progressive fall in exercise capacity. The longitudinal study reported that age, severity of

airflow obstruction and chronic pseudomonas infections were significant factors in mortality of bronchiectasis patients in moderate to severe stage of disease (King et al., 2010). In 2016, bronchiectasis was a major cause of illness in the Australians over 60 years of age (AIHW, 2018). There were 381 deaths caused by bronchiectasis. The hospitalization rate with a principal diagnosis of people with bronchiectasis for females was almost twice that for males (AIHW, 2018). Lately, the Australian Institute of Health and Welfare (AIHW) has reported that half of Australians had a chronic disease such as asthma, COPD, cancer and diabetes but there are still limited data available on the incidence and prevalence of bronchiectasis in Australia. In 2015, the Australian Bronchiectasis Registry (ABR) was established purposely for collecting data on patients with non- CF bronchiectasis and to research the causes and treatments of disease for this ailment. The ABR has enrolled more than 1500 patients with bronchiectasis at the time of submission of this thesis.

2.1.5 Bronchiectasis treatments

To date, there is a lack of studies supported by high quality clinical trials and clinical practice guidelines for treatment of bronchiectasis patients (Polverino et al., 2017). There is no cure in bronchiectasis because the damage to the airways cannot be reversed, but treatment can help patients to reduce symptoms, prevent flare-ups, minimize disease progression and maintain or improve lung function. The cornerstones of management include exercise and physiotherapy to maximize airway clearance, antibiotics to treat infections and vaccination to reduce the impact of pneumococcal and influenza infection and guideline based treatment of underlying comorbidity (Asthma, COPD). The treatment of exacerbations depends on the severity of the exacerbation. For the beginning of an exacerbation, a sputum sample should be sent for microscopy, culture and sensitivity. Previous airway culture and sensitivity results are also used to guide antibiotic choice otherwise empirical therapy is commenced while culture results are awaited (Visser et al., 2018). Although there are a variety of potential treatments available to recommend to patients, the treatments remain largely based on the specialist opinion. Mainly treatments are medication and chest physical therapy. In the most cases, treatment involves a combination of medication and airways clearance techniques. For infection treatment, antibiotics are commonly used even when a specific bacteria has not been identified. This is described as empiric prescription. The EMBARC mentioned that a long- term suppressive antibiotics was the first ranking of research priority in bronchiectasis treatment in Europe (Aliberti et al., 2016).Hill et al. (1986) demonstrated that the penicillin based antibiotic amoxycillin was capable of clearing both purulent and mucoid sputum effectively in most patients, and was able to decrease the number of exacerbations and reduce the bacteria burden in the airways (ten Hacken et al., 2007). Australia and Asia lead the way with studies of

macrolide antibiotics in bronchiectasis. It was not until 2012 that Wong et al. (2012), from NZ, published the Effectiveness of Macrolides in patients with Bronchiectasis using Azithromycin to Control Exacerbations (EMBRACE) study, arguably the first data to prove the efficacy of any therapy for Non- CF bronchiectasis. In 2013, David Serisier published the Bronchiectasis and Low-dose Erythromycin Study (BLESS) that confirmed the benefits of macrolide antibiotics, using the short-acting agent erythromycin rather than the more ecologically costly, long-acting azithromycin (Serisier et al., 2013). Recently, Kelly et al. (2018) noted that the effects of macrolide antibiotics treatment, especially with an azithromycin, can reduce the frequency of flares and improve the quality of life in patients. Such clinical researchers argued that although antibiotics are widely treated for lung infections in bronchiectasis patients, the mechanisms that modify inflammation is still not clear [(Chalmers et al., 2012), (Tsang et al., 1999),(Evans et al., 2007), (Visser et al., 2018)]. Not all patients with bronchiectasis need antibiotics all the time. If the cause of cough is confirmed to be related to retained secretions and patient's symptoms do not meet the criteria for exacerbation, the treatment should focus on airway clearance.

The chest physical therapy (CPT) or chest physiotherapy is a technique to improve respiratory efficiency and eliminate excess mucus from the respiratory system (see Figure 3). This method is effective for clearing the airways allowing the efficient transfer of oxygen throughout the lungs. In addition, Murray et al.(2009) identified that bronchiectasis patients with a regular CPT had higher significant benefit for improving mucus clearance and control of cough than patients did not have regular CPT. However, CPT therapy needs more studies to support its treatment efficiency (Mandal et al., 2012). Some patients may be suggested to have a pulmonary rehabilitation, especially if fatigue and breathlessness limits their exercise tolerance. Pulmonary rehabilitation is a routine exercise program designed to treat patients with chronic lung diseases (Zanini et al., 2015). This exercise program can be started when patients are stable or have recovered from an acute exacerbation. Lee et al. (2014) highlighted that bronchiectasis patients who have a regular pulmonary rehabilitation program for eight weeks reduced the number of flare-ups over one year. Mandal et al. (2012) mentioned that a combination of a regular exercise and an airway clearance program can reduce cough. Other therapies have been introduced to bronchiectasis patients in order to reduce the number of flare-ups. For example, Rea et al. (2010) showed that a long- term humidification therapy had significantly reduced the flare-ups days, increased time before the first exacerbation and improved lung functions in patients with COPD or bronchiectasis. Oxygen is only useful for those with severe disease when the blood levels of oxygen are demonstrated to be low. In the particular case of bronchiectasis associated with asthma, inhaled corticosteroids are the most effective controllers for this particular condition.

Surgery to resect the bronchiectatic lung resection can be considered, if bronchiectasis is radiologically localized and associated with frequent infections, recurrent haemoptysis and chronic symptoms. In carefully selected patients, lung resection is associated with significant improvements in symptoms and a low risk of mortality (Fan et al., 2015). Lung transplant can be considered if symptoms and lung function and exercise tolerance is severely impaired (Kutlay et al., 2002).

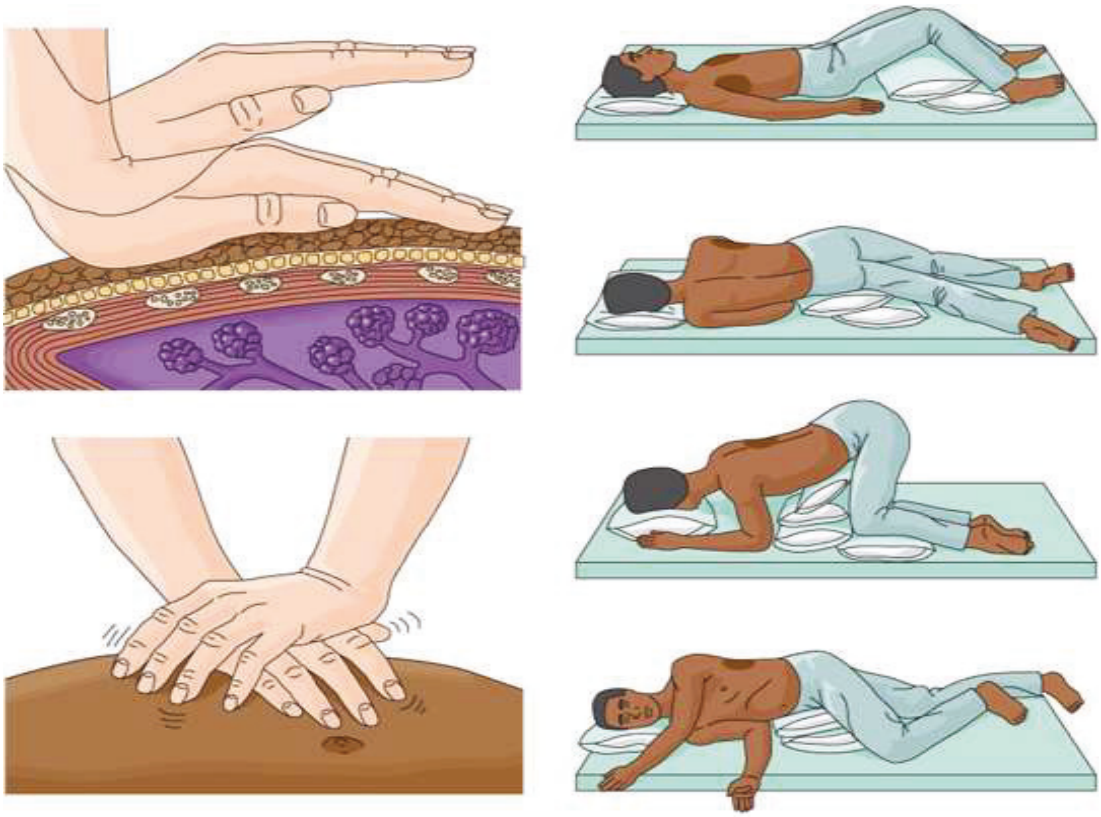

Figure 3 Chest physiotherapy and Postural Drainage
(Source: https://coursewareobjects.elsevier.com)

Treatment strategies require improvement and development for linking patients to primary health care and hospital facilities to ensure they are aware of treatment options, with prevention of the lung infection and further lung damage a high priority. Bronchiectasis patients have sensitivity to airways infections. They thus should avoid some situations with increased risk of lung infection such as mixing with people with colds, being in a crowded place, in areas with chemical pollution and smoking areas. Keeping up with their annual vaccinations against flu and pneumonia may shield them from seasonal illness. The recent COVID-19 pandemic has illustrated this point. Although, at the time of submission, no publications had described the impact of SARS CoV infection on lung function or exacerbation for any large series of patients with bronchiectasis, anecdotally, physical distancing, home isolation and careful attention to

hand hygiene had protected Australian patients from exacerbation, with dramatically reduced rates of hospitalization and reduced influenza and other viral infections (personal communication Morgan 2020). In summary, all the treatments described in this chapter aim to reduce the day to day burden of symptoms and reduce the frequency and severity of exacerbations. Despite evidence based management, many patients with clinically significant bronchiectasis do end up in hospital. The frequency of hospital admission is a marker of disease severity and a predictor of adverse outcomes for the patients at risk of death and cost to the community (Aliberti et al., 2016).

2.1.6 The Australian Refined Diagnosis Related Groups

Casemix classifications provide the health care industry with a consistent method to group types of patients with a similar level of treatment and associated hospital cost. It was first suggested by Florence Nightingale in 1852. She stated that it was necessary to categorize patients according to their illness for analyzing the pattern of treatments and costs with different types of illness (Fetter, 1999). The concept of casemix and how it related to modern hospital resource use was commenced at Yale University in the USA in 1970. The fundamental challenge was to define the products of a hospital in terms of quality control, the link between the financial and clinical aspects of care, statistical approaches for predicting the hospital resource use, and medical meaningfulness. This became known as diagnosis – related groups (DRGs). The initial DRG was used for payment purposes in the State of New Jersey in the US and since then, the DRG system was the principal system for government reimbursement of hospitals in many countries (Goldfield, 2010). In 1983, the DRG classification was implemented by the Australian Federal Government for Medicare and became known as the Australian Refined Diagnosis Related Groups (AR-DRGs) classification system (Duckett, 2000). This became federally funded in 1987. The AR-DRG classification helps to explain the relationship between types of patients and treatment costs and also provides a method for comparing the performance of different hospitals on the basis of clinical outcomes, efficiency and variation in resource use. The classification is based on similarities in cost rather than necessarily having the same cause or pathology. For example, whooping cough (a specific disease caused by the bacteria Bordatella pertussis) and acute bronchiolitis (an illness that leads to wheezy cough and breathlessness and caused by a variety of bacterial and viral pathogens) are grouped to E70A as their conditions have similar hospital resource consumption and costs despite different pathogens. The AR-DRG classification system is updated every two years. The current version of AR-DRG classification is Version 9.0. For each of the released versions, the number (e.g. Ver. 4.0, Ver. 5.0) indicates a major change whether adding or removing structure in the AR-

DRG classification system. The AR-DRG classification process can be briefly summarized as following:

● Patient Discharged and Discharge Summary Completed

●The Health Data manager reviews the medical record: discharge summary, progress notes, operation report and investigation reports

● Medical record is coded by using ICD-10 AM coding system

● Codes are entered into the hospital database

● ICD-10 AM codes are transmitted to the Australian Refined Diagnosis Related Groups (AR-DRG) by computer software

● DRG is allocated

● Assigned DRGs are transmitted to the Department of Health for hospital funding

The hospital budget depends on the number and type of patients treated in hospital. A grouping types of patients based on the AR-DRG classification system is used for payment purposes. Approximately 45% of the efficient growth of activity based services (an estimated additional $2.9 billion in funding for public hospital services) are paid by the Commonwealth in 2017-2020 (AU, 2018). In August 2011, the Commonwealth established the Independent Hospital Pricing Authority (IHPA) as part of the National Health Reform Agreement (NHRA) to contribute the National Efficient Price (NEP) and the National Efficient Cost (NEC) for the Australian public hospital services. The NEP and NEC have been released every year since 1 July 2014.The aim of NHRA is to improve patient access to health care services and enhance hospital efficiency through the use of Activity Based Funding (ABF).

The NEP provides a benchmark on the efficient cost of public hospital services and is used to determine the Commonwealth Government funding but NEC is used when the activity levels are not suitable for funding such as rural hospitals. The NEP is based on the average cost of an admitted acute episode of care provided in public hospitals for each financial year. Each episode of care is allocated a National Weighted Activity Unit (NWAU). NWAU is a measure of hospital activity expressed as a common unit. The price of each public hospital service is calculated by multiplying the NWAU allocated to that service. For example, in financial year 2018, the price weight is $5,012 per NWAU. A tonsillectomy has a weight of 0.7158 NWAU which equates to $3,588.Cots et al. (2004) analyzed how the relationship between hospital structural level and length of stay outliers affects hospital funding based on the fit of a logistic regression model and odd ratios regarding to acute inpatient hospital discharges from the Catalan Health Service. They pointed out that the outlier payment would not be appropriate because of the difference in cost per case is due to the hospital structural level and cannot explain the relation to its DRGs cost pattern. Jackson (2001) reviewed the use of data from

hospital management in Australia to estimate hospital funding used in Victoria with the accelerating rate of change in medical technology Funders need frequent replication in which the validity and reliability of DRG associated cost payment can be reasonably estimated without excessive costs for data collection. The cost–modeling approach in Germany uses actual length of stay as primary data and assigns expenditures based on the hospital's DRG which is determined by a selected 30-50 hospitals data sample where it is assumed that the rest of the hospitals are distributed as for the reference hospitals (Schreyögg et al., 2006). Duckett and Agius (2002) claimed that because of the inadequate DRG payment there is a temptation for hospitals to avoid treating the most severe patients in order to reduce costs. In addition to the hospital costs, Curtis et al. (2011) have compared the AR-DRG allocated costs and the actual costs of 206 trauma patients in New South Wales, Australia. They identified that 62.80% of them were underfunded for acute trauma patient episodes. This resulted in an overall loss of $113,921 during a three-month period (November 2006 to January 2007).

In summary, the AR-DRG codes are used to categorize approximately 10,000 diseases into about 800 groups based on diagnosis, age, performance of an operation, and co-morbidities. Each of inpatient care episode is assigned to one AR-DRG. It can lead to consideration of the hospital funding for that episode which includes input for hospital resources such as clinician attendance, pharmacy, radiology, average length of stay in hospital (ALOS) and other hospital costs whereas the outputs of hospitals are used to determine changes in clinical study, research grants and changes in a level of hospital funding. Although the AR-DRG system is widely used in the healthcare system, it has always been criticized in terms of the medical efficiency and transparency. This criticism is pretty much related to the lack of recognition of different levels of complexity of illness within any AR-DRGs. If the AR-DRG category do not adequately control for differences between groups of patient in provided hospital services, treatment costs of highly complex cases may be underestimated. Consequently, patients could receive insufficient treatment toward earlier hospital discharges if there is less money provided for the care (Mihailovic et al., 2016). The AR-DRG system is not only related to healthcare costs, but also reflects on the healthcare treatment. Curtis et al. (2011) have pointed out that the use of AR-DRG system may not be an accurate tool to provide hospital reimbursement. It is possible that some hospitals may have some groups of AR-DRG in which their patients always have a higher severity of illness than other hospitals. For instance, patients admitted to the Alfred Hospital in Melbourne, which provides treatment for heart transplantation, trauma and cystic fibrosis, are more complex and expensive than what the AR-DRG arrangements would indicate (Antioch and Walsh, 2004). These issues contributed to the development of the AR- DRG classification system to reflect changes in clinical practice, and to ensure the classifications remain clinically relevant and robust. For example, in 2014, the Australian Commission on

Safety and Quality in Health Care and the Independent Hospital Pricing Authority (IHPA) has reported the impact of the hospital-acquired diagnoses on cost and the length of stay in hospital (LOS). A set of models were addressed to estimate the effect of incremental cost and the length of stay of hospital-acquired conditions on the overnight episodes of care. The study noted that the conditions with a very high cost impacts per episode; sepsis, gas embolism and complication of transplants represent a very low number of episodes of care. For this reason, the total cost of this condition was not very high compared with the other conditions. In contrast there were a number of other conditions which had a lower cost per episode, but they had larger numbers of the episodes, so the total cost impact was very high (HPA, 2013). Bronchiectasis has been long recognized as a condition where the ARDRG system did not accurately reflect the cost of the admission. At the commencement of this thesis, there was no specific AR-DRG code. Bronchiectasis patients had been coded into a variety group of diseases such as Heart Failure, a Chronic Obstructive Airways Disease and Respiratory System Disorder. In 2018, following submission by clinicians in Australia, bronchiectasis has been recorded in the AR-DRG classification system as E77A (Minor Complexity) and E77B (Major Complexity) in an effort to more accurately reflect the clinical needs of this patient group.

2.1.7 Length of hospital stay

Hospital length of stay (LOS) refers to the time between hospital admission and discharge, measured in days (AIHW, 2018). The LOS is a key driver of hospital costs and affects the capacity of the healthcare system. The Council of Australian Governments (COAG) has identified that the LOS as one of the indicators of hospital performance, for example, a shorter length of stay (LOS) is more efficient in order to make available more beds in hospital. The LOS is used to calculate the price of an Activity Based Funding (ABF) activity. The ABF is the pricing framework for Commonwealth funding of Australian public hospitals. The price of an ABF activity, regarding to NEP 2015-16, has been demonstrated as the following formula:

Price of an admitted acute ABF activity

$$= (\{[PW \times A_{Paed} \times (1 + A_{SPA}) \times (1 + A_{Ind} + A_{Res} + A_{RT} + A_{Dia}) \times (1 + A_{Treat}) + (A_{ICU}\text{ICU hours})] - [(PW + A_{ICU} \times \text{ICU hours}) \times A_{PPS} + LOS \times A_{Acc}]\} - PW \times A_{HAC}) \times NEP.$$

A_{Paed} means the Paediatric Adjustment

A_{SPA} means the Specialist Psychiatric Age Adjustment

A_{Res} means each Patient Residential Remoteness Area Adjustment

A_{Ind} means the Indigenous Adjustment

A_{RT} means the Radiotherapy Adjustment

A_{Dia} means the Dialysis Adjustment

A_{Treat} means the Patient Treatment Remoteness Area Adjustment

A_{ICU} means the Intensive Care Unit (ICU) Adjustment

A_{PPS} means the Private Patient Service Adjustment

A_{Acc} means the Private Patient Accommodation Adjustment applicable to the state of hospitalization and length of stay in hospital

A_{HAC} means the Hospital Acquired Complications Adjustment

ICU hours means the number of hours spent by a person within a specified ICU

LOS means length of stay in hospital (in days)

NEP refers to National Efficient Price 2019-20

PW refers to Price Weight for an ABF activity.

Adjustments to Price Weights (expressed as NWAU) are to be applied in the manner and in the order indicated by the formula for determining the NWAU value (price) of an ABF Activity (NEP 2015-16). LOS for each of care episode leads to the average length of stay in hospital (ALOS) with a particular illness, with patients grouped into a specific AR-DRG code. The average length of stay (ALOS) for each selected AR-DRG code is calculated by dividing the total number of days that patients stayed in hospital during a year by the number of discharge days. Each AR-DRG code provides an average of length of stay (ALOS) of patient and Inliers for each episode of care. For example, E65A, which is the Chronic Obstructive Airways Disease (Major Complexity), has ALOS about 5.7 days. The lower bound and upper bound of E65A is 2 days and 18 days respectively (AIHW, 2018). The ALOS is a central point in the distribution of a length of stay (LOS) for a particular AR-DRG group of patients. The Inliers refer to the majority episode of care which has a length of stay (ALOS) between the statistical lower and upper bound as illustrated in Figure 4. Regarding the NSW ABM/ABF compendium 2015/16, all inliers for a particular AR-DRG code has the same price weight. If the lower bound and the AR-DRG code are not for the same day admission, the price weight assigned is based on the short stay outlier base rate and a per-day weight. If a patient has the average length of stay (ALOS) in hospital greater than the upper bound, the price weight is based on the mean of inlier price weight added to the long stay outlier per day weight then multiplied by the number of days beyond the upper bound.

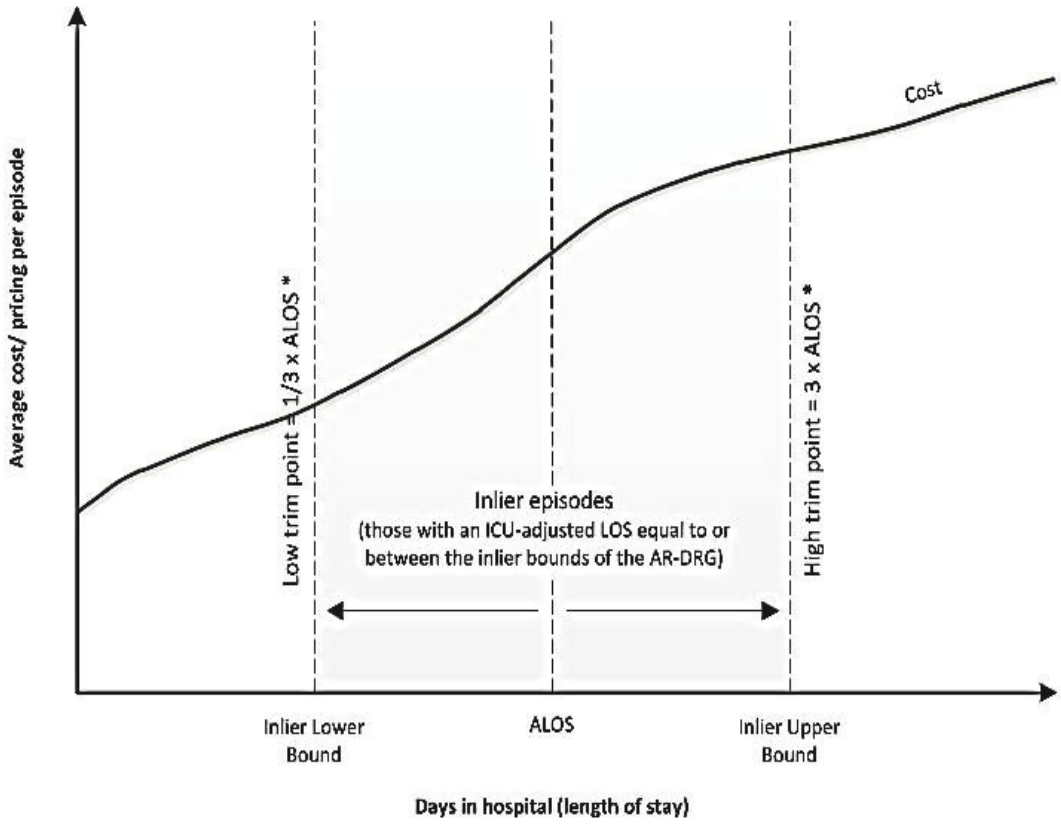

Figure 4 Inlier bound (ALOS) calculation
(Source: IHPA National Pricing Model 2017-18)

The Organization for Economic Co-operation and Development (OECD), which is an international economic organization with 36 member countries, uses ALOS for overnight separations as a crucial indicator of hospital efficiency. Their indicators related to the Australian healthcare system performance are presented as following (AIHW, 2018).

●Adverse events treated in hospitals: the number of incidents in which harm resulted to a person receiving health care

●falls resulting in patient harm in hospitals: the number of falls in hospital which caused patient harm

● Rate of services: hospital procedures

● cost per casemix-adjusted separation for acute care episodes

● Relative stay index (RSI) which is calculated by dividing the actual number of patient days for acute care separations in selected AR-DRGs by the expected number of patient days adjusted for casemix

● Average length of stay for selected AR-DRG

A study, Khalifa (2017), has mentioned that although shorter stays will decrease the cost per discharge, the shorter stays in hospital tend to have more intensive treatment and are more costly per day. A patient who has too short a LOS could have an adverse effect on their health recovery. The shorter LOS could influence to time to readmission to hospital. This particular issue has been represented in Chapter 5 of my thesis. Data on Health at a Glance 2017 has reported the health status of populations and health system performance in the OECD and partner countries across 35 member countries which indicated that the ALOS has fallen from 10 days in 2000 to 8 days in 2013 (OECD, 2011). In Australia, during 2014-15, the number of hospitalizations rose by average 3.2% for public hospitals and 4.0% for private hospitals. ALOS for public and private hospitals decreased slightly from 2010-11 by average 3.0 days to 2.8 days and was longer in public hospitals (3.2 days) than private hospitals (2.3 days), overall. This might reflect the number of elective procedures (e.g. endoscopy) performed in private hospitals over recent times.

The AIWH demonstrated that Australia had ALOS overnight separations of about 5.5 days (2016-17) which was lower than the OECD average length of stay of 8.3 days (AIHW, 2018). Even though the LOS is a well-accepted indicator for hospital performance, there is a substantial variation in LOS due to out-of -control factors. The reasons for difference in LOS unless among similar hospitals are not always clear from performance data. The Victorian Auditor-General Report, 2016, examined the research on 21 hospitals in Australia to seek the reasons for variations in LOS. The results indicated that there were similar factors in both positive and negative influencers to LOS. These included intensive care management, continuing care in the community, delays of diagnosis and the ability to access healthcare facilities such as rehabilitation and residential age care. Moreover, AR-DRG, patient age, patient complexity (e.g. mild, moderate, severe), discharge destination and arrival mode (e.g. emergency or planned admission) influenced the LOS variation by 29%. In contrast, the hospital size and location have not affected on the variation of the LOS. Chronic lung conditions deserve specific consideration. Mushlin et al. (1991) have investigated the necessary length of stay (LOS) per admitted patient with an exacerbation of chronic pulmonary disease in hospital compared with the length of stay assigned by the DRG system. They pointed out that patients required a length of stay in hospital between 6 and 7 days on average. For any patient with bronchiectasis, the presence of *P. aeruginosa as a pathogen chronically infecting the airways*, confers a longer length of stay in hospital (LOS) and that leads to high costs of treatment (de la Rosa Carrillo et al., 2018). The National Hospital Morbidity Database (NHMD), which collects data about hospital care provided to admitted patients in Australian Hospitals, showed the hospitalization rate of bronchiectasis patients as a principal diagnosis in 2015-16 increased steadily from 2006-07 approximately 7 per 100,000 population. This report

identified that bronchiectasis was the principal diagnosis for 7,082 hospitalizations. The overall average length of stay in hospital (ALOS) was 6.7 days. By 2018, bronchiectasis had been already recorded in the AR-DRG classification as E77A (Major complexity) and E77B (Minor complexity). The average length of stay in hospital (ALOS) of the E77A was about 8.1 days and 4.9 days for the E77B (IHPA, 2019). This suggests that for patients with bronchiectasis, the actual length of stay in hospital (LOS) is much higher than the average length of stay in hospital (ALOS). It may result in the cost of the treatment for each episode of care of bronchiectasis patients higher than the cost in which they were determined based on their AR-DRG groups of disease.

2.2 Statistical models

This section presents the statistical approaches used for the analysis of data on people with bronchiectasis collected by the Australian Bronchiectasis Registry (ABR). Linear regression models are constructed to explore the relationship between the observed length of stay in hospital (LOS) and the average length of stay in hospital (ALOS) based on the assigned AR-DRG codes that can be related to the hospital treatment cost. This study has explored the impact of patient characteristics on the length of stay in hospital (LOS). Discrete-time survival models are considered to evaluate time to readmission in hospital of this cohort of patients between 2011 and 2017.

2.2.1 Linear Regression models

Linear regression model allow us to model the expected value of the response when the predictor is fixed at $X = x$ which can be expressed as $E(Y|X)=\beta_0 + \beta_1 X$. This mean function has two parameters which are an intercept β_0 and a slope β_1. The relationship between the mean of response and the predictor variable is assumed to be a straight-line. The goal of the linear regression model is to determine how the distribution of response Y changes as the predictor X is varied. A few assumptions should be met regarding the model estimates before using the model to make predictions:

-Mean value of response variable varies linearly with the predictor variable.

-Residuals are independently and normally distributed with zero mean and variance σ^2.

To check the assumptions, plots of residual and fitted values are considered for the models diagnostics.

● **Residuals vs Fitted values**: It is a scatter plot of residuals on the Y- axis and the predictor value on the X-axis. The plot is useful for checking the assumption of whether the relationship between the response and predictor variables is a linear relation. A well-behaved plot will spread randomly and form roughly around a horizontal line without distinct patterns. For

example, Figure 5, plots in case 1 has no obvious pattern compared with case 2 which seems to be obviously a parabola shape.

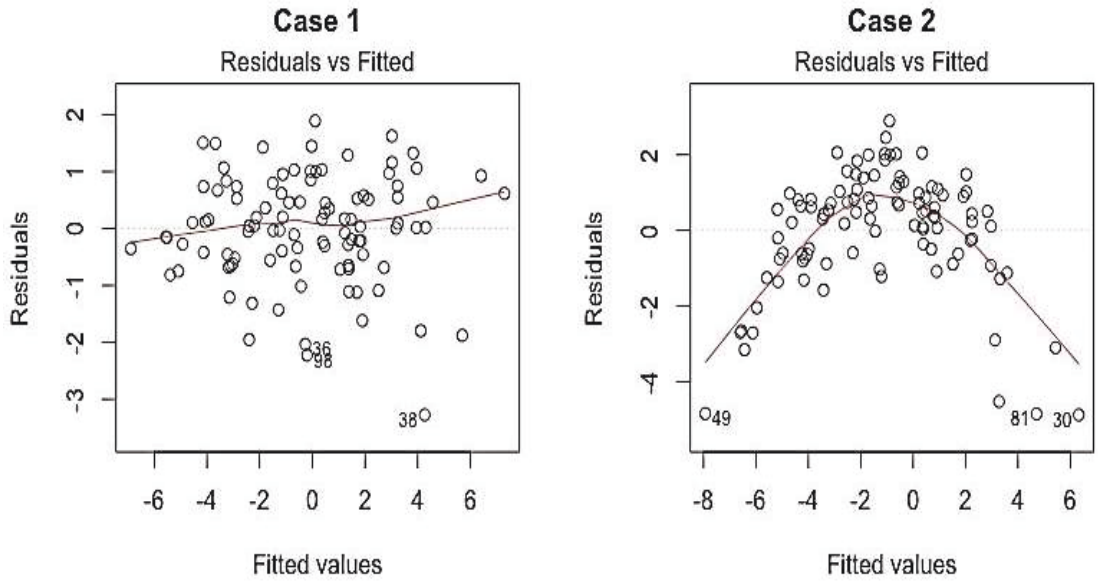

Figure 5 Residuals vs Fitted Plots

(Source: https://data.library.virginia.edu/diagnostic-plots)

● **Normal Q-Q plots**: The quantile – quantile (Q-Q) plot are used to determine whether the residuals follow a normal distribution. Normality is indicated by a roughly linear plot on a diagonal. The Q-Q plot in Figure 6, case 1 is roughly linear, confirming that the residuals are normally distributed. For case 2, the points form a curve rather than a straight line.

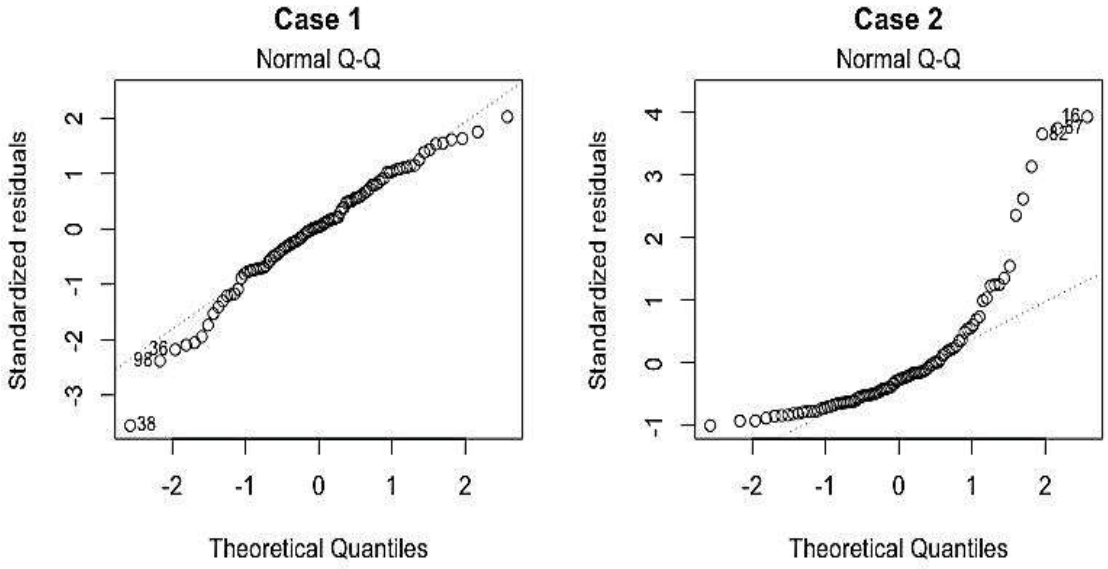

Figure 6 Quantile-Quantile plots

(Source: https://data.library.virginia.edu/diagnostic-plots)

In clinical research, multiple linear regression models are often used to identify and characterize what factors are influencing the outcome as the form: $E(Y_i|X_i)=\beta_0 + \beta_1 X_{i1} + \ldots + \beta_k X_{ik}$. The models are widely used because they are quite straightforward to implement. For example, it may be of interest to describe how patient characteristics (e.g. age, weight, gender) are associated with greater high blood pressure (Schneider et al., 2010). The linear regression models are applied to investigate many areas of healthcare service and efficiency [(Newman et al., 2018) , (Garbarino et al., 2019), (Lisk et al., 2019). Combes et al. (2014)] have presented the linear regression model for predicting an approximate length of stay in hospital (LOS) of new patients at the emergency department. The task is to build a predictive model which corresponds to LOS. They have observed that LOS is linked with some biology tests. Three variables (Computer X-ray, X-ray and Echography) were determined as the most correlated factors to the LOS variable. The relationship between the LOS and the predictor variables was described by the equation: LOS = 153 + 127 (Comp. X-ray) - 41.1 (X-ray) +133 (Echo.) + 347(Biology). However, they have pointed out that the outliers are the main problem affecting the slope of this model.

Another clinical study, Austin et al. (2003) applied the linear regression models to investigate the association between patient characteristics and their hospital costs following the surgical treatment (coronary artery bypass). The study was performed with several models including the log-transformed model for dealing with skewed data. This classic approach can reduce either right- or left- skewed distributions and make the original data conform more closely to the normal distribution. However, a marked disadvantage of this approach is that the cost data with zero value are removed from the analysis. Another limitation of the log transformation is an indirect interpretation on its initial scale (Skrepnek et al., 2012).

2.2.2 Multilevel models

Multilevel models and Hierarchical models are alternative terms for what are broadly called generalized linear mixed models (GLMMs). The multilevel models allow researchers to handle hierarchical, clustered or grouped data. The models have become popular for the analysis in many research areas. For example in educational research, there is much discussion about the so called ‘unit of analysis’ problem where students from the same school tend to be more alike in educational achievement than students chosen randomly from different schools (Burstein et al., 1980). In previous educational research, Martin (1979) studied the relationship between teacher behavior and student achievement across the levels of analysis. Three different levels of data were constructed; students (Level1) nested within reading groups (Level2) nested within classes (Level3) in order to prove that the students’ academic achievements are not only influenced by

their teacher effectiveness but also affected by many factors at the individual student or school levels. In addition, Marsh et al. (1999) represented the methodological guidelines to establish more clearly the association between the student's academic self-concept and academic achievement. They suggested that the academic self-concept and academic achievement should be based on multiple indicators of at least three items per factor and should be measured at least twice or more with the appropriate control method when the observed groups are collected on multiple occasions. In clinical studies, multilevel models have become increasingly popular for solving public health problems, for example, the relationship between patient satisfaction on hospital services (Hofoss et al., 2003). Basically, patients are treated not only by different physicians but also by different hospitals. Although physicians use standardized treatment protocols, there are individual differences in their skills, training and selection process for applying these protocols (Beidas and Kendall, 2010). These factors may affect the treatment outcome. Similarly, differences in the demographics, families and diagnostic methods used by different clinics might reasonably affect the success of the intervention (Southam-Gerow et al., 2006). The multilevel model allows for the possibility that the outcomes for patients treated within a hospital are expected to be more similar to each other than the outcomes for patients from a different one. Pullicino et al. (2016) examined the performance of healthcare providers in urban and suburban regions in Malta.

Multilevel model was addressed with three levels (Level 1: patients, level 2: clinics, level 3: regions). The results showed that the effects of physician-level activities differed amongst clinics as well as between urban and suburban. Patient in suburban were prone to be able to recover better with their illness after they visited their GP. The role of locality in population health is one of the attractive issues of the multilevel models for public health research. Jones and Moon (1993) highlighted that where people live including regions, neighborhoods, areas and workplaces makes a differences to their health. These environments play a crucial role in shaping health and health inequalities in the population. Multilevel models are straightforward for dealing with the observational data is clustered within units or a longitudinal data in which the data are repeated in different time periods such as readmission to hospital of people with cancer, HIV patients may be followed up over time and bronchiectasis patients may constantly experience flares-up. For clustered data, Park and Lake (2005) indicated that the multilevel models can solve the issue when using of conventional linear regression model which lead to an underestimation of the standard errors affecting the statistical tests. They also emphasized that the multilevel models could eliminate the aggregation bias in the conventional linear regression model.A two-level model can be expressed as the level-1 units (e.g. individuals, patients, students) is nested within the level-2 groups (e.g. regions, hospitals, schools, neighborhoods, workplace, families) as illustrated in Figure 7 below.

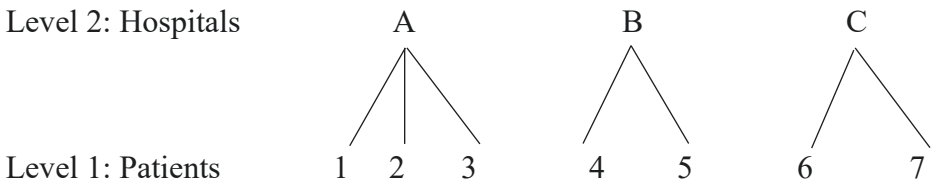

Figure 7 A two- level hierarchical structure of patients in hospitals

Multilevel models with a single explanatory variable for the i^{th} individual in group j^{th} can be written as following: $Y_{ij} = \beta_0 + \beta_1 X_{ij} + u_j + e_{ij}$. The model is called a random intercept model. The overall relationship between Y and X is represented by a straight line with the intercept β_0 and slope β_1. This model consists of two components: a fixed part: $\beta_0 + \beta_1 X_{ij}$ and a random part: $u_j + e_{ij}$. The group-level residual is written as u_j and the individual-level residual is represented as the error term e_{ij}. The residuals at both levels are assumed to be normal distribution with zero means: $u_j \sim N(0, \sigma_u^2)$ and $e_{ij} \sim N(0, \sigma_e^2)$. The total variance includes the between-group variance ${\sigma_u}^2$ and the within-group variance ${\sigma^2}_e$.

For A two-level model, the intra-class correlation, the classic reference is Shrout and Fleiss (1979), can be calculated by $\frac{\sigma_u^2}{\sigma_u^2+\sigma_e^2}$, which is the correlation between the y-values of two randomly selected individuals within group. In other words, the intra-class correlation reports a ratio of the amount of variance due to variation between groups relative to the total variance. The number of repeat measures is an important factor for the intra-class correlation calculation. For example, in the dataset with relatively few repeat measures; the intra-class correlation estimate is less robust than the same calculation with more repeats (Pleil et al., 2018).

2.2.3 Survival Analysis Models

Over past 50 years, survival analyses have been developed massively in a wide range of research such as educational research, medicine, biology, epidemiology, demography and engineering. The classic source of survival analysis is represented by Cox and Oakes (1984). Survival analysis or time-to-event analysis refers to methods for analysis of survival data in which the outcome is the time until the occurrence of an event of interest, for instance, time until a heart attack, time until death from cancer or time to hospital readmission and so on. A key complication in survival analysis is the censoring which refers to the event may not have occurred for all subjects prior to the end of the study. There are three types of censoring: right censoring, left censoring and interval censoring. The most commonly encountered form is right censoring. Suppose patients are followed in a study for five years. Those patients who are still

at risk of the event but they have not had the event by the end of year are censored. This period of study is said to be right censored. The core component of the survival analysis depends on whether the time variable, T, indicating the duration of non-occurrence of an event, is assumed to be continuous or discrete. A case of T is a continuous random variable presenting time to event of interest, $f(t)$ and $F(t)$ are the density and cumulative distribution function of T, they are defined as the form:

$$f(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t+\Delta t)}{\Delta t}, \text{ where } t > 0 \text{ and } F(t) = P(T \leq t).$$

The survival function S(t) indicates the probability of nonoccurrence of an event until time t. It can be demonstrated as $S(t) = P(T > t) = 1 - F(t)$. Another function which plays a vital role in survival analysis is the hazard function. It expresses the risk of experiencing an event at $T = t$ given that the event of interest has not occurred before time t, denoted by the following function $h(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t+\Delta t \,|\, T \geq t)}{\Delta t}$. The relationship of $h(t)$ and $S(t)$ can be described as follow:

$$S(t) = \exp\left\{-\int_0^t h(s)ds\right\} \text{ or } S(t) = \exp\{-H(t)\}, t > 0.$$

Where $H(t)$ refers to the cumulative hazard that describes the accumulated risk up to time t. A case of T is a discrete random variable which is the time of occurrence of an event, and t_i is the discrete time point i and the duration of nonoccurrence of an event is t_{i-1}, the probability of experiencing an event of interest at time $T = t_i$ is given by $f(t_i) = P(T = t_i)$. The survival function $S(t_i)$ indicates the probability that event of interest has not occurred at $T = t_i$ which can be written as:

$$S(t_i) = P(T > t_i) \text{ or } S(t_i) = 1 - P(T \leq t_i).$$

The hazard function in the discrete time is the conditional probability that the event occurs at $T = t_i$, given that the event did not occur before the time $T = t_i$ which is demonstrated: $h(t_i) = P(T = t_i | T \geq t_i) = \frac{f(t_i)}{S(t_{i-1})}$. A well- known regression model for analysis of survival data with continuous time is the Cox Proportional Hazard model which was proposed by Cox (1972). The models involve regression with the conditional probability of occurrence of an event at each time t_i given survival up to that point. The Cox Proportional Hazards model, where the hazard function for individual with covariates x_i at time t, is written as: $h\big((t|x_i)\big) = h_o(t)\exp(x_i'\beta)$. In this model, $h_0(t)$ is known as the baseline hazard function which is not directly estimated but the cumulative hazard, and $\exp(\beta x_i')$ is the relative risk associated with the set of characteristics x_i. The Proportional Hazard model is widely used in medical research to interpret the relationship of the hazard function to predictors or risk factors for time to the occurrence of an event of interest. As the baseline hazard is not directly estimated, it is not required to make assumption underlying probability distribution of the outcome data but still estimate and test hypothesis about the predictors. In healthcare research, there are a lot of

studies dealing with binary outcome such as death (yes/no), disease recurrence (yes/no) and readmission to hospital (yes/no). Therefore, after restructuring the data, the occurrence of an event of interest can be analyzed by any appropriate models for binary outcomes such as a logistic regression model (Allison, 1982). The outcome of interest is not only whether or not an event occurred, but also when that event occurred. The time to the occurrence of the event (e.g. hospital readmission, death) can be measured in discrete of units of time such as days, weeks, months and years, especially with retrospectively collected data. To record event occurrence in discrete intervals, time periods can be divided into the sequence $(0, t_1]$,$(t_1, t_2]$,.., $\left(t_{j-1}, t_j\right]$,…, and so forth. Some events may occur more than once for each individual over the observation period. For example, patients may be readmitted in hospital for many episodes of care or they may be treated several times with therapy. When events are repeatable, the repeated events can be analysed by using multilevel model. The hazard of an event in interval t of episode i of individual j is denoted by h_{tij} , the model may be represented as

$$logit\left(h_{tij}\right) = \alpha(t) + \beta' X_{tij} + u_j$$

where covariates X_{tij} may vary across time intervals, episodes or individuals. The log-odds of an event in interval t is shifted up or down by an amount of u_j for a given individual. The u_j term refers to the random effect. The random effect is assumed to follow a normal distribution with zero mean and variance σ_u^2.

●Kaplan-Meier Survival Curves

The Kaplan-Meier curves are widely used in clinical research introduced by Edward L Kaplan (1920-2006) and Paul Meier (1921-2011) in 1958 (Stalpers and Kaplan, 2018). They created the Kaplan-Meier estimator as a method for measuring the number of patients surviving medical treatment. Later on, the Kaplan-Meier method becomes a better way for survival analysis. The Kaplan-Meier curves are used in epidemiology to investigate time to event. Time to event means the time from beginning of a study until a particular event happening (Etikan et al., 2017). This method is used to determine the patients who lost to follow-up or drop out of the study, those who developed the disease of interest or survived from the disease. Basically, the curves show the probability of surviving in a given time interval. The curves are the graphical displays of time until the cohort of study developed a particular event or endpoint, often death, or an event such as recurrence of cancer, criminal recidivism and readmission to hospital. Normally, the curves are used to compare between two groups in a study. Because of the individuals started the study at different time- point, each individuals have been followed- up for a different length of time. Many of them may or may not have the event of interest, so their outcome will be unknown. The graph is displayed as a step-down when the individual has an event. In addition, the graph often shows as a small vertical line for the individuals who have

not had the event at which they were last observed. The followed-up time can be any time interval such as days, weeks, months and years. For example, Figure 8 below presents the Kaplan-Meier survival graph taken from the paper by Coltman (1971) from MD Anderson Cancer Center with Edward Gehan as the biostatistician shows the results of chemotherapy for solid tumors (Stalpers and Kaplan, 2018).

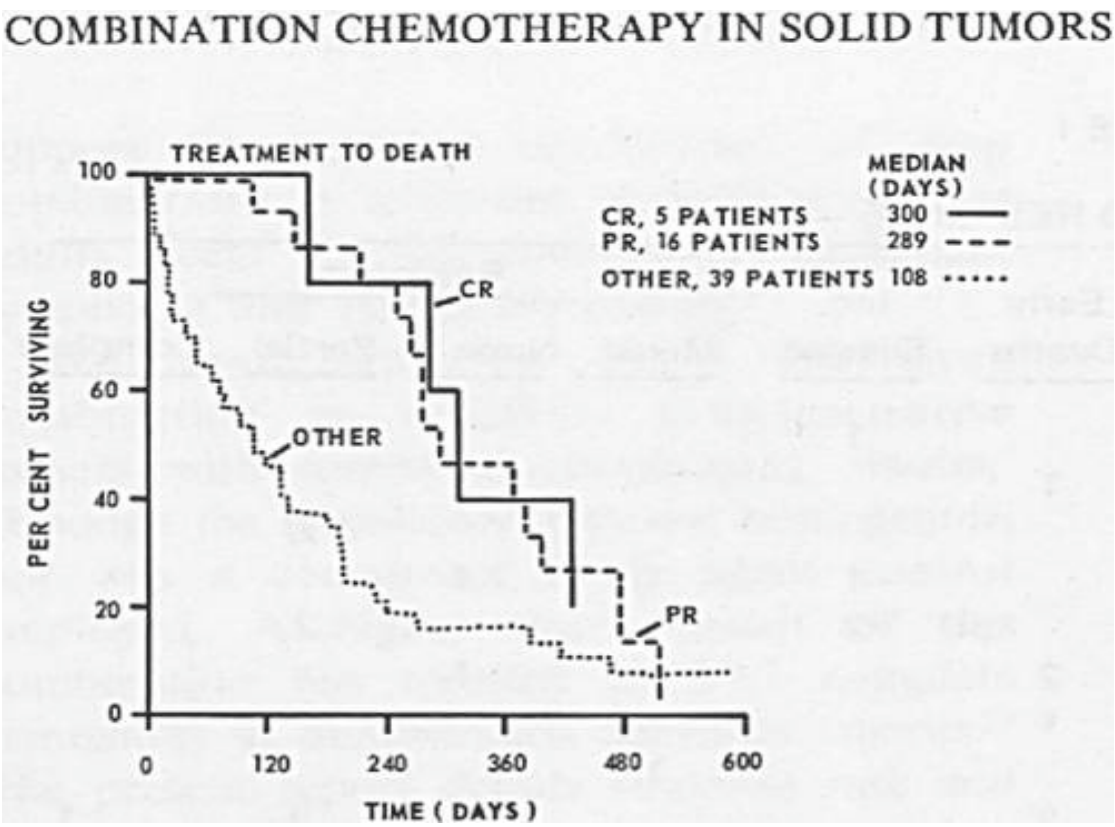

Figure 8 Survival curves after chemotherapy for solid tumors stratified by tumor response (Coltman et al., 1971)

2.3 Conclusion

This chapter provides a review of literature with regard to this thesis. The first part introduces the reader to the pathophysiology of bronchiectasis and tries to explain why there is such heterogeneity in the clinical course of any individual admission. This chapter summarises the current literature regarding prevalence and treatment and highlights the gaps in our understanding of what factors contribute to the complexity of hospital admission, lengths of hospital stay (LOS), the average of length of stay (ALOS) and the accuracy of the AR-DRG classification system for Australians with bronchiectasis. The second part introduces the concepts of length of hospital stay (LOS) the average length of stay in hospital (ALOS) and the AR-DRG classification system. A review of the literature in this part describes a mismatch

between the predicted and actual costs associated with admission for bronchiectasis. Researchers have studied the effect of reduced patient length of stay (LOS) on the total hospital costs[(Taheri et al., 2000) (Mihailovic et al., 2016), (Evans et al., 2018)]. With regard to AR-DRG codes, patients with similar clinical conditions are grouped into the same code in this system. Each code of AR-DRG provides ALOS for that disease. However, the ALOS of the AR-DRG codes may not reflect the actual ALOS of the examined disease. Prior to 2018, some bronchiectasis patients were grouped into Chronic Obstructive Airways Disease, major complexity (E65A) which had the ALOS about 6.7 days. The relationship between LOS and ALOS based on assigned AR-DRGs was investigated by using regression analysis with a log transformation model used to reduce skewness.

In 2018, bronchiectasis had a specific code in the AR-DRG classification as E77A (major complexity) which had the ALOS about 8.1 days. The actual LOS of bronchiectasis may be different from the ALOS of a group of disease that patients with bronchiectasis were assigned into the AR-DRG classification system. This may lead to an underestimation of the hospital costs related to ALOS. For this reason, the relationship between LOS of bronchiectasis and the ALOS related to the group of diseases in the AR-DRG that patients with bronchiectasis were assigned to this system has been investigated in this study. Moreover, hospital readmission of bronchiectasis patients has been addressed by using the longitudinal data and survival analysis to analyze how LOS and patient characteristics affecting to hospital readmission.

CHAPTER 3
The Data

This chapter presents a clinical and statistical overview of a cohort of patients admitted to hospital with bronchiectasis in Australia between July 2011to June 2018.

3.1 Background to the data

This project utilized the de-identified health data of 299 adult patients with bronchiectasis admitted to Concord Hospital during July 2011- June 2018.

3.1.1 Definitions

This section gives a brief description of keywords used in this research related to an admitted inpatient care provided in Australian's public and private hospitals as below (AIHW, 2019).

- **Separations** refers to the act of a patient administratively leaving the hospital following death, discharge, or transfer.) The number of separations is used for the utilization of hospital services. Counts of separations are categorized for same-day and overnight separations. The same-day indicates when a patient has an admission and is discharged from hospital on the same date. An overnight separation occurs when a patient has an admission and discharge from hospital on different dates.
- **The principal diagnosis** refers to the condition considered to be mainly responsible for occasioning the patient's admission to the hospital, according to the ICD-10-AM coding and reporting.
- **Inpatient care** refers to medical treatment delivered once a person has been admitted to hospital and requires at least one overnight stay.
- **Admission** refers to a formal process, using registration procedures, in which a patient is accepted by hospital or district health service for treatment as an inpatient.
- **Discharge** refers to the point at which the patient no longer needs to receive hospital care or clinical procedures and either leaves hospital or is transferred to another healthcare facility such as rehabilitation or nursing home.
- **Episode of care** is a period of admitted patient care between a formal admission and a formal discharge from hospital, characterized by only one care type.
- **Readmission** is an episode of care when a patient who has been discharged from hospital readmits to hospital in a particular time interval.

● **Average Length of Stay (ALOS)** is an average number of days that patients spent in hospital, excluding patients who are admitted for the same-day. For selected AR-DRG, ALOS is calculated by dividing the total number of all inpatient days during a year by the number of admissions or discharges (OECD, 2011). The ALOS is the vital factor for considering hospital funding in the healthcare system.

3.1.2 Australian Admitted Patient Care during 2017-18

The main measure of hospital activity is the number of separations, or the episode of admitted patient care. An admitted patient care refers to a patient who has a hospital admission process for treatment. The AIHW has reported that in 2017-18 there were over 30.2 million days of inpatient care in Australia. The average length of stay in hospital (ALOS) was about 5.4 days for public hospitals and 5.2 days in private hospitals. During 2017-18, the number of separations (for all causes) from public and private hospitals in Australia was about 11.3 million episodes of care. It can be summarized as below:

●In 2017-18, there were 423 separations per 1,000 population. They rose by 3.8% on average each year since 2013-14. The average of the number of separations for public hospitals was greater than the private hospital over the same period (1.6% per year).

●Females had 5.9 million separations (52%) and males had 5.3 million separations. Both males and females had an increased rate of separations markedly for those aged 55 and over compared with other age groups.

●Separations are more common for older patients, with the majority of all separations being for people aged 65 and over. Between 2013-14 and 2017-18, the number of separations for people aged 65 to 74 increased by 28%. For people aged 85 and over, the number of separations decreased by 20 % overall in this financial year.

●Aboriginal and Torres Strait Islander people accounted for 4.9% of overall separations. Additionally, they were hospitalized approximately 2.6 times the rate of hospital's admission for other Australians. The most common group of conditions for separations was digestive system disease. It was approximately 9% of the total of separations. The group of respiratory system diseases had approximately 4.5 % of all separations.

●The number of separations in both public and private hospitals is shown as the Table 2.1. They are characterized by the principal diagnosis in ICD-10-AM. The majority of principal diagnose is diseases of digestive system (K00–K93). They amounted to 1,068,277 separations for both public and private hospitals in this financial year. Diseases of the respiratory system had 507,620 total of number of separations (4.5 % of all separations).

Table 3.1 Separations, by principal diagnosis, between public and private hospitals (July 2017-June 2018)

	Principal diagnosis	Public hospitals	Private hospitals	Total
A00-B99	Certain infections and parasitic disease	160,099	29,803	189,902
C00-D48	Neoplasms	317,859	375,451	693,310
D50-D89	Diseases of the blood and blood-forming organs and certain disorders	125,843	172,152	197,995
E00–E89	Endocrine, nutritional and metabolic diseases	120,876	81,705	202,581
F00–F99	Mental and behavioural disorders	239,445	227,748	467,193
G00–G99	Diseases of the nervous system	194,934	142,303	337,237
H00–H59	Diseases of the eye and adnexa	120,917	308,068	428,985
H60–H95	Diseases of the ear and mastoid process	41,912	31,713	73,625
I00–I99	Diseases of the circulatory system	389,662	194,261	583,923
J00–J99	Diseases of the respiratory system	393,641	113,979	507,620
K00–K93	Diseases of the digestive system	513,144	555,133	1,068,277
L00–L99	Diseases of the skin and subcutaneous tissue	129,885	49,418	179,303
M00–M99	Diseases of the musculoskeletal system and connective tissue	248,115	546,784	794,899
N00–N99	Diseases of the genitourinary system	292,079	208,521	500,600
O00–O99	Pregnancy, childbirth and the puerperium	391,744	125,620	517,364
P00–P96	Certain conditions originating in the perinatal Period	57,347	10,415	67,762
Q00–Q99	Certain conditions originating in the perinatal Period	26,363	11,822	38,185
R00–R99	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	622,691	307,216	929,907
S00–T98	Injury, poisoning and certain other consequences of external causes	608,880	173,102	781,982
Z00–Z99	Factors influencing health status and contact with health services	1,728,242	961,285	2,689,527
Not reported		3,097	1	3,098
Total		**6,726,775**	**4,526,500**	**11,253,275**

Source: AIHW Admitted patient care 2017–18 Australian hospital statistics

3.1.3 Bronchiectasis hospitalizations in Australia

In 2017-18, bronchiectasis was the principal diagnosis for 7,719 hospitalizations and additional diagnosis with COPD, cystic fibrosis and pneumonia for a further 10,803 hospitalizations. Bronchiectasis hospitalizations accounted for a small proportion (0.2%) of all hospitalizations. The rate of hospitalization for bronchiectasis has increased steadily from 2006-07 to 2016-17 (AIHW, 2019). The rate was about 25 to 34 per 100,000 population for females and 12 to 18 per 100,100 population for males as in the Figure 9 below. There are highly differences in

admission rates between males and females .For this time period, the hospitalization's rate for females is almost double that for males. For both CF and non-CF bronchiectasis, women were notably more commonly affected and more severely than men for this particular disease (Morrissey and Harper, 2004).

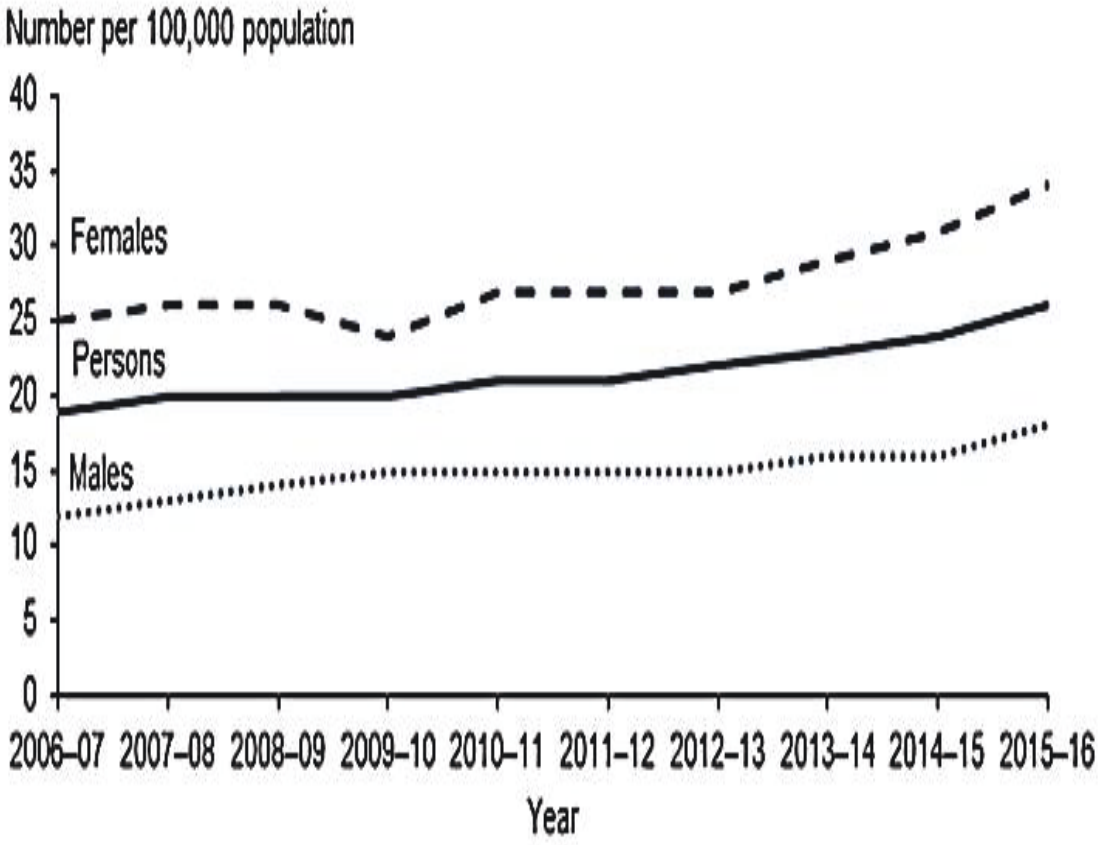

Figure 9 Rate of hospitalizations of bronchiectasis from 2006-07 to 2016-18
(Source: AIHW National Hospital Morbidity Database)

Additionally, in 2018, approximately 96% due to bronchiectasis was an underlying cause occurred in the elderly people (aged 60 and over) (AIHW, 2018). The number of bronchiectasis mortality had increased to 596 deaths. Although bronchiectasis treatment in recent years has more efficiency comparing the last ten years, the number of hospitalizations and mortality are gradually rising.

3.1.4 Hospital Performance Indicator: Average length of stay

The average length of stay in hospitals (ALOS) is often used as indicator of hospital efficiency. A shorter LOS will reduce the cost per episode of care and increase more efficient bed management. Some studies claimed that the number of inpatient days in hospital results in

decreased risk of infection and medication side effects, improvement in the quality of treatment and hospital cost (Bueno et al., 2010), (Rotter et al., 2010). In Australia, overnight separations, the numbers of ALOS in financial year 2017-18 have increased slightly than 2013-14 by an average 0.3 % each year over this period (AIHW, 2019). The overall ALOS that excludes same-day separations in both public hospitals and private hospitals is about 5 days during 2013-2017 financial years. However, the ALOS in public hospitals have decreased from 5.7 days in 2013-14 to 5. 4 days in 2017-18 as the following table. The reduction of ALOS may be related to the admission practices and improvement in the treatment (AIHW, 2019).

Table 3.2 Average length of stay (ALOS), publics and private hospitals from 2013 to 2018 (*Source:* AIHW; Admitted patient care 2017-18 financial year)

	2013-14	**2014-15**	**2015-16**	**2016-17**	**2017-18**
ALOS (days)					
Total Public hospitals	3.3	3.2	3.2	3.2	3.0
Total Private hospitals	2.3	2.3	2.2	2.2	2.2
All hospitals	2.9	2.8	2.8	2.8	2.7
ALOS, excluding same-day separations (days)					
Total Public hospitals	5.7	5.7	5.7	5.7	5.4
Total Private hospitals	5.1	5.2	5.2	5.2	5.2
All hospitals	5.5	5.5	5.5	5.6	5.3

In 2018, bronchiectasis has been recorded as E77A (Major complexity) and E77B (Minor complexity) in the AR-DRG system. The disease has been reported the ALOS of the E77A was 8.1 days and 4.9 days for the E77B (IHPA, 2019) while the ALOS for all hospitals in 2017-18 excluded same-day separations was about 5.3 days.

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3.2 The Australian Bronchiectasis registry (ABR)

A growing burden of bronchiectasis is recognized in both CF bronchiectasis and non- CF bronchiectasis in Australia and worldwide but there is limited information about accurate prevalence data and high-quality evidence providing for efficiency of patient treatments. Delays in diagnosis and coexistence of bronchiectasis with other chronic respiratory disease such as COPD and asthma are also recognized increasingly. The Australian Bronchiectasis Registry

(ABR) was established in 2015 by Lung Foundation Australia (LFA) and the Australasian Bronchiectasis Consortium (ABC), an independent steering committee composed of Australia's and New Zealand's leading respiratory physicians with experience, interest and skill in both clinical management and research. The principal aim of the registry is to identify and collect longitudinal health information on patients with non-cystic fibrosis bronchiectasis in order to facilitate epidemiological research, improve clinical care and maximise opportunities for patients to participate in clinical trials. The registry has international collaborations with US, European and New Zealand researchers to build on the existing evidence base, leverage knowledge, expertise, protocols, and ideas in order to optimise research outcomes through international sharing of data.

Aims of the Australian Bronchiectasis Registry are to map and track natural history of this chronic disease and impact on quality of life of all bronchiectasis patients, and to encourage a platform of research projects in the country including the international collaborations. The crucial aims of the ABR are briefly outlined as follow:

● help for clinical trial and epidemiological researcher collaboration with the US Bronchiectasis Registry and the European Bronchiectasis Registry via sharing of data, protocols, research topics and expertise
●collect a quality data set including longitudinal data regarding the causes of disease, morbidity, mortality, pattern of treatment, healthcare resource utilization for patients with bronchiectasis
●support bronchiectasis patients and their families by assessing local groups, rehabilitation programs and educational resources
● develop a secure registry web - based IT platform of bronchiectasis patients and to provide data for national and international clinicians
●create networking between Australian bronchiectasis clinicians and bronchiectasis patients
Source: (https://bronchiectasis.com.au/registry)

The ABR focuses on a collaborative epidemiological, non- interventional and multi-centre web-based clinical registry for the prospective collection of standardized clinical and demographic information about non- CF bronchiectasis patients. It began in January 2016 at Concord Hospital, New South Wales (NSW), and expanded throughout NSW and to each other state and territory once required research ethics approvals were received. My study focused on a cohort of bronchiectasis patients who were all cared for at Concord Hospital in Sydney, NSW. The cohort was refined to include all those admitted for > 24 hours to Concord Hospital with the principal cause for admission identified as bronchiectasis. This cohort was collated with the

assistance of the SLHD Medical Records Department as an internal audit. This data set contained a limited list of demographic features, Medical Record Number (MRN), admission date, discharge date, date of birth, gender, smoking status, DRG, LOS and ALOS. For this cohort, we had 299 separate patients with 505 episodes of hospital admission of >24 hours. Day only admissions (< 24 hours) were excluded as these were all accounted for by presentation for replacement therapy (Intravenous immunoglobulin infusion for immunoglobulin deficiency syndromes) and not for treatment of exacerbation. Patients were recorded into a variety of diseases in the AR-DRG classification system.

The ALOS used in this study were extracted from the National Efficient Price Determination (NEP) for 2014 -2017 financial years and The National Hospital Cost data Collection (NHCDC) for 2011-2013 financial years since the earlier years of the NEP did not provide the data on the ALOS based on the groups of disease. Some patients had more than one episode of care in hospital. A cohort of 185 patients were recruited to the ABR though Concord Hospital. This group was recruited as outpatients via an opt-out consent process.The data dictionary for this cohort was more extensive and included comorbidities, medications and treatments, quality of life assessments, lung function and sputum microbiology. For this group we also had information about exacerbations that had not required hospitalization. Only 29 patients enrolled in the ABR from Concord Hospital after 2015, were also admitted to Concord Hospital up to 2017.

3.3 Bronchiectasis patients in Concord Hospital 2011-2018

The bronchiectasis data set used in this study was based on administrative hospital data for 299 bronchiectasis patients with 505 episodes, excluding single day stays, in Concord Hospital, Sydney, Australia. The oldest date of admission was on 16th December 2011 and the most recent date of admission was on 22nd June 2018. Patients were recorded into a variety of diseases as the AR-DRG classification. The ALOS used in this study were extracted from the National Efficient Price Determination (NEP) for 2014 -2017 financial years and The National Hospital Cost data Collection (NHCDC) for 2011-2013 financial years since the earlier years of the NEP did not provide the data on the ALOS based on the groups of disease. There were a total of 505 episodes of care because some patients had more than one episode of care in hospital.

Patient characteristics were examined for evidence of any factors potentially affecting a patient's length of stay in hospital and readmission to hospital for this study. Descriptive statistics on patient characteristics can be summarized as below.

● **GENDER** From the 16th December 2011 to the 22nd June 2018, there were 123 male and 176 female patients admitted to Concord Hospital as shown in Figure 10. The percentage of males to females was similar between ABR and non ABR

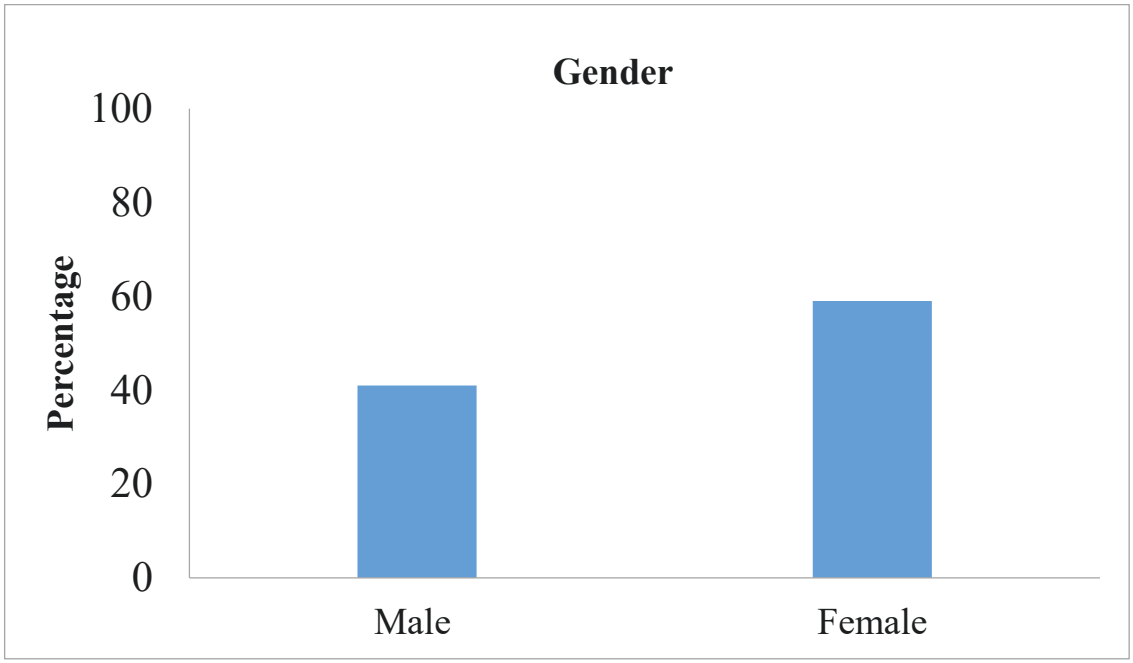

Figure 10 Differences by gender in patients admitted with bronchiectasis to Concord Hospital (July 2011- June 2018)

Table 3.3 Percentage of bronchiectasis patients in Concord Hospital by gender, July 2011-June 2018

Status	Male	Female	Overall
Participated in ABR	4.01% (12)	5.69% (17)	9.7% (29)
Non-participated in ABR	37.12% (111)	53.18% (159)	90.3% (270)
Total	41.13% (123)	58.87% (176)	100% (299)

● **AGE-GROUPS:** Age was recorded at admission date. There are 505 admissions (or episodes of care) for this study group. The group of adult patients was categorized into three groups; 20- 39, 40-59, and ≥ 60 years old. Most admissions (87.13%) occurred in the group > 60 years old. In addition, older patients were more likely to have multiple admissions.

Table 3.4 Number of episode of bronchiectasis patients in Concord Hospital by age-groups, July 2011- June 2018

Groups	Age-groups	Number of episodes	Percentage
Group 1	20-39	27	5.3%
Group 2	40-59	38	7.6%
Group 3	≥60	440	87.1%
Total		**505**	

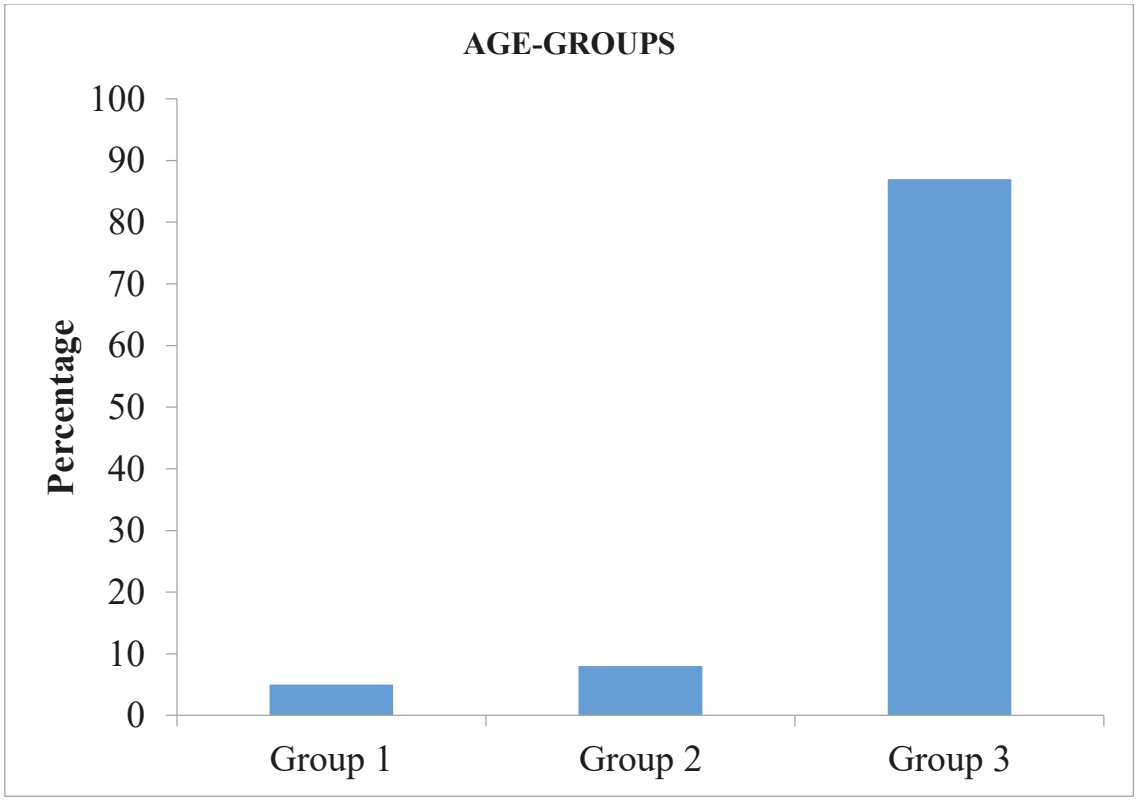

Figure 11 The proportion of age- groups (Group 1: 20-39, Group 2: 40-59, Group 3: ≥60) of bronchiectasis patients in Concord Hospital, July 2011- June 2018

● **SMOKING STATUS:** In this study, patients were categorized in two groups based on their self-stated smoking history. Those who had claimed never to be a smoker were classified as never smokers and current or former smokers were classified as ever smokers. Of the patients with recorded smoking status, 34.4% were identified as ever smoker and 65.6% as never smoker.

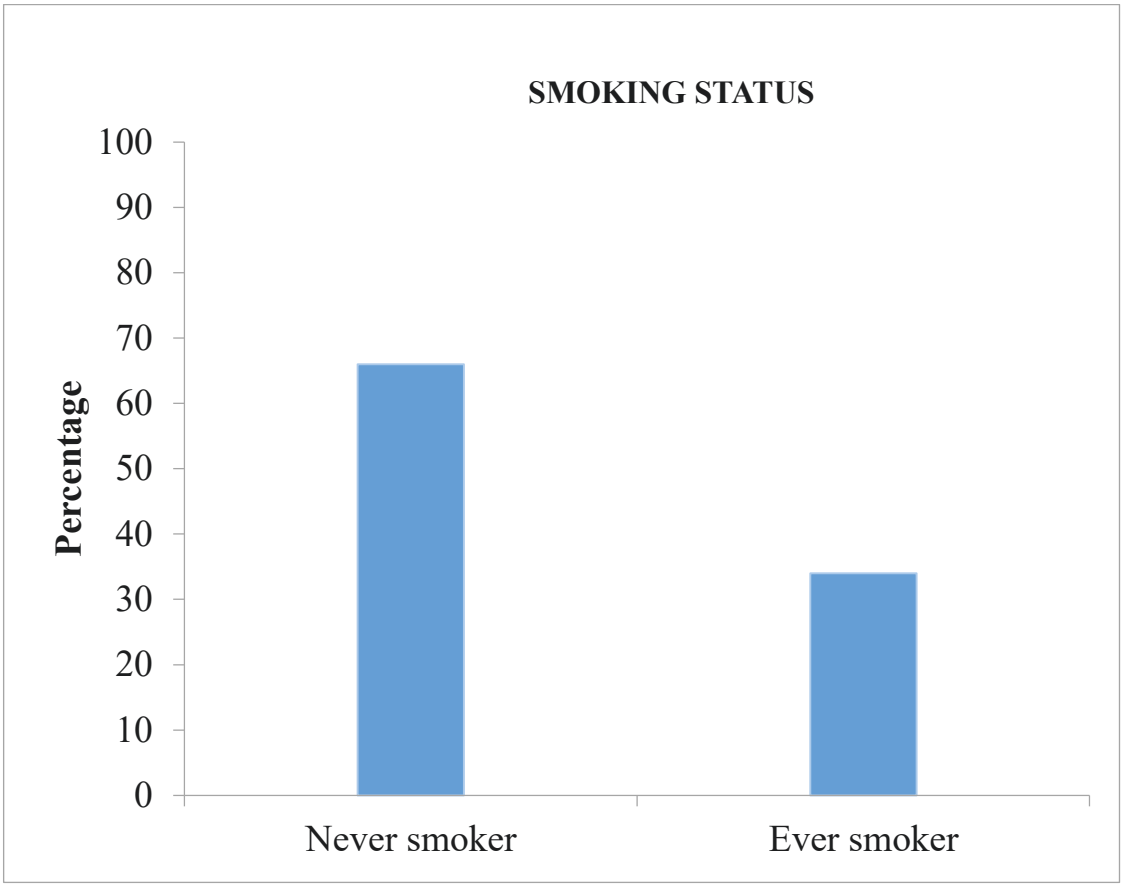

Figure 12 Proportion of bronchiectasis patients in Concord Hospital, by smoking status, July 2011- June 2018

● SEASONALITY

Because of bronchiectasis is a lung disease, seasonality could affect frequency of exacerbations. The flare-ups or exacerbation usually happen when respiratory infection causes inflammation, increase in sputum volume and purulence, increasing cough and fever. These symptoms may occur often during winter when respiratory viruses are more prevalent. Hospital admissions for bronchiectasis are more common in winter and spring than summer or autumn (Bibby et al., 2015). We postulated that, seasonality might affect frequency of admission and LOS. In this cohort, patient admissions were classified into seasons in Australia: *summer*, December to February; *autumn*, March to May; *winter*, June to August; and *spring*, September to November. Total hospital admissions are detailed in Table 3.5. For all bronchiectasis hospitalization during July 2011- June 2018, patients had the highest rate of admission during winter, declined in spring and summer, then slightly increased in autumn. During autumn and winter, patient admissions were approximately 56.2% of all admissions. Figure 13 illustrates the number of admission of bronchiectasis patients on seasonal monitoring during a 6 years period at Concord Hospital.

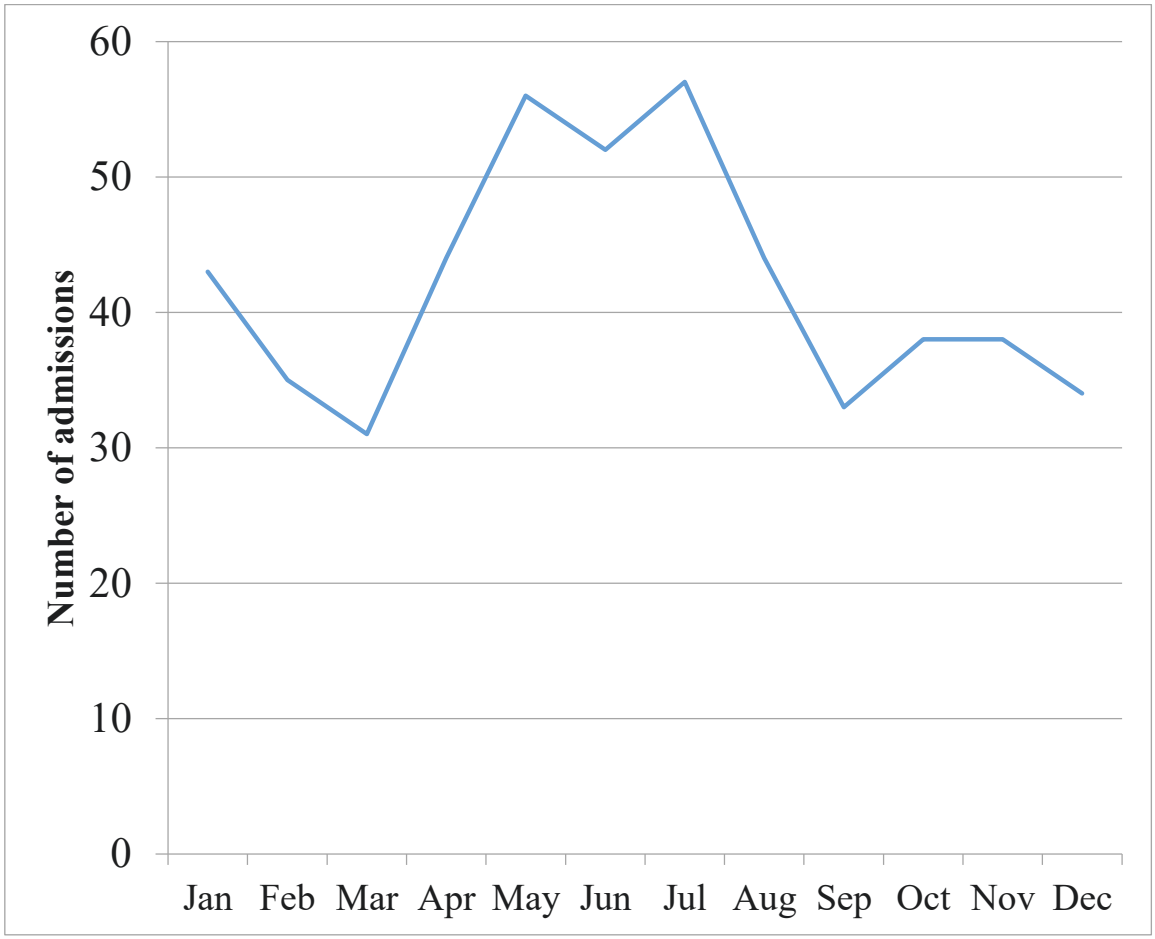

Figure 13 Admissions for exacerbation of bronchiectasis to Concord Hospital, July 2011-June 2018

Table 3.5 Bronchiectasis hospital admissions categorized by seasonality in Concord Hospital during July 2011- June 2018

Season	Months	Number of episodes	Percentage
Summer	Dec - Feb	112	22.2%
Autumn	Mar - May	131	25.9%
Winter	Jun - Aug	153	30.3%
Spring	Sep - Nov	109	21.6%
Total		**505**	

3.4 Conclusion

Rates of hospitalization for bronchiectasis are steadily increasing. In the decade 2006 to 2017, the hospitalization rate of bronchiectasis has been reported to increase from 25 to 34 per 100,000 for females and 12 to 18 per 100,000 for males (AIHW, 2019).In 2018, bronchiectasis had a specific code in the AR-DRG system as E77A (Major complexity) and E77B (Minor Complexity). The ALOS of E77A and E77B had been reported as 8.1 and 4.9 days respectively. In addition, the overall ALOS for all hospitals in 2017-18 was 5.30 days (IHPA, 2019).

Compared with the overall ALOS, the mean of LOS for Bronchiectasis patients with Major complexity is higher than the overall ALOS based on AR-DRG coding system (Kingkam et al., 2017). In this study, 299 patients with 505 inpatient episodes of care were analyzed. The highest rates of admission occurred in age-groups above 60 years old (87.13%). This is in keeping with local and international reports that age contributes to severity of bronchiectasis and is a risk factor for hospital admission (Menéndez et al., 2017). Consistent with AIHW reports, the majority of our cohort was females (58.86%) and most were never smokers (65.60%). For this cohort over the 7 year period of study, hospitalizations were mostly during the cooler months.

CHAPTER 4
Models for Analyzing Patient Length of Stay in Hospital

The main purpose of this chapter is to present the models for investigating the relationship between the actual length of stay in hospital (LOS) and the average length of stay in hospital (ALOS) for bronchiectasis patients based on the group of diseases in the AR-DRG coding system. Although the hospital funding system allocates funding to hospitals associated with the average of length of stay (ALOS) in hospital based on the group of disease or the AR-DRG classification system, bronchiectasis did not have a specific code in the system prior to 2018 (Kingkam et al., 2017). The models in this part may clarify the general idea of how underestimating the actual length of stay in hospital (LOS) of bronchiectasis patients affects the hospital costs. In addition, a multilevel model approach has been used to expand the analysis to include how patient characteristics influence their length of stay in hospital.

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4.1 Average length of stay in hospital (ALOS)

The Australian Refined Diagnosis Related Groups (AR-DRG) classification plays a crucial role in the Australian healthcare system. It is used to classify patients treated in a hospital into groups of diseases whose complexity and costs of care are similar. The assigned AR-DRG coding is part of the determination of the hospital funding for each episode of patient care. The AR-DRGs system is used to ensure that the Medicare reimbursement for the hospital bill is correctly paid. The end of episode of care is used for the purpose of reporting the average length of stay in hospital (ALOS), which refers to the average number of actual lengths of stay in hospital (LOS) that inpatients spend in hospital during the financial year. The ALOS is a well-accepted indicator of hospital efficiency and resources use, and among indicators, it is the simplest and most important indicator for measurement of hospital outcomes (Nakagawa et al., 2011), (AIHW, 2019). This indicator is used for several different purposes such as management of hospital, hospital planning and quality control.

The ALOS is often used for a variety of clinical purposes such as patient flow, considering interventions to reduce discharge delays and evaluating health policy impact. For this reason, accurate ALOS calculations are important and should be considered carefully. For any particular disease, ALOS may not be consistent with its LOS regarding to the AR-DRG classification system, such as when some bronchiectasis patients were recorded as E 65A in the AR-DRG classification system during financial year 2017-2018 .This code had recognized the ALOS as 6.7 days while the actual LOS of these patients may be higher than they were assigned into the AR-DRG system. This may underestimate the cost of high-cost inpatient hospital

services. LOS is a crucial indicator and is mostly used in medical research for analysis of the impact on hospital costs [(Taheri et al., 2000),(Winslow et al., 2002), (Moss, 2018) and (Cadilhac et al., 2019)]. These studies highlighted that a shorter LOS indicates better hospital performance; patients are treated and discharged more quickly and that could point to a hospital's efficiency and lower costs (Langland-Orban et al., 1996), (Shi, 1996), (Brown et al., 2003). The lower LOS may also reflect a better quality of treatment. Patients who recover more quickly may possibly be receiving a better quality of healthcare. On the other hand, a lower LOS could be related to being prematurely discharged from hospital before complete treatment. Additionally, greater LOS may possibly be associated with more complex treatment. Hospitals that treat more severe cases would be expected to have higher values of LOS for this group of patients. In a disease as heterogenous as bronchiectasis, where every patient is different and every exacerbation is different but complexity of both remains high, there is potential for ongoing and systematic underfunding.

Therefore, an important issue is to study factors influencing LOS if the LOS is to be used as a hospital performance measure. In this chapter, the two main purposes were to investigate the relationship between LOS and ALOS of patients who were admitted to Concord Hospital for treatment of bronchiectasis and to explore characteristics that affected this LOS.

4.2 Bronchiectasis in the AR-DRG classification system

Although the AR-DRG is widely used in the healthcare system, it was mentioned in the AR-DRG version 9.0 Final Report of Australian Consortium Classification Development 2016 as lacking clinical distinctiveness (IHPA, 2016). It was noted that Chronic Obstructive Airways Disease (COPD) closely resembles the clinical characteristics of patients with bronchiectasis (exacerbations of cough and breathlessness) but does not exactly mirror the pathophysiology, symptom burden nor LOS. Prior to 2018, bronchiectasis did not have a specific AR DRG and admissions were variably, and inaccurately, coded by comorbidity or diagnosis of "best fit". In this cohort study, there are 299 patients with 505 episodes in Concord hospital during the financial years 2011-2017. Most were coded as COPD (E65A or E65B). The Table 4.1 demonstrates the common groups of respiratory diseases that bronchiectasis patients were often assigned to. Obviously, a Chronic Obstructive Airways Disease Major Complexity (E65A), a Chronic Obstructive Airways Disease Minor Complexity (E65B) are the most common groups of the assigned AR-DRG coding system in this cohort study. The number of episodes for these groups (E65A, E65B) was 217 out of 505 episodes of care and accounted for 42.97% of all episodes.

Table 4.1 The most common assignment for bronchiectasis patients in Concord Hospital July 2011- June 2018

AR-DRG	Description	Number of episodes of care	Percentage
E41A	Respiratory System Disorders, Major Complexity	9	1.78%
E42A	Bronchoscopy, Major Complexity	14	2.77%
E42B	Bronchoscopy, Intermediate Complexity	19	3.76%
E62A	Respiratory Infections and Inflammations, Major Complexity	37	7.33%
E62B	Respiratory Infections and Inflammations, Minor Complexity	10	1.98%
E65A	Chronic Obstructive Airways Disease, Major Complexity	110	21.78%
E65B	Chronic Obstructive Airways Disease, Minor Complexity	107	21.19%
E67A	Respiratory Signs and Symptoms, Major Complexity	7	1.39%
E69A	Bronchitis and Asthma , Major Complexity	8	1.58%
E75A	Other Respiratory System Disorders, Major Complexity	7	1.39%
E76A	Respiratory Tuberculosis , Major Complexity	14	2.77%
	Total	342	67.72%

The top six groups of the AR-DRG codes which patients were mostly assigned to in the system were Chronic Obstructive Airways Disease (E65A, E65B), Respiratory Infections and Inflammation (E62A, E62B) and Bronchoscopy (E42A, E42B). These codes accounted for 67.72% of all admissions. However, the dataset contained some patients admitted to the hospital for a diverse range of other conditions, including J68A (Major Skin disorders), F62A (Heart Failure and Shock, Major complexity) and L60A (Kidney Failure, Major Complexity) as shown in Figure 14. This reflects that sometimes the admission was not driven by the respiratory symptoms and also reflects the co morbidity for this group of patients.

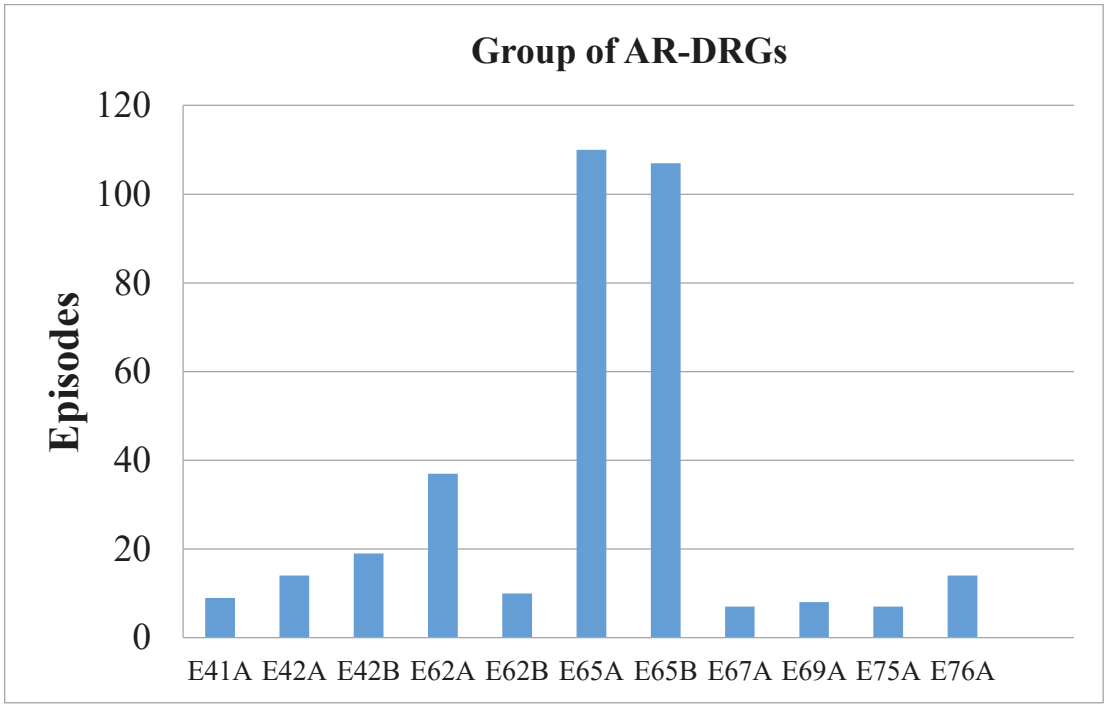

Figure 14 Groups of 8 (AR- DRGs) for 299 bronchiectasis patients in Concord Hospital during July 2011- June 2018

The group of diseases that bronchiectasis patients were recorded in the AR-DRG system after they were discharged from hospital can identify their average length of stay in hospital (ALOS) for that particular financial year. For example, for patients who were diagnosed as E65A (Chronic Obstructive Airways Disease, Major Complexity) and discharged in the financial year 2016, their average length of stay in hospital (ALOS) would be recorded in the system as 7.1 days even if their actual length of stay in hospital (LOS) was more than 7 days. The Australian Hospital funding system allocates funding to hospitals based on the average of length of stay in hospital (ALOS) of the AR-DRG allocated. Hospital funding system allocates funding to hospitals associated with the average of length of stay in hospital (ALOS) based on the group of disease or the AR-DRG coding system. If the AR-DRG codes do not adequately control for differences between patient groups or differences in hospital services, payments could be too low for highly complex inpatient care or too high for less-complex inpatient care. The challenges are to ensure that hospitals have operated under appropriate funding and to balance between hospital activity and expenditure on care that is complex enough. For this reason, it is vital for bronchiectasis patients to have the appropriate AR-DRG code. In the AR-DRG v 9.0 Final Report 2016, a determination was made for the assignment of a distinct AR- DRG code for bronchiectasis in the health system. Finally in financial year 2018, bronchiectasis has been assigned the new codes in the AR-DRG classification system as E77A for Major Complexity and E77B for the Minor Complexity.

4.2.1 Bronchiectasis length of stay in Concord Hospital (2011-2018)

Length of stay in hospital is one marker of quality of healthcare. Length of stay is related to the annual cost of hospital beds. Shorter stays can increase the availability of hospital beds for providing care for other patients. Length of stay is also related to the AR-DRG coding as represented in 4.1.1. The length of stay of 299 bronchiectasis patients with 505 admissions in Concord Hospital during July 2011-June 2018 have been reported to provide a clear picture of the relationship between their actual length of stay (LOS) and their average length of stay in hospital (ALOS), based on the AR-DRG system. This data has been included in the ABR data set. All episodes have a length of stay in hospital of more than one day (LOS≥ 2). There were 206 occasions of repeated admissions. Length of stay is summarized in Table 4.2 and describes that the maximum LOS was 93 days while a maximum of ALOS was about 28.80 days. The differences between the actual longest stay in hospital (LOS) and the largest ALOS that they were grouped in the AR-DRG system were large. The mean of the actual length of stay in hospital (LOS) of bronchiectasis patients in this particular group is 11.19 days while the mean of their average length of stay in hospital (ALOS) is about 7.5 days. Clearly, the mean LOS is higher than the ALOS mean recorded in the AR-DRG system. Bronchiectasis patients are prone to have an actual length of stay in hospital more than the average length of stay in hospital for the AR-DRG groups to which they were assigned, even including the outlier cases. This suggests that the AR-DRG codes that they were recorded as in the healthcare system may not be suitable for this disease.

Table 4.2 Bronchiectasis patient length of stay in Concord Hospital, July 2011-June 2018

Variables	Minimum (days)	Mean (days)	Maximum (days)
LOS	2.00	11.19	93.00
ALOS	1.00	7.50	28.80

Additionally, the distributions of ALOS and LOS are shown as histograms in Figure 15 and 16. The histograms indicate that the distribution of length of stay is the skewed right. Most values of LOS were less than 40 days while most of ALOS were less than 15 days. This leads to the assumption that the actual length of stay in hospital (LOS) of bronchiectasis patients in Concord Hospital during July 2011- June 2018 may be higher than the length of stay in hospital (ALOS) expected following the AR-DRG system. Moreover, it could be assumed that longer LOS was associated with higher hospital costs because patients with longer LOS were more likely to receive more intensive treatments.

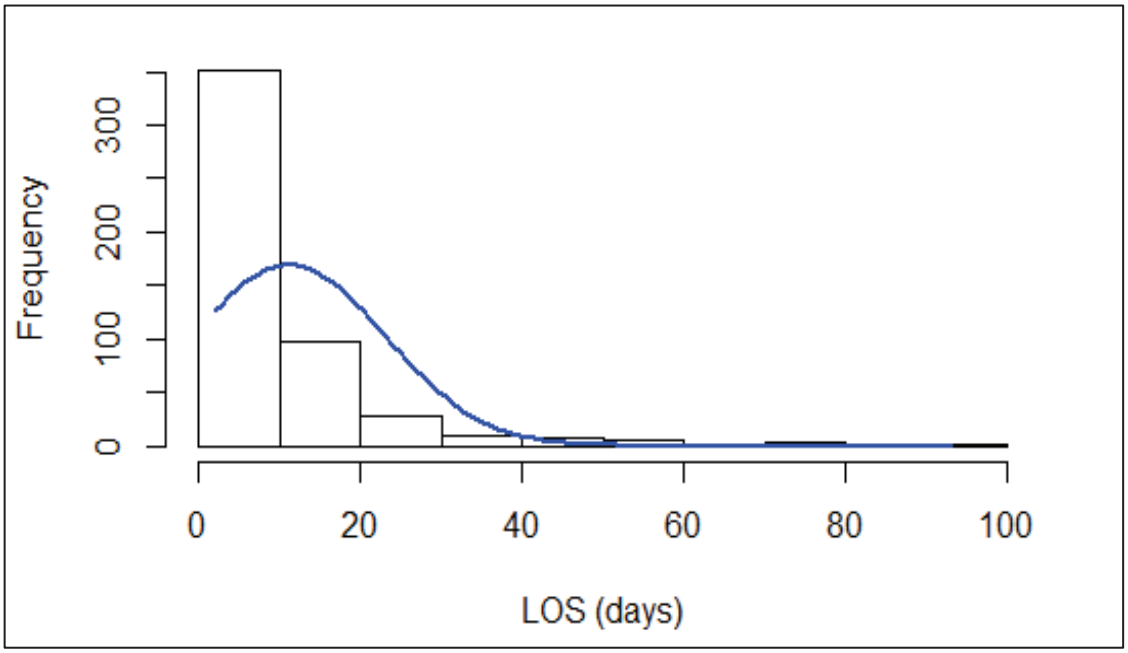

Figure 15 LOS histogram with a normal distribution curve superimposed for bronchiectasis patients, Concord hospital, July 2011- June 2018

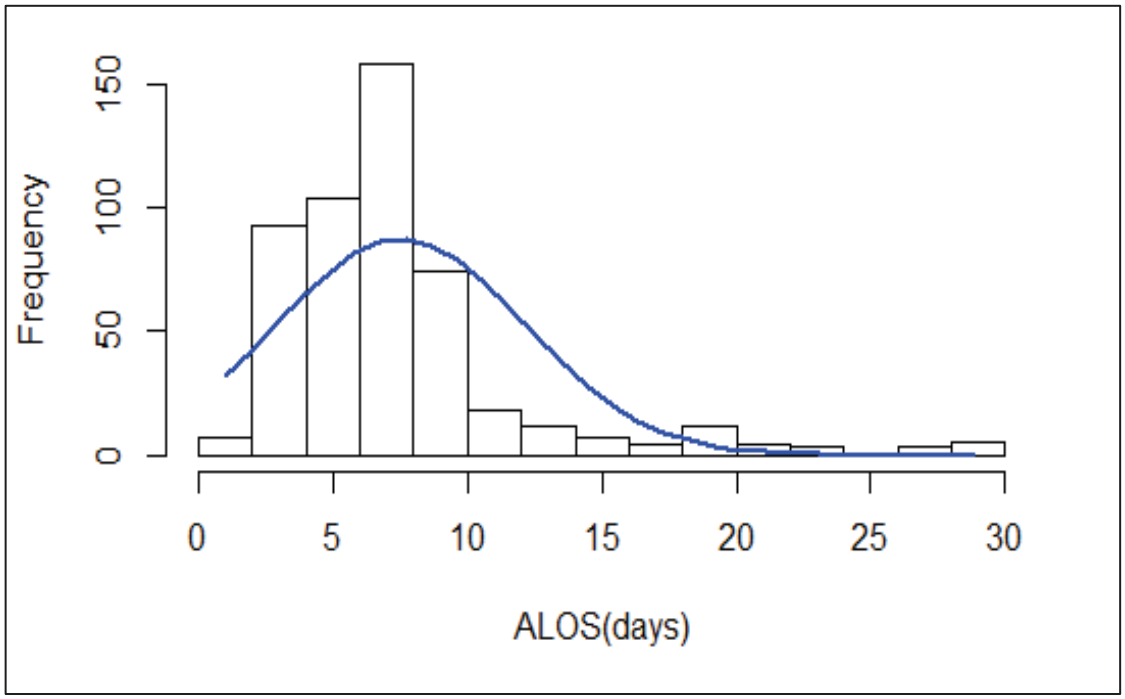

Figure 16 LOS histogram with a normal distribution curve superimposed for bronchiectasis patients, Concord hospital, July 2011- June 2018

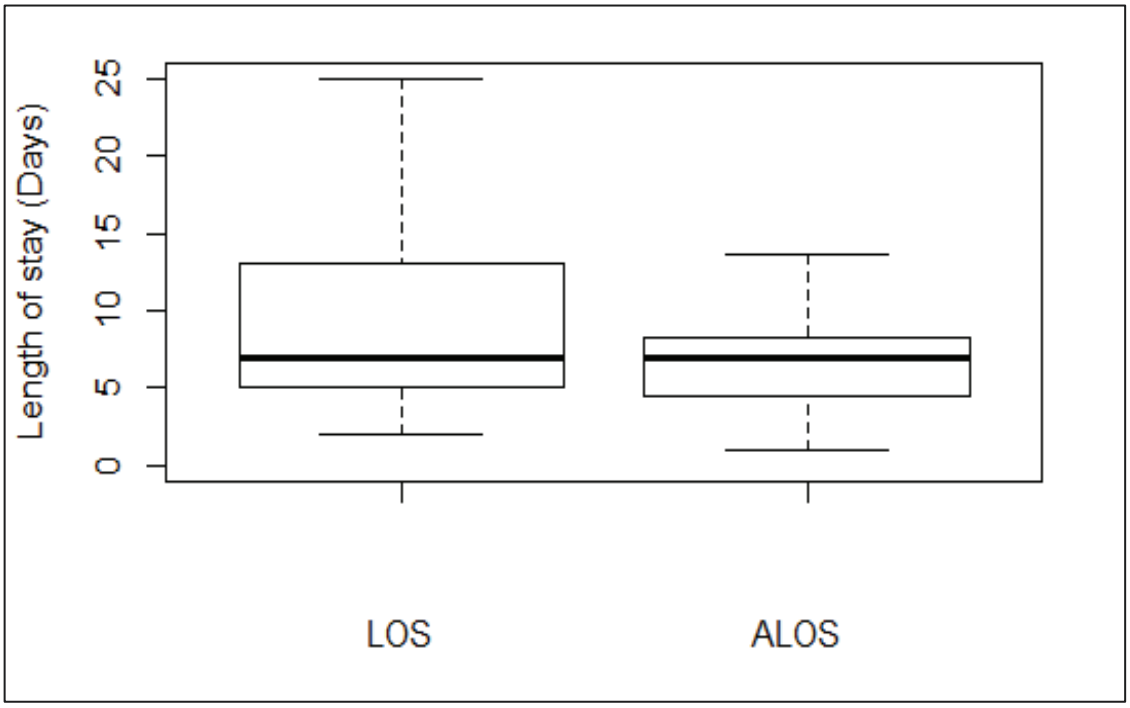

Figure 17 The boxplots of the actual length of stay (LOS) and the average length of stay (ALOS) in hospital of bronchiectasis patients in Concord Hospital, July 2011- June 2018

As above, the boxplots demonstrate that most of patients have a length of stay in hospital (LOS) less than 15 days. The long upper whisker in both groups suggests that the length of stay is varied amongst the upper quartile group. The first and third quartiles of ALOS are 4.5 days and 8.2 days respectively while the median is 6.9 days. In addition, for $LOS \leq 15$, there are 411 admissions out of 505 admissions (81.39 %). On the other hand, LOS for this group is much higher than ALOS; the first quartile and third quartile are 5.0 days and 13.0 days with 7.0 days for the median. This also confirms that bronchiectasis patients tend to have longer stays than their average length of stay in hospital.

Bronchiectasis has been recorded in the AR-DRG coding system as E77A and E77B for the July 2018 – June 2019 period. A comparison of the ALOS of bronchiectasis between the common group of diseases to which bronchiectasis patients were mostly assigned before July 2018, the actual average of LOS and the ALOS of bronchiectasis in the AR-DRG coding system in July 2018- June 2019 has been represented in Table 4.3. It shows that bronchiectasis (E77A) has an ALOS higher than the ALOS of groups of diseases to that patients were likely coded in the AR-DRG classification system especially with the two most common disease groups (E62A, E65A). In addition, the mean of the actual length of stay (LOS) of this group of bronchiectasis patients is about 11.19 days which is greater than both the average length of stay (ALOS) that they were assigned into a variety group of diseases during 2011-2017 financial

years and the ALOS of bronchiectasis in the AR-DRG system in financial year 2018. The relationship between the ALOS of groups of diseases to which patients were likely coded in the AR-DRG classification system and the actual LOS of bronchiectasis in this cohort will be addressed in section 4.4.

Table 4.3 Comparison of ALOS (days) for bronchiectasis (E77A) compared with the two most common disease groups (E62A, E65A) into which bronchiectasis patients were likely to have been coded (2018-19)

Group of disease (AR-DRG , 2018-19)	Mean LOS (days)	ALOS (days)
● Bronchiectasis, (E77A)	11.19	8.1
● Respiratory Infections and Inflammations, (E62A)	-	6.4
● Chronic Obstructive Airways Disease, (E65A)	-	6.1

4.3 Bronchiectasis Patient Characteristics

Bronchiectasis is a very heterogenous disease both in underlying aetiology, pathophysiology and patient characteristics. Other groups have reported some of the individual patient characteristics that contribute to length of stay in hospital (LOS). These characteristics include age-groups, gender, payment classification, source of referral, specialty of physicians, ect [(Lave and Frank, 1988), (Liu et al., 2001), (Badgal, 2015), (Aghajani and Kargari, 2016), (Eckert et al., 2017)]. We sought to similarly stratify our cohort. These characteristics used in this study are represented as in the following section.

● **GENDER**: From the 16th December 2011 to the 22nd June 2018, there were 123 male and 176 female bronchiectasis patients in Concord Hospital. Figure 10 shows that females, the majority of bronchiectasis patients, accounted for 58.86% of all patients. Comparison of LOS by gender is presented in Figure 18. This figure shows that females have higher LOS than males. Moreover, female has the number of admissions (293 admissions) higher than male (212 admissions). This concurs with the study of the AIHW in 2017-18 which indicated that the hospitalization rate of female patients with a principal diagnosis of bronchiectasis was twice as high as for males (AIHW, 2019).

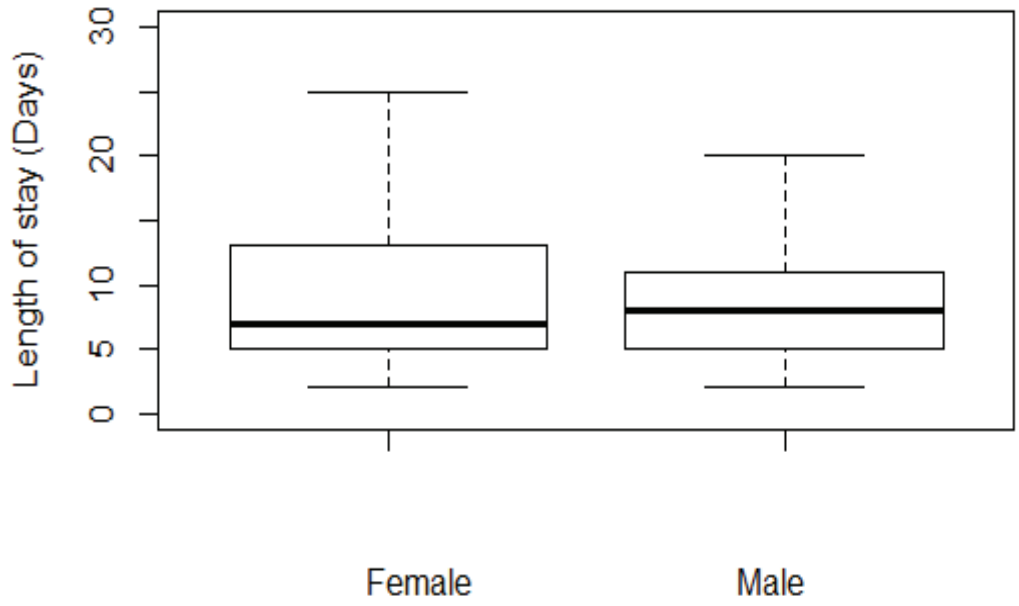

Figure 18 LOS of bronchiectasis patients by gender, Concord Hospital during July 2011- June 2018

●**AGE-GROUPS :** Older patients stay longer in hospital independent of the cause for their admission (Liu et al., 2001). For this study, we anticipated that age would influence LOS for bronchiectasis. The 505 episodes of care of bronchiectasis patients in Concord hospital (July 2011- June 2018) were classified into three groups: (1) 20- 39 years, (2) 40-59 years, and (3) 60 years and over, as shown in figure 11. During the period of study, many patients had more than one episode of admission per year. The elderly patients were the majority of admissions for this cohort. From 505 episodes of care, there were 440 episodes for patients who were 60 years and older. The elderly age group was accounted for 87.13% while the youngest group was accounted for only 5.35% of all episodes. However, in general, the mean of LOS of the elderly patients was shorter (11.20 days) than the younger groups (G1:18.72 days and G2:12.93 days).

Table 4.4 Comparison of age groups of bronchiectasis patients during July 2011- June 2018 in Concord Hospital

Age-Groups	Episodes	Percentage
Group1(20 −39)	27	5.35
Group2(40-59)	38	7.52
Group3(≥ 60)	440	87.13

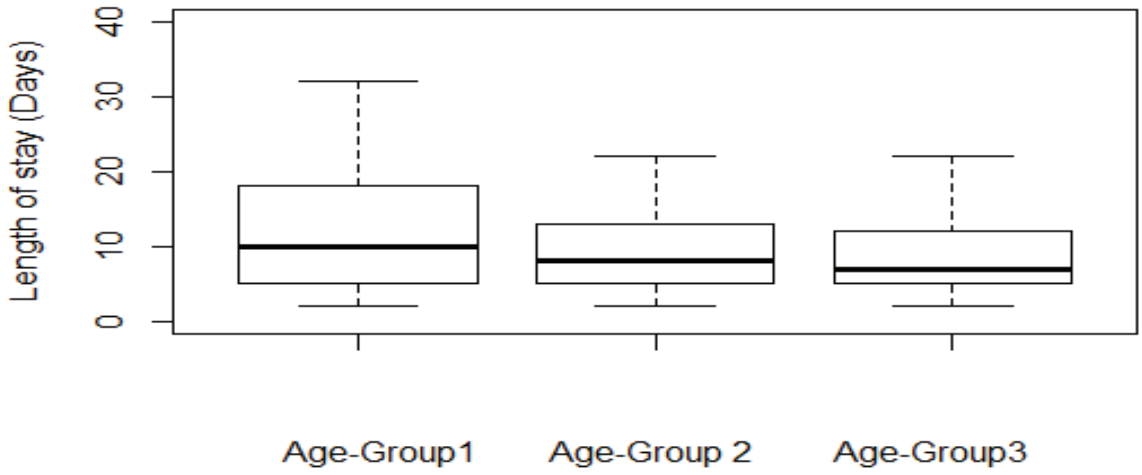

Figure 19 Boxplots of LOS by age groups of bronchiectasis patients in Concord Hospital (July 2011- June 2018)

● **SMOKING STATUS**: As bronchiectasis is a chronic respiratory disease, smoking is assumed to be an important factor for the disease, potentially affecting both the frequency hospitalization events and severity. There is evidence that cigarette smoking and passive smoking exacerbates respiratory conditions, however, a definitive causal link between smoking status and bronchiectasis has not been shown (AIHW, 2019). This study provides an analysis of the relationship between patients' smoking status and their LOS. Groups of bronchiectasis patients' smoking status are categorized into never-smoker, ever smoker, as in Figure 20. In addition, Figure 12 shows that most of bronchiectasis patients had not been smokers (65.55%).

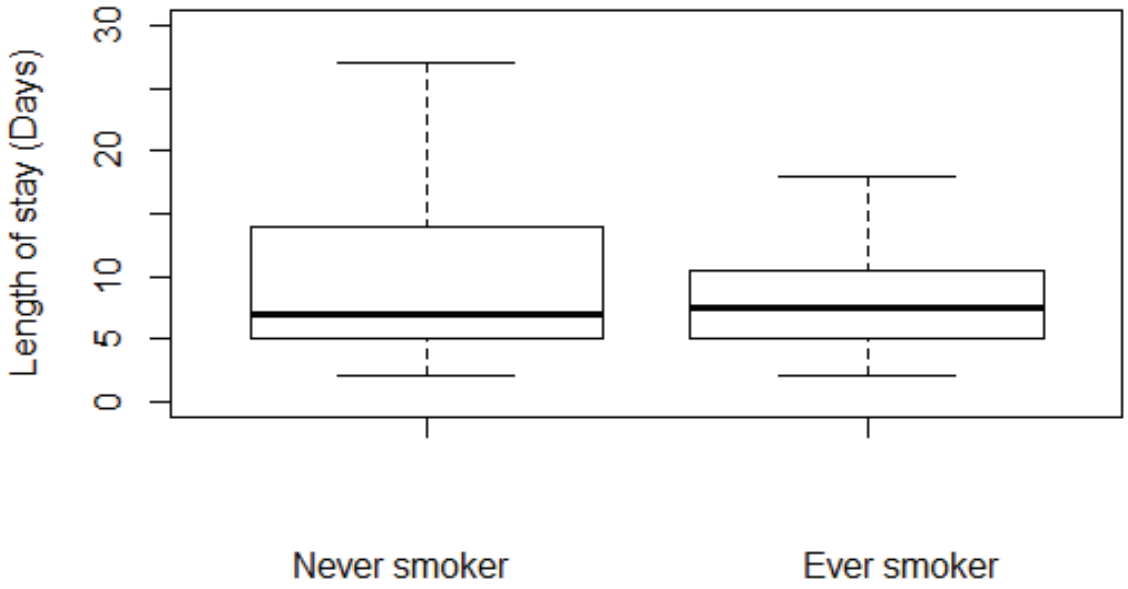

Figure 20 LOS of Bronchiectasis patients by smoking status, Concord Hospital, July2011-June 2018

●**REGISTRY STATUS:** During the 16th December 2011 to the 22nd June 2018 period, there were 505 episodes of care with 299 bronchiectasis patients in Concord Hospital. Of the 299 patients included in this study, most were not participants in the ABR registry (270 patients). There were approximately 10% of all patients for participants with the ABR registry. Boxplots show the distribution of LOS for both groups as Figure 21. Overall, the ABR registry group of patients had lower LOS than the non ABR registry group.

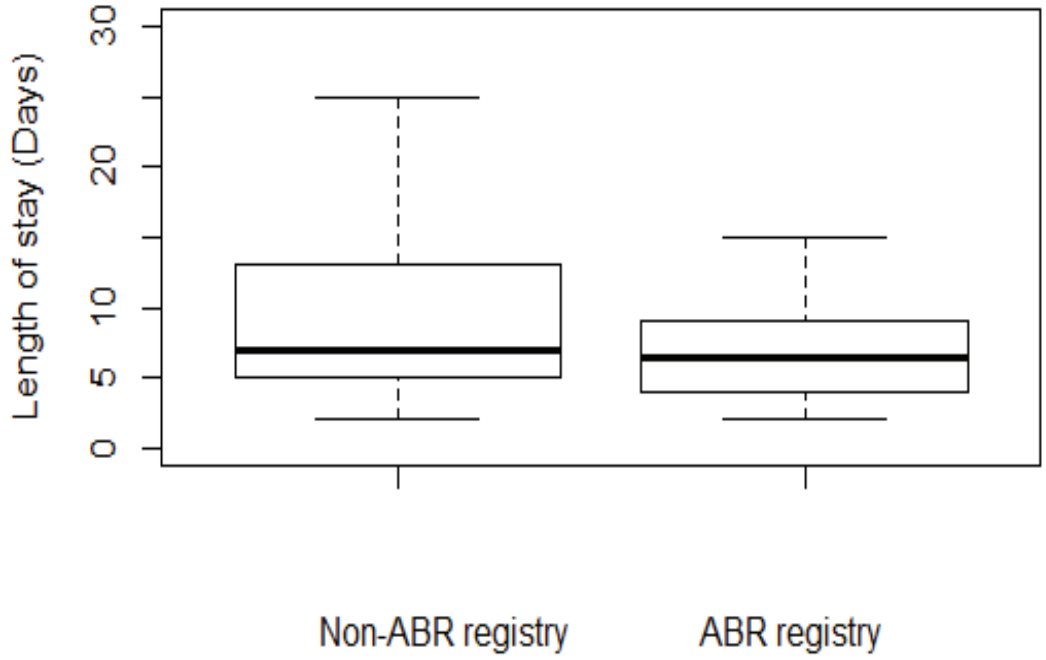

Figure 21 Bronchiectasis patients by registry status, Concord Hospital, July 2011- June 2018

4.4 Model Assumptions

In this chapter, the relationship between the length of stay in hospital (LOS) of bronchiectasis patients and their average length of stay in hospital (ALOS) based on the AR-DRG system has been examined. As first, linear regression model is familiar and straightforward to implement in order to investigate whether the actual length of stay (LOS) is consistent with the average of length of stay (ALOS) to which they were assigned in the AR-DRG coding system. The model assumption can be simply described as $LOS = \beta_0 + \beta_1 ALOS + \varepsilon$ where the error term is assumed to be normally distributed with mean 0 and constant variance σ^2, i.e. $\varepsilon \sim N(0, \sigma^2)$. If the payment system functions as nominally intended, LOS would be approximately equal to ALOS, so we might expect β_0 to be close to zero and $\beta_1$to be close to 1. Where the linear regression model applied to analyze the length of stay in hospital of bronchiectasis patients may perform poorly is when the residuals show clear signs of non-normality, such as skewness.

When this occurs, the data can be log transformed and a simple linear regression model looking at log (LOS) and log (ALOS) applied. This typically reduces skewness, making the skewed distribution more symmetric and closer to normality. The models can be checked for the normality assumption and their outcomes compared by using residual plots, histograms and QQ-plots.

To study the relationship between the length of stay in hospital (LOS) of bronchiectasis patients and their average length of stay in hospital (ALOS) based on the AR-DRG system. Regarding the relationship between LOS and ALOS, the LOS may be influenced by other factors such as bronchiectasis patients in the same hospitals or wards might be correlated due to hospital policy. In addition, the length of stay in hospital (LOS) for patients visiting the same hospitals may not be different as much as patients visiting different hospitals. In this case, multilevel models can be used to analyze the data set instead of the conventional linear regression models. An expansion of analysis in this part is to use the multilevel model for analysis crucial factors impacts on bronchiectasis patients' length of stay in hospital. These factors are considered such as patient age at admission date, gender and patient's smoking status. Previous studies support the inclusion of these factors into the model since the prevalence of bronchiectasis is higher in males and more severe in females (Vidaillac et al., 2018a). Additionally, the condition is most common in the elderly (AIHW, 2019) and smoking is known not to cause bronchiectasis, but it can make the symptoms much worse (ELF, 2018).

The purpose of this study is to investigate whether or not these factors have an impact on bronchiectasis hospital LOS since there is lack of evidence that patient characteristics significantly influence the hospital LOS. The assumption is that the different admissions between patients may influence the length of stay in hospital (LOS). To analyze this assumption, the two-level model can be applied to this study. The multilevel model is simply written with two-level model as follow:

Let Y_{ij} be the response variable of i^{th} admissions (level-1 or *individual level*) for the j^{th} patients (level-2 or *group level*).
The model can be defined as:

$$Y_{ij} = \beta_{0j} + \beta_1 X_{ij} + \varepsilon_{ij} .$$

$$\text{by writing} \quad \beta_{0j} = \beta_0 + u_j .$$

Where X_{ij} represents the single continuous explanatory variable defined at level 1. The i and j subscripts on X show that its values vary from individual to individual within a group.

The group level residual u_j is assumed to follow a normal distribution $u_j \sim N(0, \sigma^2_u)$. The term ε_{ij} is an individual level residual with the assumption $\varepsilon_{ij} \sim N(0, \sigma^2_e)$. For this model, the overall (cross-group) relationship between the bronchiectasis hospital lengths of stay (Y) and patient characteristics (X) have been represented by a straight line with the intercept β_{0j} and slope β_1. However, the intercept for a given group patient j is $\beta_0 + u_j$, which will be higher or lower than the overall intercept β_0 . Here, σ_u^2 represents the between-group (patient) variance based on departures of group means from the overall mean and σ_e^2 represents the within-group (patient) variance based on individual departures from group means. The intra-class correlation between two individuals from the same groups is denoted by $\rho\left(Y_{ij}, Y_{kj}\right) = \frac{\sigma_u^2}{\sigma_u^2+\sigma_e^2}$. The ρ value has ranges from 0 (no group differences, i.e. σ_u^2 = 0) to 1 (no within-group differences, i.e. $\sigma_e^2 = 0$). For example, if the ρ = 0.6, it would say that 60% of the variation is between groups and 40% for within-groups. A larger ρ value indicates that randomly chosen individual in the same group are more closely related. The model can be fitted by using MLwiN, which is a specialized software package for fitting multilevel models (Rasbash et al., 2009). MLwiN was designed to support applied multilevel models for both continuous or binary responses. It can provide fast estimation by iterative generalized least squares (IGLS) resulting in maximum likelihood estimation and by Bayesian estimation using Markov chain Monte Carlo (MCMC).

4.5 Results

This section is provided the two main results as follows; 1) the relationship between the LOS and ALOS based on the AR-DRG system and 2) the relationship between LOS or ALOS and their patient characteristics.

4.5.1 Regression models for analyzing the relationship between LOS and ALOS

The simple linear regression model and log transformed model were carried out to examine how well the average length of stay (ALOS) in the AR-DRG system predicted the length of stay in hospital (LOS) of bronchiectasis patients. The main purpose for this analysis is to explore whether or not the ALOS is consistent with the actual LOS. At first, the relationship between ALOS and LOS were assumed to be in a linear relationship as $Y = \beta_0 + \beta_1 x$ where Y is the expected length of stay LOS with each values of predictor ALOS with the intercept β_0 and slope β_1. Then, the log transformed model was applied to the linear regression model as the results below:

Table 4.5 Models Summary

Model	Sample Size	Multiple R Squared	Adjusted R Squared	Regression Std. Error
Model 1 Simple linear Regression	505	0.2805	0.2790	10.12
Model 2 Log transformed model	505	0.2510	0.2495	0.6596

Table 4.6 Parameter Estimates

Model	Estimate	Std. Error	t- value	Pr(>|t|)
Model 1 (Intercept)	0.9379	0.8957	1.091	0.276
Model 2 (Intercept)	0.6510	0.1144	5.693	0.000
Model 1 ALOS	1.3668	0.0976	3.758	0.000
Model 2 ln(ALOS)	0.7635	0.0588	-4.022	0.000

Note: 1) Response variables: Model 1: LOS, Model 2: ln(LOS)

2) t- test for (intercept) β_0 =0 and (slope) β_1 =1

Table 4.7 Analysis of variance table

Model	DF	Sum Sq	Mean Sq	F value	Pr(>F)
Model 1 ALOS	1	20084	20084	196.1	0.000
Residuals	503	51524	102		
Model 2 ln(ALOS)	1	73.32	73.32	168.5	0.000
Residuals	503	218.82	0.44		

The results in Table 4.7 confirm that the simple linear regression model (Model 1) and the log-log linear regression model (Model 2) have statistical significance in predicting the length of stay in hospital of bronchiectasis patients by a significant predictor ALOS. The t-test in Table 4.6 confirms that there is significant evidence to suggest that the slope coefficients for both models are not 1 ($\beta_1 \neq 1$). The slope coefficient (β_1) of Model 1 and Model 2 shifts higher than the expected line. However, the residual plot of the simple linear regression model (Model 1) in Figure 22 does not support the normality assumption.

In addition, the Q-Q plot in Figure 24 shows that the points are not close enough to a straight line. Both suggest that the normality assumption seem implausible. Since the data is a right-skewed distribution, the log transformed model (Model 2) was applied to reduce right skewed data. As seen in Figure 23, the residual plots against fitted values for the log transformed model (Model 2) suggest that the zero mean assumption seem to be much more reasonable compared with the residuals plots of simple linear regression model (Model 1) in Figure 22. Additionally, the Q-Q plot of the log transformed model (Model 2) in Figure25 demonstrates that the points lying close to the line support the normally distributed assumption while the Q-Q plot of the simple linear regression model (Model1) in Figure 24 throws some doubt on the normality assumption. For this comparison, it suggests that the log transformed model (Model 2) seems to be suitable to predict the relationship between the LOS and ALOS.

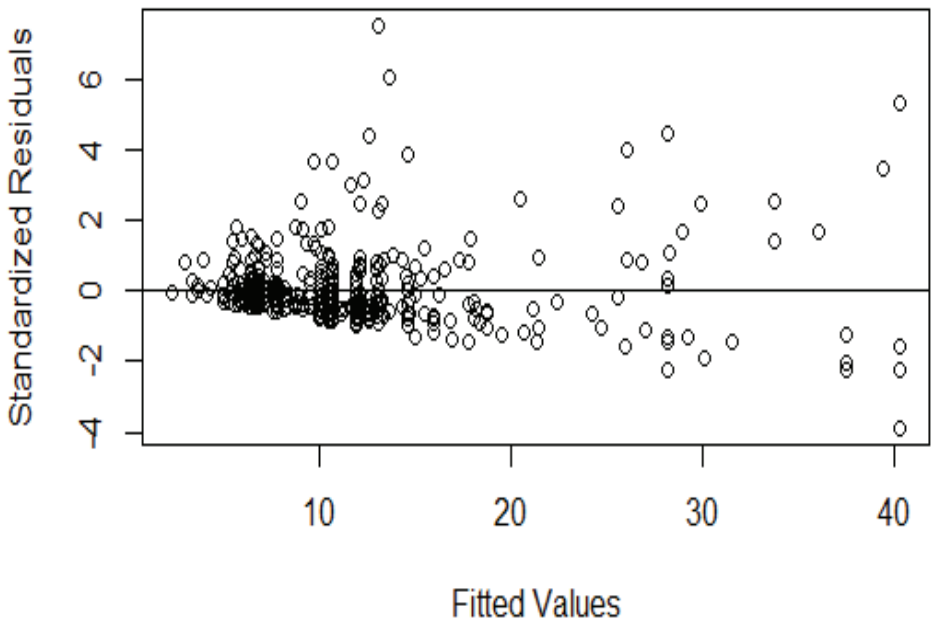

Figure 22 Residuals VS fitted Values for simple linear regression model

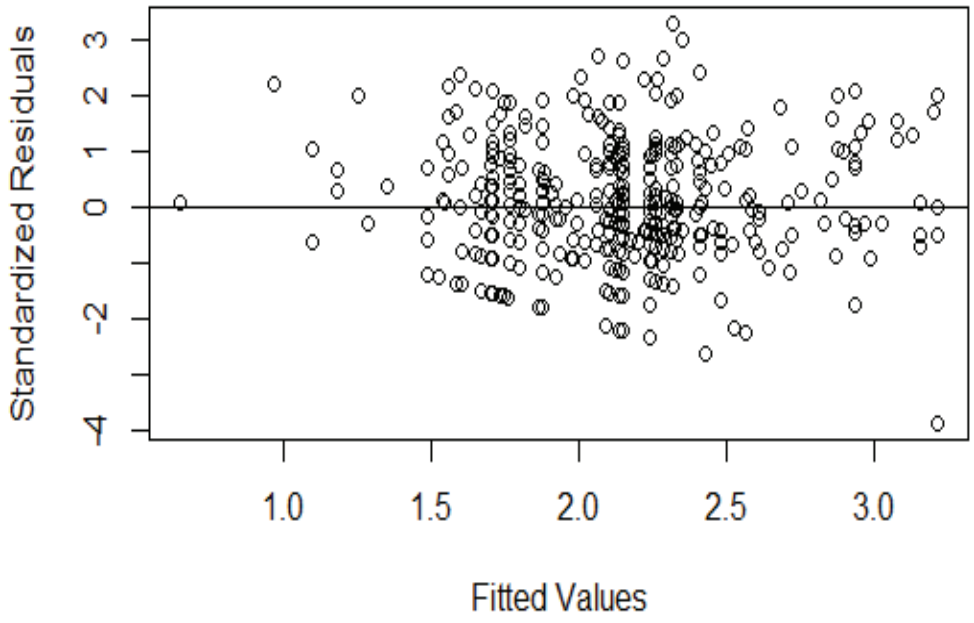

Figure 23 Residuals VS fitted values for log-log linear regression model

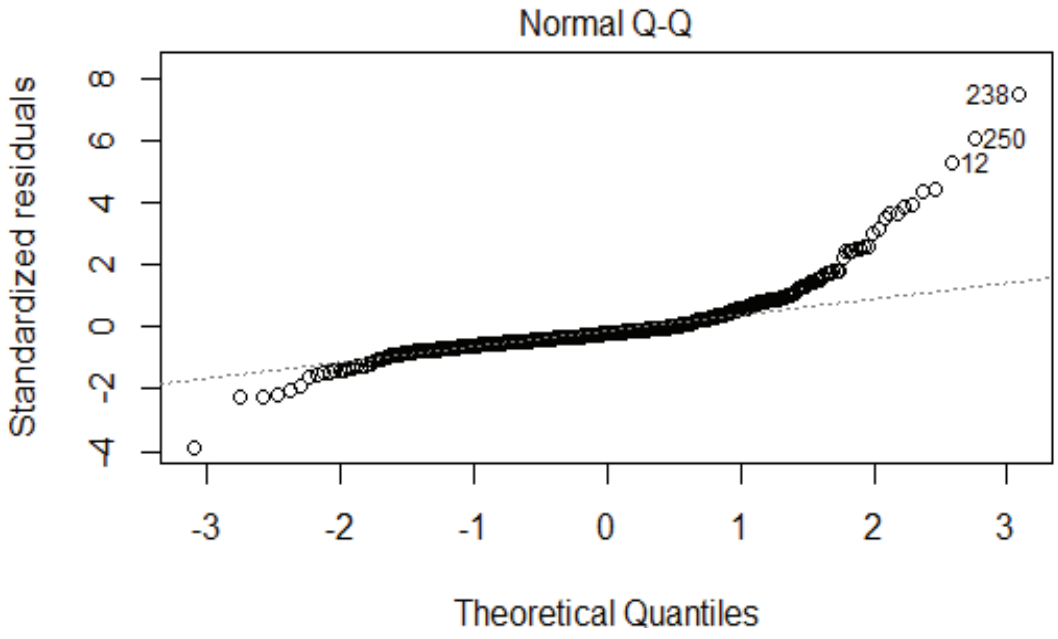

Figure 24 Q- Q plot for simple linear regression model

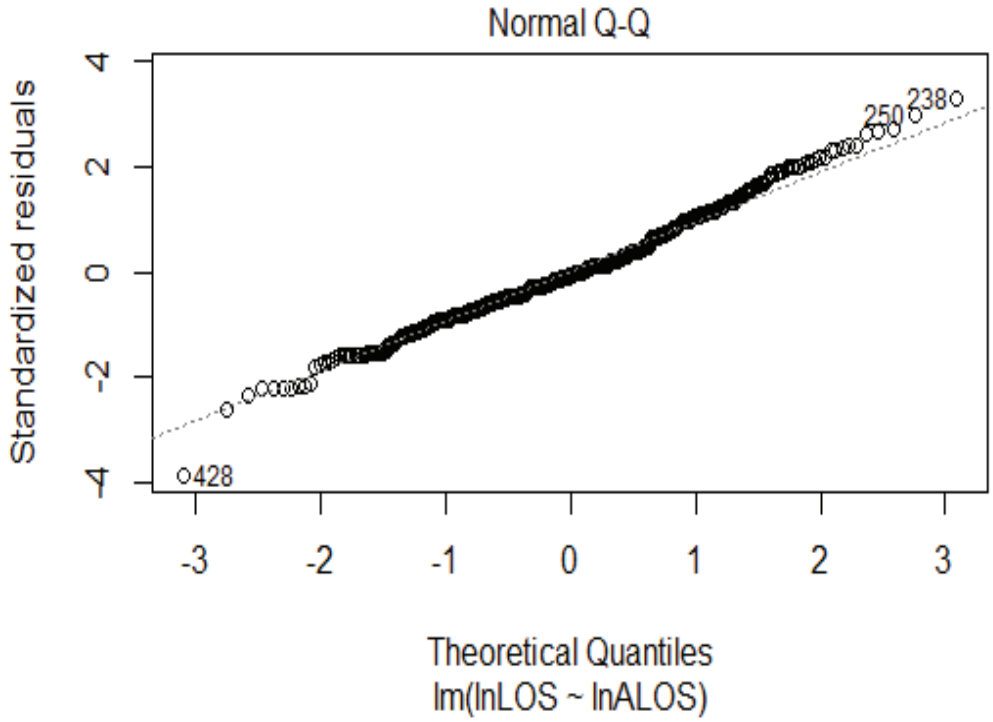

Figure 25 Q-Q plot for log- log linear regression model

In conclusion, the results indicated that the linear regression model (Model1) has statistical significance in predicting the hospital LOS of bronchiectasis patients by a significant predictor ALOS and there is significant linear correlation. However, the residuals plot (Figure 24) is not obviously supporting the normality assumption. Whereas, the log transformed model (Model 2) is more appropriate for examining the relationship between the hospital LOS and ALOS of bronchiectasis patients assigned to the AR-DRG coding system. For this analysis, the results of the log transformed model have demonstrated that the hospital LOS for bronchiectasis patients is shifted significantly higher than the ALOS associated with the AR-DRG classification system. By implication, patients admitted for bronchiectasis stay longer in hospital than predicted based on the ARDRGs available. In addition, the complexity of these admissions is under recognized and the admissions are underfunded. In particular, the admission has equal and less than 15 days for most of patients (75%). In financial year 2018, bronchiectasis has had a specific code in the AR-DRG classification system as E77A and E77B. This system has recorded the ALOS for bronchiectasis (major complexity) as 8.1 days. As Figure 26, it indicates that the new code is related with the under-estimated the resources associated with patients' length of stay in hospital (LOS). This may imply that the cost of the hospital treatment for inpatient care of bronchiectasis patients is more likely to be higher than the hospital cost based on their assigned AR-DRG classification system.

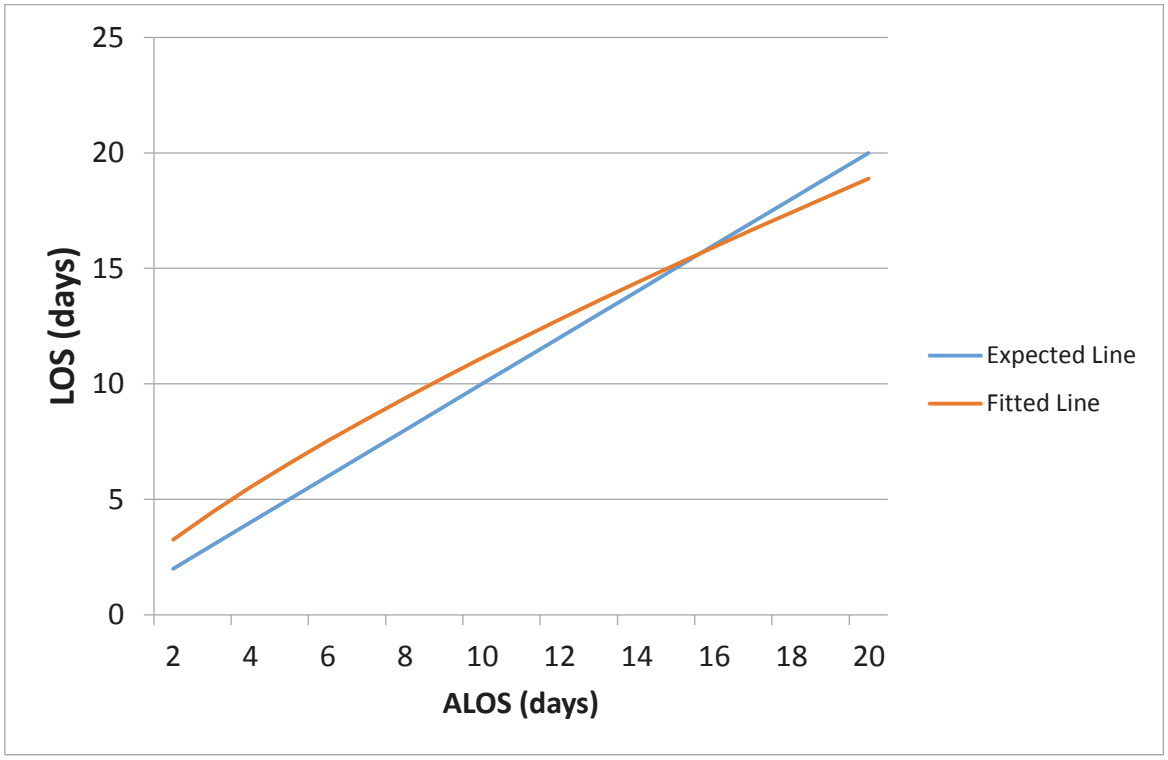

Figure 26 The relationship between the LOS and ALOS of bronchiectasis patients in Concord Hospital (July2011- June 2018) by the log transformed model

4.5.2 Two–Level hierarchical models for investigating the relationship between LOS and ALOS

One application of the multilevel model is for the analysis of repeated data (Griffiths et al., 2004). The repeated episodes of bronchiectasis patients in this cohort have been analyzed with the multilevel model to consider the factors influencing the length of stay in hospital. This is achieved by treating the ln LOS as the response variable and the ln ALOS as a predictor variable. Further predictor variables can be added into the model, including patient characteristics and season. These predictor variables have been introduced in this section as below:

- Gender
- Age: patients' age on admission date were categorized into 3 groups; Group1:20- 39, Group2:40-59, Group3:≥60
- Smoking status: patients were distinguished into two categories; patients who have ever been smoked, patients who never smoked as recorded on their hospital admissions.
- Registry status: some patients in this cohort were participants in the ABR registry but most of them in this cohort were not members of the ABR registry.
- Seasonality: season when patients were admitted to the hospital

This cohort consisted of 229 bronchiectasis patients with 505 admissions (episodes). The effect of patient characteristics and season were modeled with the simple two- level model structure: episodes (level 1) nested within patients (level 2). For the i^{th}episode in the j^{th} patient, the two-level model can be specified as a single composite model:

$$\ln LOS_{ij}=\beta_0+\beta_1 \text{Patient characteristics}_j+u_j+e_{ij}.$$

The model can be thought of consisting of two components: a fixed part which specifies the relationship between the mean of lnLOS and predictor variables, and a random part that contains the residuals. The fixed part is $\beta_0+\beta_i X_j$ $(X_{ij}-\text{the covariates})$ with fixed part parameters β_0, β_1.The random part is u_j+e_{ij} with the random part parameters $\sigma^2{}_u$ and $\sigma^2{}_e$. $MLwiN$ has been used to carry out a multilevel analysis of this data set as follows. At first, three models have been represented as Table 4.8-4.10: **Model 1**) one-level model with one predictor variable (lnALOS), **Model 2**) the empty multilevel model and **Model 3**) the two-level model with one predictor variable (lnALOS). The three models are presented below. The predictor variables (patient characteristic and season) have been considered for how they may affect the length of stay in hospital of bronchiectasis patients, one by one. The relationship between hospital LOS and hospital ALOS has been performed as linear regression model in the Section 4.5.1: $\ln LOS=\beta_0+\beta_1 \ln ALOS+\varepsilon$. The log transformed model was extended to two-level model as **Model 3**, lnALOS has been added to the empty model as shown in Table 4.9. The multilevel model for the relationship between LOS and ALOS can be written as: $\ln LOS_{ij}= \beta_0+\beta_1 \ln ALOS_{ij} + u_j + \varepsilon_{ij}$. The model allows the intercept to vary across group (patient).

Models for investigating the relationship between LOS and ALOS

Firstly, the results of the simple one level model (**Model 1**) was carried out by using the MLwiN as Table 4.8 below.

● **Model 1:** single-level model with one predictor variable (lnALOS)

The results show equivalent parameter estimates values as in the Table 4.6 for the log-log linear regression model. They indicate that on average one unit increase in lnALOS increases lnLOS by 0.7635 units. The variance is 0.4333. Based on the assumption that the episodes for the same patients are often more similar than randomly selected episodes from different patients and the variances may be different from the single level model, then, the two-level model was carried out as the Table 4.9 and Table 4.10

Table 4.8 single-level model with one predictor variable (lnALOS)

Model 1: $\ln LOS_i = \beta_0 + \beta_1 \ln ALOS_i + \varepsilon$.

Parameters	**Coefficient**	**S.E.**
Intercept (β_0)	0.6510	0.1141
Coefficient of lnALOS (β_1)	0.7635	0.0587
	Variance Component	**S.E.**
σ^2_e	0.4333	0.0273
Deviance 1010.7963		

● **Model 2:** the simplest multilevel model

The simplest multilevel model or the random intercept model with no predictor variable is called the empty intercept model. In this study, two models have been presented as **Model 2.1**) $\ln LOS_{ij} = \beta_0 + u_{oj} + e_{ij}$, and **Model 2.2**) $\ln ALOS_{ij} = \beta_0 + u_{oj} + e_{ij}$. Table 4.9.1-4.9.2 show the results from fitting a random intercept model (Level-1: episodes, Level-2: patients) with no predictor variables, but estimates the total variance of the response variable, and distinguish it into within group (e_{ij}) and between group (u_{oj}) variances. From the Table 4.9.1-4.9.2, the models show the estimates of the average of the (log) length of stay (LOS and ALOS in hospital (β_0), the variance of the patient effect (u_{oj}) and the variance of episode within patient (e_{ij}). Goodness-of-fit was assessed by comparing model deviance with lower values of the deviance (minus twice the log-likelihood or -2LL) indicating a better fit to the data.

Table 4.9.1 Parameter estimates of the empty multilevel model 1 (null model)

Model 2.1 $\ln LOS_{ij} = \beta_0 + u_{oj} + e_{ij}$,

Fixed Effects	**Coefficient**	**S.E.**
Intercept (β_0)	2.0981	0.0394
Random Effects	**Variance Component**	**S.E.**
σ^2_u	0.1537	0.0422
σ^2_e	0.4388	0.0398
Deviance 1144.6613		

Table 4.9.2 Parameter estimates of the empty multilevel model 2 (null model)
Model 2.2*)* $\ln ALOS_{ij} = \beta_0 + u_{oj} + e_{ij}$.

Fixed Effects	**Coefficient**	**S.E.**
Intercept (β_0)	1.8977	0.0264
Random Effects	**Variance Component**	**S.E.**
$\sigma^2{}_u$	0.0795	0.0190
$\sigma^2{}_e$	0.1800	0.0166
Deviance 719.2180		

The parameter estimates are shown in the Table 4.9.1-4.9.2 as the MLwiN-output. The ***first*** output (Table 4.9.1), the overall average of lnLOS is 2.098, which is the simple average of lnLOS across all episodes and patients. The level-1 (episodes) variance is estimated as 0.4388 and the level-2 (patient) variance is estimated to be 0.1537. The intra-class correlation, calculated by $\rho = \frac{0.154}{0.592} \approx 0.26$. Thus, 26% of the total variance is between patients or the unexplained variability in lnLOS is due to variation between patients.

The ***second*** output (Table 4.9.2), showing the estimated mean of lnALOS is 1.8977 for this cohort during the six years observation period. The variance between episodes is 0.1800 and the variance between patients is 0.0795. The intra-class correlation (ρ) is about 0.31 (or 31%), the unexplained variability in lnALOS according to variation between patients. From both models, the results indicate that there is similar correlation within patient with respect to LOS and ALOS.

●**Model 3:** two-level model with one predictor variable (lnALOS)

This model is the two-level model, expanding the relationship between ln LOS and ln ALOS that has been presented as Model 1**.** To Model 3 a fixed explanatory variable is added (x_1), lnALOS, to the empty intercept model. The model can be written as $\ln LOS_{ij} = \beta_0 + \beta_1 \ln ALOS_{ij} + u_{oj} + e_{ij}$. The overall relationship between lnLOS and lnALOS is represented as the straight line with intercept β_0 and a slope β_1.The intercept for any patient *j*varies between $\beta_0 + u_j$. As above, u_j is a patient level variance which is assumed to follow a normal distribution with mean zero and

variance σ_u^2 .The output in Table 4.10 shows that the lnALOS, which is a fixed effect, is statistically significant. The average of lnLOS is estimated to increase by 0.7549 for every a unit increase in lnALOS. The variance component declined slightly compared with the empty model (Model 2.1), from 0.4388 to 0.3586 for the level-1 and from 0.1537 to 0.0791 for the level-2 variance. By adding lnALOS, $-2LL$ of Model 3 is now 1003.1467, the model deviance falls below the $-2LL$ value of the Model 2.1, suggesting a better overall model fit. The reduction of $-2LL$ (Model 3) shows a significant improvement ($\rho < 0.05$). The residual correlation of two episodes of care with a patient is $\frac{0.0791}{0.4377} \approx 0.18$ and thus approximately 18 % of the total residual variation are due to the patient level. Of course, the intra-class correlation (ICC) might be reduced by adding predictor variables to explain more of the episodes-level variation. As the intra-class correlation decreases, showing that the ALOS is more likely correlated within patient as shown as Table 4.9.1.

Table 4.10 Two-level model with one predictor variable (lnALOS)

Model 3: $lnLOS_{ij} = \beta_0 + \beta_1 \text{ lnALOS}_{ij} + u_{oj} + e_{ij}$.

Fixed Effects	**Coefficient**	**S.E.**
Intercept (β_0)	0.6651	0.1162
Coefficient of lnALOS (β_1)	0.7549	0.0588
Random Effects	**Variance Component**	**S.E.**
$\sigma^2{}_u$	0.0791	0.0291
$\sigma^2{}_e$	0.3586	0.0315
Deviance 1003.1467		

In the next section, the Model 2.1 from the Table 4.9.1 has been investigated by adding each of the patient characteristics: patient age, gender, smoking status, registry status and season as the predictor variables for analyzing their effect on the length of stay in hospital (LOS).

4.5.3 Factors affecting bronchiectasis hospital length of stay

As in the previous chapter, length of stay in hospital has been described as two types: the actual length of stay (LOS) and the average length of stay (ALOS) based on the AR-DRG system. During July 2011- June 2018, 75% of bronchiectasis patients in Concord Hospital had LOS and ALOS of about 13 and 8 days respectively. In this part, by using the two-level models, patient

characteristics and season have been analyzed as to whether or not they affect the hospital LOS. Regarding bronchiectasis patient characteristics, some studies have pointed out that **1)** females have been diagnosed as having bronchiectasis at a higher rate than males in Australia, **2)** the elderly were the majority of bronchiectasis patients in Australia (AIHW, 2018), and **3)** there was no strong evidences linking either cigarette smoking and bronchiectasis (AIHW, 2019).
This leads to the study of factors affecting hospital length of stay of bronchiectasis patient. Based on the assumption that patient characteristics (gender, age, smoking status, ABR- registry status) and other environmental factors would be important factors in influencing hospital length of stay, the two-level models have been applied to analyze the data from the Concord Hospital cohort. The results of fitting a two-level model between these factors and both lnLOS and lnALOS can be summarized as following.

● **AGE-GROUPS:** For the 505 episodes of care in this cohort, the age- groups can be summarized into three groups as follow: *Group(1*) 20-39 year olds (27 episodes), *Group(2*) 40-59 year olds (38 episodes), and *Group(3*) ≥ 60 year olds (440 episodes). Clearly, most of episodes were in the elderly age group (440 out of 505 episodes or 87.13 % of all episodes). The results as Table 4.11and 4.12 indicate that there is no statistical significance regarding to age groups influencing on the length of stay in hospital. This also shows that very little of differences of the lengths of hospital stay is explained by the age groups.

Table 4.11 Parameter estimates by including age groups into a two-level model 1
Model 4: $lnLOS_{ij} = \beta_0 + \beta_1 \text{Group1}_j + \beta_2 \text{Group2}_j + u_j + \varepsilon_{ij}$

Fixed Effects	**Coefficient**	**S.E.**
Intercept (β_0)	2.0870	0.0423
Coefficient of Group1 (β_1) (REF:Group3)	-0.0258	0.1512
Coefficient of Group2 (β_2)	0.2128	0.1647
Random Effects	**Variance Component**	**S.E.**
$\sigma^2{}_u$	0.1548	0.0422
$\sigma^2{}_e$	0.4362	0.0396

Deviance 1142.9243

Table 4.12 Parameter estimates by including age groups into a two-level model 2
Model 5: $lnALOS_{ij}$= β_0+β_1Group1$_j$+β_2Group2$_j$ +u$_j$ + ε_{ij}

Fixed Effects	**Coefficient**	**S.E.**
Intercept (β_0)	1.8880	0.0283
Coefficient of Group1 (β_1) (ref: Group3)	0.1369	0.1093
Coefficient of Group2 (β_2)	0.0148	0.1008
Random Effects	**Variance Component**	**S.E.**
$\sigma^2{}_u$	0.0774	0.0188
$\sigma^2{}_e$	0.1806	0.0166
Deviance 717.6558		

●**GENDER:** There are gender differences in chronic respiratory disease, including bronchiectasis. Differences are evident in disease prevalence, severity and outcome. A recent study has reported that the prevalence of bronchiectasis was higher in males whereas females were more likely to present with another disease such as asthma (Vidaillac et al., 2018a). The study revealed that, compared with males, females tend to have a worse clinical outcome in bronchiectasis such as poorer lung function, increased exacerbation and mortality (Rosenfeld et al., 1997).

For this cohort, the hospitalization rate for females with a diagnosis of bronchiectasis was about (293 admissions) 1.4 times higher than the rate for males (212 admissions). Looking for a relationship between the length of stay in hospital (lnLOS, lnALOS) and gender we found none; the results in Table 4.13 and Table 4.14 show that gender has no significant effect on the length of stay in hospital. The ratio of the estimate of the parameter associated with male to its estimated standard error is $\frac{0.0922}{0.0802}$ = 1.15 and $\frac{0.0490}{0.0538}$= 0.91 for the models in Table 4.13 and 4.14 respectively. If the ratios are less than1.96 then the parameters are not significant at the 5% level.

Table 4.13 Parameter estimates by adding gender as a predictor of a two-level model 1

Model 6: $lnLOS_{ij} = \beta_0 + \beta_1 \text{Male}_j + u_j + \varepsilon_{ij}$

Fixed Effects	**Coefficient**	**S.E.**
Intercept (β_0)	2.0604	0.0514
Coefficient of Male (β_1) (ref: female)	0.0922	0.0802
Random Effects	**Variance Component**	**S.E.**
σ^2_u	0.1557	0.0423
σ^2_e	0.4360	0.0396
Deviance 1143.3429		

Table 4.14 Parameter estimates by adding gender as a predictor of a two-level model 2

Model 7: $lnALOS_{ij} = \beta_0 + \beta_1 \text{Male}_j + u_j + \varepsilon_{ij}$

Fixed Effects	**Coefficient**	**S.E.**
Intercept (β_0)	1.8777	0.0345
Coefficient of Male (β_1) (ref=female)	0.0490	0.0538
Random Effects	**Variance Component**	**S.E.**
σ^2_u	0.0803	0.0190
σ^2_e	0.1791	0.0165
Deviance 718.3905		

● **SMOKING STATUS:** Smoking status: there were two groups in this study; patients who were smokers (34.40%) and never-smokers (65.60%). As has been stated earlier, smoking is not a cause of bronchiectasis but it makes the condition and symptoms worse (ERS, 2018). From the results below (Table 4.15- Table 4.16), there is no evidence an association between patients who were smokers patients on the length of stay in hospital significantly.

Table 4.15 Parameter estimates by including smoking status as a predictor of a two-level model 1 **Model 8**: $lnLOS_{ij}$= β_0+$\beta_1$smoking_status$_j$ +u$_j$ + ε_{ij}

Fixed Effects	**Coefficient**	**S.E.**
Intercept (β_0)	2.0149	0.0656
Coefficient of never-smoker (β_1)	0.1294	0.0819
(Reference group: ever-smoker)		
Random Effects	**Variance Component**	**S.E.**
$\sigma^2{}_u$	0.1508	0.0419
$\sigma^2{}_e$	0.4381	0.0397
Deviance 1142.1752		

Table 4.16 Parameter estimates by including smoking status as a predictor of a two-level model 2 **Model 9**: $lnALOS_{ij}$= β_0+$\beta_1$smoking_status$_j$ +u$_j$ + ε_{ij}

Fixed Effects	**Coefficient**	**S.E.**
Intercept (β_0)	1.8959	0.0444
Coefficient of never-smoker (β_1)	0.0030	0.0553
(Reference group: ever-smoker)		
Random Effects	**Variance Component**	**S.E.**
$\sigma^2{}_u$	0.0797	0.0191
$\sigma^2{}_e$	0.1798	0.0166
Deviance 719.2148		

● **ABR- REGISTRY STATUS**: There were only 29 out of 299 patients who registered as participants in the ABR i.e., patients who were recorded in the ABR registry system were about 10% of the total of all patients in this group. Comparing with patients who were participants in the ABR registry, the estimated slope (patients who were not were participants in the ABR registry) was shifted 0.2436 for the lnLOS above the reference group (participants with ABR

registry) as the Table 4.17- 4.18. This shows that patients not being registered with the ABR registry system have a longer stay in hospital than the registered group. The non-registry factor increases in lnLOS by 0.2436 units, producing the t-test value $\approx \frac{0.2436}{0.1210} \approx 2.013$.Thus, the ABR registry is a significant predictor of the length of stay in hospital. In addition, the results in Table 4.18, Model 11 shows that the non- registry factor is also likely to be a significant parameter (t-test =2.14) for the lnALOS. Comparison of the deviance between the null model (Model 2.1) and Model 10 shows $-2LL$ has reduced by 3.9722 from adding the registry factor parameters into the model. The p-value, p = 0.042 <0.05, is significant at the 5% significance level. This is evidence to conclude that the registry variable is overall significant for the response lnLOS. Moreover, by adding the non ABR-registry factor into the Model 11 (lnALOS), the results is also showing significance between the non ABR-registry factor and the response lnALOS. This suggests that bronchiectasis patients who participated with **ABR-registry** is tend to have length of stay in hospital shorter than patients who did not register in the ABR. However, non ABR-registry is not significant effect on hospital LOS by adding this factor to the Model 3 as shown in Model 12 (Table 4.19). By including non ABR-registry as Model 12, the slope of lnALOS is reduced slightly as well as the deviance compared with Model 3.

In addition, this can be summarized that patients who participated with the ABR-Registry are associated with the shorter hospital LOS through ALOS but does not influence over the LOS once the ALOS is controlled. This indicate that patients who participated in ABR- registry is associated with being less severe disease when allocated ALOS in the AR-DRG classification system. The ABR only started towards the end of our cohort period. Running the same analysis on the cohort 2015-2020 might identify whether ABR registration was biased towards those with milder or more severe disease, or towards female patients. Participation in the ABR also facilitates more regular clinical review and participation in clinical trials all factors that could (we hope) improve clinical status, reduce exacerbations and plausibly change the ALOS. Patients who participated with the ABR-registry have opportunity to check up with their clinician constantly. This could be a reason why patients who are participated in the ABR-registry may have shorter length of stay in hospital and less severe disease when they were admitted to the hospital. However, gathering patients in the ABR-registry with longitudinal follow-up is an ongoing challenge. Patients may be recruited with the ABR based on the physician who provides their care or their abilities to access healthcare payments. Other challenges include how to retain patients in a registry and linking the ABR-registry to other hospitals or healthcare services.

Table 4.17 Parameter estimates by including non ABR-registry status as a predictor of a two-level model 1 **Model 10**: $lnLOS_{ij}$= β_0+$\beta_1$nonRegistry$_j$ +u$_j$ + ε_{ij}

Fixed Effects	**Coefficient**	**S.E.**
Intercept (β_0)	1.8823	0.1137
Coefficient of non-ABR Registry (β_1)	0.2436*	0.1210
(Reference group: Registry)		
Random Effects	**Variance Component**	**S.E.**
$\sigma^2{}_u$	0.1407	0.0411
$\sigma^2{}_e$	0.4436	0.0400
Deviance 1140.6891		

Note: * (P≤ 0.05)

Table 4.18 Parameter estimates by including non ABR-registry status as the predictor of a two-level model 2 **Model 11**: $lnALOS_{ij}$= β_0+$\beta_1$nonRegister$_j$ +u$_j$ + ε_{ij}

Fixed Effects	**Coefficient**	**S.E.**
Intercept (β_0)	1.7423	0.0766
Coefficient of non-Registry (β_1)	0.1751*	0.0815
(Reference group: Registry)		
Random Effects	**Variance Component**	**S.E.**
$\sigma^2{}_u$	0.0797	0.0191
$\sigma^2{}_e$	0.1798	0.0166
Deviance 714.7082		

Note: * (P< 0.05)

Table 4.19 Parameter estimates by including non ABR-registry status and lnALOS as predictors of two-level **Model 12**: $lnLOS_{ij}$=β_0+$\beta_1$lnALOS$_j$ + $\beta_2$nonRegistry$_j$+u$_j$ + ε_{ij}

Fixed Effects	**Coefficient**	**S.E.**
Intercept (β_0)	0.5780	0.1398
Coefficient of lnALOS (β_1)	0.7485	0.0591
Coefficient of non-ABR Registry (β_2)	0.1129	0.1017
(Reference group: Registry)		
Random Effects	**Variance Component**	**S.E.**
$\sigma^2{}_u$	0.0768	0.0288
$\sigma^2{}_e$	0.3592	0.0315
Deviance 1001.9195		

● **SEASONALITY**

Seasonal variations have been mentioned as potentially having a significant effect on the rate of hospital admission and length of stay in hospital in patients with chronic conditions (von Mackensen et al., 2005), (Argha et al., 2018). To investigate the impact of environmental factors on bronchiectasis patient hospital length of stay, a season effect has been considered as a predictor variable in the two-level models as shown in the tables below. Patients' admission dates have been categorized by season .For this group of bronchiectasis patients, hospital admissions (Table 4.20) increased in winter and slightly decreased in spring. Particularly, in winter, the number of episodes of care was higher than in the other seasons. It accounted for about 30.3 % of all episodes. Winter seems to be a crucial period for bronchiectasis hospitalization. Most patient admissions were observed to be higher in winter.

The results as Model 13 –14 show that patients tend to have higher length of stay in hospital (LOS) during winter relative to autumn (reference group) than the other periods. Although there is an increase in length of actual hospital stay (LOS) during winter months, the coefficient of winter factor is not statistically significant because the standard error is almost as big as the value of coefficients. While, bronchiectasis patients who are admitted to the hospital during winter and spring tend to have higher ALOS in the AR-DRG system than the other seasons. This indicates that patients who are admitted in hospital during both seasons are more likely to have severe symptoms than other periods.

Table 4.20 Number of bronchiectasis patient admissions in Concord Hospital during July 2011- June 2018

Seasonality	**Autumn** Mar-May	**Winter** Jun-Aug	**Spring** Sep-Nov	**Summer** Dec-Feb
Number of admissions	131	153	109	112
Percentage (%)	25.90	30.30	21.60	22.20

Table 4.21 Parameter estimates by including season as a predictor of a two-level 1
Model 13: $\ln LOS_{ij} = \beta_0 + \beta_1 Winter + \beta_2 Spring_j + \beta_3 Summer_j + u_j + \varepsilon_{ij}$

Fixed Effects	**Coefficient**	**S.E.**
Intercept (β_0)	2.0211	0.0677
Coefficient of Winter (β_1)	0.1331	0.0870
Coefficient of Spring (β_2)	0.1014	0.0959
Coefficient of Summer (β_3)	0.0670	0.0932
(Reference group: Autumn)		
Random Effects	**Variance Component**	**S.E.**
σ^2_u	0.1635	0.0427
σ^2_e	0.4294	0.0392
Deviance 1142.2295		

Table 4.22 Parameter estimates by including season as a predictor of a two-level 2
Model 14: $\ln ALOS_{ij} = \beta_0 + \beta_1 Winter + \beta_2 Spring_j + \beta_3 Summer_j + u_j + \varepsilon_{ij}$

Fixed Effects	**Coefficient**	**S.E.**
Intercept (β_0)	1.8053	0.0444
Coefficient of Winter (β_1)	0.1489	0.0561
Coefficient of Spring (β_2)	0.1273	0.0620
Coefficient of Summer (β_3)	0.0919	0.0599
(Reference group: Autumn)		
Random Effects	**Variance Component**	**S.E.**
σ^2_u	0.0930	0.0196
σ^2_e	0.1680	0.0157
Deviance 711.8630		

4.6 Conclusion

This chapter has examined the relationship between the average length of stay (ALOS) in hospital of bronchiectasis patients which are assigned to the AR-DRG classification system and their observed length of stay (LOS). The data set used is based on the 299 patients with bronchiectasis in Concord hospital during the period July 2011- June 2018. By using a log linear regression model, the analysis demonstrated that the actual length of stay (LOS) for bronchiectasis patients is shifted significantly higher than the average length of stay (ALOS) associated with the AR-DRG system in particular. For the majority of admissions – those assigned an ALOS of up to 15 days - patients tended to have actual lengths of stay which exceeded the periods allocated for funding purposes, as shown in Figure 26. Prior to 2018 when bronchiectasis gained its own specific code in the AR-DRG system, these patients were assigned to the AR-DRG group of diseases, which clearly did not capture the complexity of severity of their conditions or care needs. Patients admitted for bronchiectasis stayed longer in hospital (LOS) than predicted based on the ARDRGs available. By implication, the complexity of these admissions is under recognised and the admissions are underfunded (Kingkam et al., 2017). Even with the disease specific AR-DRG, and despite admission to a hospital that specializes in the care of patients with bronchiectasis, the LOS and ALOS for admission for where bronchiectasis is the major contributor to the admission, relatively under recognize complexity and under fund the admission.

The multilevel mode has been addressed in this chapter for expansion of the analysis of the factors (e.g. patient characteristics and seasonality) influencing the hospital LOS. The analysis results revealed that there is no statistical significance between the hospital LOS and those factors but non-ABR registry factor as the represented model in the Table 4.19. Patients who did not enroll with the ABR-registry are prone to have the hospital ALOS longer than registered patients. Being participants in the ABR- registry results in not only for shorter hospital ALOS but also reducing healthcare costs for patients. This finding suggests that participation in the ABR, apart from helping patients, may help hospitals by improving LOS. Although others factors (gender, age group, smoking status and season) did not affect the hospital LOS to the same degree as participation in the ABR registry, these factors may be related to the hospital readmission, which needs to be investigated in the next chapter. For the variance components, adding category variables into the two- level model changes slightly comparing to the empty model such as the residual correlation in hospital ALOS between two episodes with a patient when non-ABR registry was added to Model 2.2 is about 0.3071 (the empty model 2.2, $\rho = 0.3063$). This shows that the most unexplained variation in hospital length of stay is due to variation between episodes rather than patient characteristics.

CHAPTER 5

Models for Analyzing time to readmission among bronchiectasis patients

The previous chapter considered modelling of the time spent in hospital for an in-patient episode. Of equal important, for an individual with a chronic illness that results in hospitalization, is the time between episodes and factor associated with reducing fast return to hospital (Rico et al., 2016). This chapter presents the statistical models for analysis of the bronchiectasis data on the Australian Bronchiectasis Registry and Concord Hospital (July 2011-June 2018) and provides interpretation of the results. A multilevel model for binary response has been applied to test the models of time to readmission into hospital. Some crucial factors (patient characteristics and hospital factors) were determined as predictor variables for this part. Section 5.1 describes the introduction of this issue. Section 5.2 provides a description of data used in this chapter. Model assumptions and results have been addressed in the final part.

5.1 Introduction to analysis

Readmission into hospital is frequently used as an indicator of quality of healthcare system. Many factors may be contributors to patient readmission such as medical diagnosis, treatments and the discharge of patients in the shortest possible time. Length of stay in hospital can result in medical complications such as hospital-acquired infection. Early hospital discharge could influence readmission risk. Sud et al. (2017) reported that a short length of stay in hospital was associated with increased rates of readmission and mortality of patients with heart failure. As the results in the previous chapter, most of bronchiectasis patients have length of stay in hospital (LOS) less than 15 days, leading to hospital costs underestimation. Staying longer in hospital is more likely related to the high costs of treatments. In general, hospital readmission can be considered in two broad categories; **1)** readmission that relates to necessary treatments such as chemotherapy and planned readmission, and **2)** unplanned readmission after hospital discharge. Hospital readmission is an issue for bronchiectasis and COPD. A report from the Division of Population Health at the Centers for disease Control and Prevention (CDC), USA, published in Chest Journal, pointed out that about 21% of COPD and bronchiectasis patients were readmitted to the hospital within 30 days of hospital discharge, however, only 7% of them were readmitted with COPD and bronchiectasis as the primary diagnosis (Ford, 2015). The days and weeks after hospital discharge are a time of high risk for recurrence of a disease, however, there is limited information on factors affecting to hospital readmission of patients with bronchiectasis. A recent study has presented the cause and factors related to readmission for an

acute exacerbation of COPD. It has indicated that respiratory-based diseases were the most common reasons for readmission (52.40%) and COPD was the most common diagnosis (28.40%). The early readmission was associated with factors such as patient status, lower household income and clinical factors (hospital length of stay (LOS), a skilled nursing facility) (Jacobs et al., 2018). Bronchiectasis, like COPD, is a chronic respiratory disease with frequent exacerbations. The exacerbations could lead to hospital readmission and increase the hospital costs. In general, bronchiectasis patients with severe conditions have an average of two or more exacerbations per year (Finch et al., 2015). For this chapter, data collection on Concord bronchiectasis hospitalization admissions have been analyzed in order to investigate the crucial factors affecting time to readmission to hospital. A two –level model for binary outcomes with a single explanatory had been considered to analyze time to readmission into hospital. This study may help hospital services or the hospital administration system has a better understanding of the characteristics of bronchiectasis patients, manage hospital beds and hospital resources for bronchiectasis patient readmission.

5.2 Preparing the data

Repeated admissions to hospital are common for this disease since bronchiectasis is a chronic lung disease. Some patients have had more than an episode of admitted patient care in hospital. All patients in this cohort were admitted to Concord hospital during 16 December 2011 to 22 June 2018. The cohort consisted of 299 patients: patients not involved in the ABR registry and those who had participated in the ABR registry. In this chapter, the main idea was to investigate time to readmission of bronchiectasis patients in Concord hospital and factors influencing the cause of return. Readmission in this study was defined as an admission into the hospital within 16 weeks of discharge from Concord hospital. All patients were identified using their medical record number. This provided a database of patient information including demographic statistics (gender and age) as well as details of initial and subsequent admission (discharge date, admission date, smoking status, length of stay).

For this group, the observed or actual length of stay for all admissions ranged from 2 to 93 days, whereas the average length of stay (ALOS) was found to be shorter (median 6.72) than the observed length of stay (median 7.00). During the 6 years period, some patients had multiple readmissions but some of them had only one episode of care. For example, patient *ID A* had been discharged from hospital on 7 June 2012 and had the first readmission to hospital on 5 August 2014 and then returned to hospital for the second readmission on 23 October 2015, whereas Patient *ID B* had been discharged on 6 March 2015 and did not return to hospital during the observation period. Of the 505 episodes of care, time to readmission was up to 80

months as shown in the histogram below. Most episodes had time to readmission to Concord Hospital less than 20 months (as Figure 27). Comparing between the readmission group and the censored group as the distribution in Figure 28, the boxplots illustrated that most of patients from the readmission or return group had a readmission time period that was between 0-11 months. The median of time between episodes for the readmission group was 3.0 months. Clearly, most of episodes for this cohort were the censored group as Figure 28, which showed that most patients had a single admission. Once patients had been discharged from Concord hospital, they rarely returned to the hospital during the observational period. This study examined the reasons for, and predictors of, readmission to hospital within 16 weeks of discharge from inpatient care. This seems reasonable for the observation period of this study since some patients may return to hospital quickly or move to other areas. The event of interest was a readmission to hospital of bronchiectasis patients (yes: 1 /no: 0). The multilevel model for binary response was considered to model the number of weeks until readmission and find out which variables influence the outcome of variable (in this case readmission), measured from the time of the previous discharge during 16 weeks. Such factors may contribute to the risk of readmission such as episodes of care and patient level. These include, for example, *Episode level*: length of stay in hospital, the previous admission, *Patient level*: age-groups, gender, patient smoking status, comorbidities, health literacy and financial capacity. For this cohort, the predictor variables affecting the risk of readmission that were considered included patient characteristics; age-groups, gender, smoking status, ABR- registry status and season (at discharge date) during the admission day as described earlier in more detail in the chapter 3.

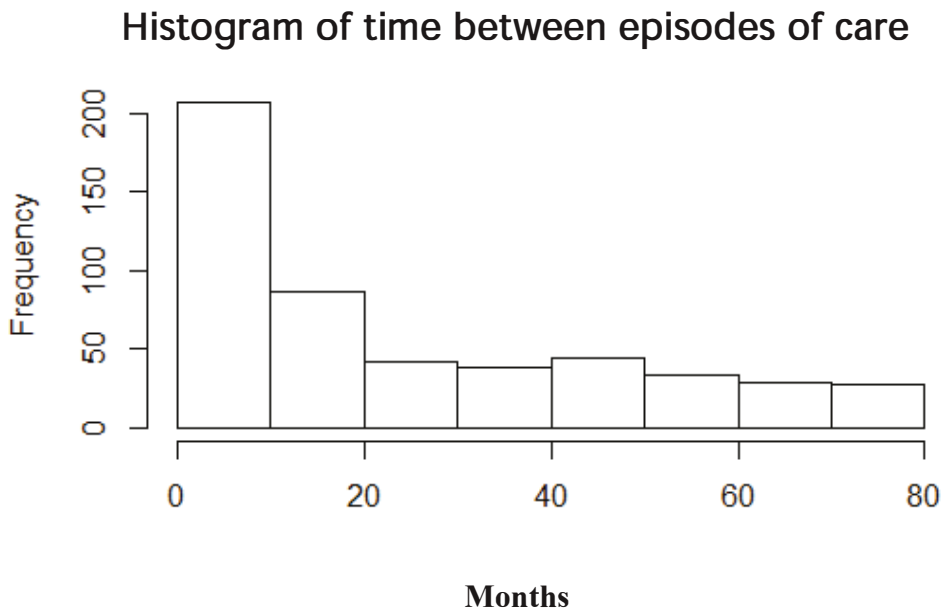

Figure 27 Histogram of time between admissions of bronchiectasis patients in months (Concord Hospital in July 2011- June 2018)

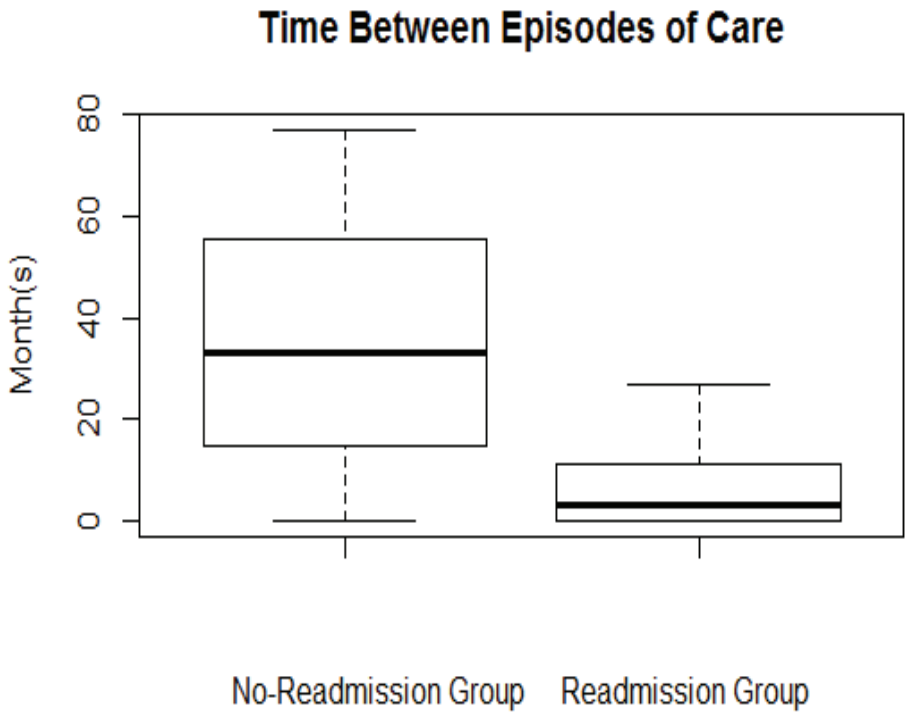

Figure 28 Boxplots shown distributions between censored group (No- readmission) and return group (readmission) of bronchiectasis patients to Concord Hospital during July 2011- June2018

5.3 Model Assumptions

Studying the impact of taking into account readmission to hospital of bronchiectasis patients seems to be limited in Australian healthcare. It would be interesting to explore what influences the time for readmission to hospital for the bronchiectasis patients. The purpose of this research is to analyze demographic and health parameters of bronchiectasis patients to contribute a statistical model to identify the time to readmission into hospital for patients over a 16 weeks period. Several variables (length of stay in hospital, age-groups, gender, smoking status, ABR registry status, season) were used to analyze how they relate to the outcome of the study (readmission; yes: 1, no: 0). Patient characteristics were assumed to be the main factors that could affect to the readmission to hospital of bronchiectasis patients (Figure 29). For example, most of patients in this cohort were the elderly people ($\geq$ 60 years old) and accounted for 440 out of 505 episodes of inpatient care.

In addition, there were 226 episodes for patients who were greater than 80 years old. This group of patients had a high risk of mortality that may have led to a low readmission. According to the (AIHW, 2019), females have a hospitalization rate two times (x2) higher than males and indicated that females may have a readmission rate higher than males. Not only readmission

outcomes may be influenced by patient characteristics but also hospital factors such as the length of time spent in episode before the next admission. For example, bronchiectasis patients discharged from hospital with the shorter LOS might return to the hospital quicker than those who had the longer LOS in hospital. However, since bronchiectasis patients were coded into a variety of lung-related groups of disease based on the AR-DRG classification system during this observational period, their average length of stay in hospital (ALOS) associated with the AR-DRG classification may be able to reflect on the readmission outcomes as well as the LOS (the observed length of stay in hospital).

In the other hand, the ALOS may not affect the readmission outcomes directly but may represent how the LOS correlates to the ALOS. In other words, since ALOS has been represented LOS of bronchiectasis patients prior to 2018, ALOS could be able to reflect on the readmission outcomes indirectly. In addition, patients who had longer ALOS (days) were tend to have longer LOS (days) rather than patients who had shorter ALOS (when they were coded on discharged date). Then, patients with longer LOS may not be readmitted in hospital quicker than shorter LOS. This may be different between gender or age-group, etc.

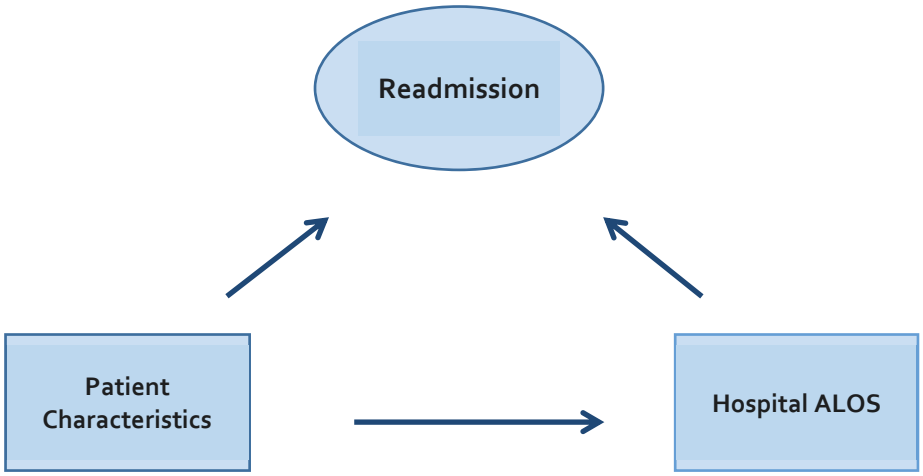

Figure 29 The relationship between hospital ALOS, patient characteristics and readmission

As Figure27, the histogram shows that time between episodes has steady declined for patients discharged from Concord hospital over the 80 months period. Most patients did not return to the hospital (70%) but some of them had multiple readmissions. For this reason, one particular interest is to use the multilevel logistic regression model to determine time to readmission to the hospital especially with the early period after leaving the hospital which may be the time of high risk for recurrence of the exacerbations resulting in hospital readmission. Weeks after the

being discharged from hospital are considered to be as time interval. Additionally, patient characteristics and their length of stay in hospital might provoke exacerbations requiring hospital readmission (Venning et al., 2017). Although, in the previous study in Chapter 4, patient characteristics have no significant effect on hospital LOS, possibly they may have an impact on their readmission. For example, bronchiectasis hospitalization rate for females was higher than males so females may have frequency of readmission higher than males. Another assumption is that patients aged ≥ 60 years old would be possible to exhibit greater readmission risk rather than the younger age –group. In contrast, the young patients with severe or rapidly progressive disease are more likely to have increased readmission risk than elderly patients with mild stage.

5.4 Modelling the time to readmission among bronchiectasis patients in Concord Hospital

In this study, a two –level model for binary outcomes with a single explanatory had been considered to analyze time to readmission into hospital. Suppose the data consisted of episodes (level one) grouped within patients (level two). The model can be expressed as

$$y_{ij} = \beta_0 + \beta_1 x_{ij} + u_{j,} \quad (5.1)$$

,where y_{ij} refers to a binary response for episode i in patient j

x_{ij} refers to explanatory variables at the patient level

u_j is the random effect at level two.

The probability of the outcome equal to one is $p_{ij}=Pr(y_{ij} = 1)$ and let p_{ij} be modeled by taking the log of the proportional hazard model. Then the two-level model can be written as:

$$\log\left(\frac{P_{ij}}{1-P_{ij}}\right) = \beta_0 + \beta_1 x_{ij} + u_j . \quad (5.2)$$

The event of interest in the multilevel logistic regression was hospital readmission of bronchiectasis patients after discharge up to 16 weeks. The response variable is dichotomized as:

$$y_{ij} = \begin{cases} 1, \text{if patient j in episode i returned to hospital} \\ 0, \text{if patient j in episode i did not return to hospital} \end{cases}$$

The explanatory variables can be added in the model one at the time. The choice of potential explanatory or predictor variables was based on the model assumption in section 5.3 and they can be categorized as following:

●patient's gender (male, female)

●patient's age-groups into three groups; Group1: 20- 39 years old, Group 2: 40-59 years old and Group 3: ≥ 60 years old

●Patient's smoking status (never- smokers, smokers)

●ABR registry status (ABR participant, non- ABR participant)

●Seasonality (summer, autumn, winter, spring)

●hospital LOS

The first analysis is to consider the models of time until a new admission occurred. Before conducting the model, the patient data set must be converted into a patient-period data set in which each patient has multiple records, one per time period of observation. The time variables must be created identifying the time period to which each record corresponds. And the outcome variable,Y, must be created using the duration and censoring. Basically, the i^{th} admission record for each jth patient contains information about;

● Duration: the length of time that a patient did not return to hospital since hospital discharge until the last time of period that he or she was observed.

● Time variables (week): (1) the set of dummy variables, $D_{1j}, D_{2j}, D_{3j}, \ldots, D_{nj}$, takes on values that identify the particular time period to which the record refers. All of time takes on 0 except for the j dummy, which has value 1. (2) Time variables are considered as week, week^2 and week^3.

●Censoring: The value of the censoring indicator indicates the patient actually experienced the event of interest in the last time period of observation (readmission to hospital) or censoring occurred (16 weeks).

●The outcome: The value Y records the value y_{ij}that indicates whether the event of interest occurred for the i^{th}admission in j^{th} patient; the value 0 if the event of interest did not occur, and 1 if the event occurred.

Then, the risk for readmission has been represented by the predicted probability of having a readmission after adjusting for predictor variables (e.g. gender, smoking status and age-groups). The purpose is to predict the probability that the patient is readmitted to the hospital within 16 weeks after discharge based on the predictor variables as above. The data set of 299 bronchiectasis patients with 505 episodes had been expanded to a person-period with weekly observations for each patient from the discharge date until the censored date. There is a total of 5453 weekly expansion in the data file. Readmission was defined for all readmissions from any cause of occurring within 16 weeks of hospitalization. Because this study used the data from a single hospital, not included were the cases in which patients discharged from this hospital were readmitted to other inpatient providers. The models were fitted by using R (Allaire, 2012) and

MLWin (Rasbash et al., 2017). The goodness-of– fit statistic used -2LL, in particular, the Akaike Information Criterion (AIC) was applied for the models comparison for the model time variables. The smaller the values are, the better fit the model demonstrate. This analysis has been represented in the next section.

5.5 Results

5.5.1 Multilevel Logistic Model for time to hospital readmission

The purpose of this section is to investigate the appropriate model for analysis of the number of weeks until readmission of bronchiectasis patients in Concord Hospital during 2011-2017 financial years and the important factors resulting in the readmission into hospital. The data have been expanded to weekly observations for each patient from the hospital discharge until the next readmissions up to 16 weeks which was the censoring time. The multilevel logistic model was conducted to fit the data set in MLwiN and RStudio Among 505 hospitalizations of bronchiectasis patients in Concord Hospital (July 2011- June 2018), 109 episodes were readmitted within 16 weeks from hospital discharge, resulting in 21.58% of all episodes. , the boxplots in Figure 28 shows that time period for readmission group was lower than the non-readmission group. In fitting the discrete time Model 5.2, each patient's duration of exposure during 16 weeks is taken into account. The cumulative hazard function is presented in the Figure 30. The shape of the hazard function is different from that represented by most other analyses. This graph below shows the highest of readmission rates was 16 weeks soon after hospital discharge.

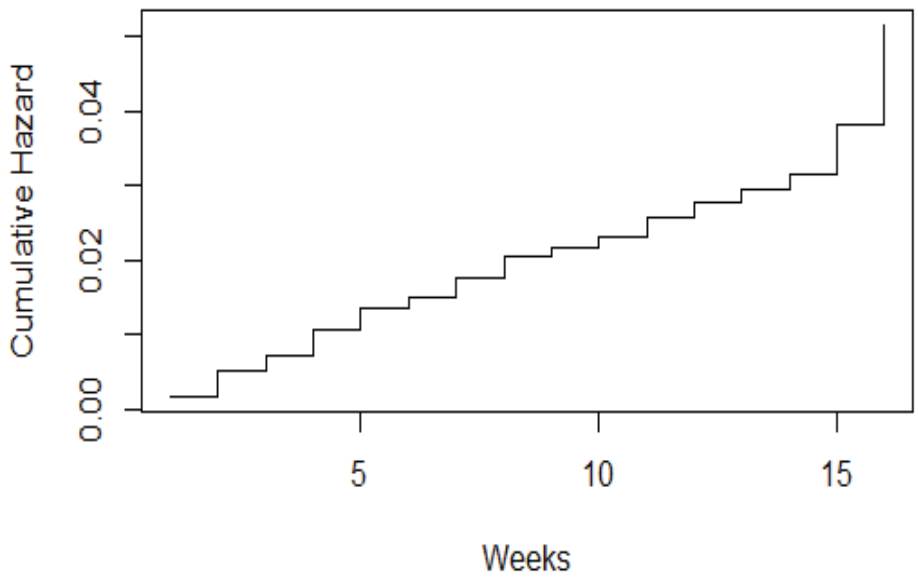

Figure 30 Hazard for Time to Readmission within 16 weeks

The first analysis is based on the 5453 weekly intervals contributed by 299 patients for either ABR participants or non- ABR participants. Time variables were used to indicate the baseline hazard function that represented the values of the outcome in this cohort without other predictor variables. The multilevel logistic model was written as an initial form of time measured by weekly intervals for time to readmission of patient j with admission i can be co as:

as in the following form:

$$\log\left(\frac{P_{ij}}{1-P_{ij}}\right) = \beta_0(t) \qquad (5.3)$$

Where $\beta_0(t)$ is presented function of time (weeks) as represented below:

1) Linear: $\beta_0(t) = \alpha_0 + \alpha_1 t$
2) Quadratic: $\beta_0(t) = \alpha_0 + \alpha_1 t + \alpha_2 t^2$
3) Cubic: $\beta_0(t) = \alpha_0 + \alpha_1 t + \alpha_2 t^2 + \alpha_3 t^3$.

In addition, time was treated as a categorical variable with a category for each time interval, leading to a step function; $\beta_0(t) = \alpha_1 D_1 + \alpha_2 D_2 + \ldots + \alpha_n D_n$, where $D_1, D_2, D_3, \ldots, D_n$ are the dummies for time intervals t=1,2,3,…,n. These forms were set up to test the significance that they varied proportionally with the baseline model. The Table 5.1 shows the estimated coefficients from fitting the Model 5.2 to the probability of readmission after hospital discharge for 16 weeks. The Model 1 (Table 5.1) represents the baseline hazard function as the dummy variables for time intervals (16 weeks). Comparing to the 1st week, the estimated coefficients suggest that the 2nd week shifts above the first week and declined by time until the 16th week.

For Model 2 (Table 5.2), the linear form of time variable provides a significant result ($p < 0.001$) compared to the others. Due to the estimated coefficients of the Model 2, the slope seems to be suitable with the risk of readmission in Figure 31 which was slightly down in line by 16 weeks. Comparing Models using differences in deviances in Table 5.2 requires that the models be nested, in the Table 5.2, Model 2, Model 3, Model 4 are nested but Model 1 cannot be compared using a drop- in deviance test. By adding $Week^2$ to the Model 2, there is a non-significant result (p =0.89507) between Model 2 and Model 3. Thus, Model 3 should be rejected. Likely, between Model 2 and Model 4, the result shows that Model 4 did not provide a significantly better fit to the data compared to Model 2 so Model 4 should be rejected as well as Model 3.

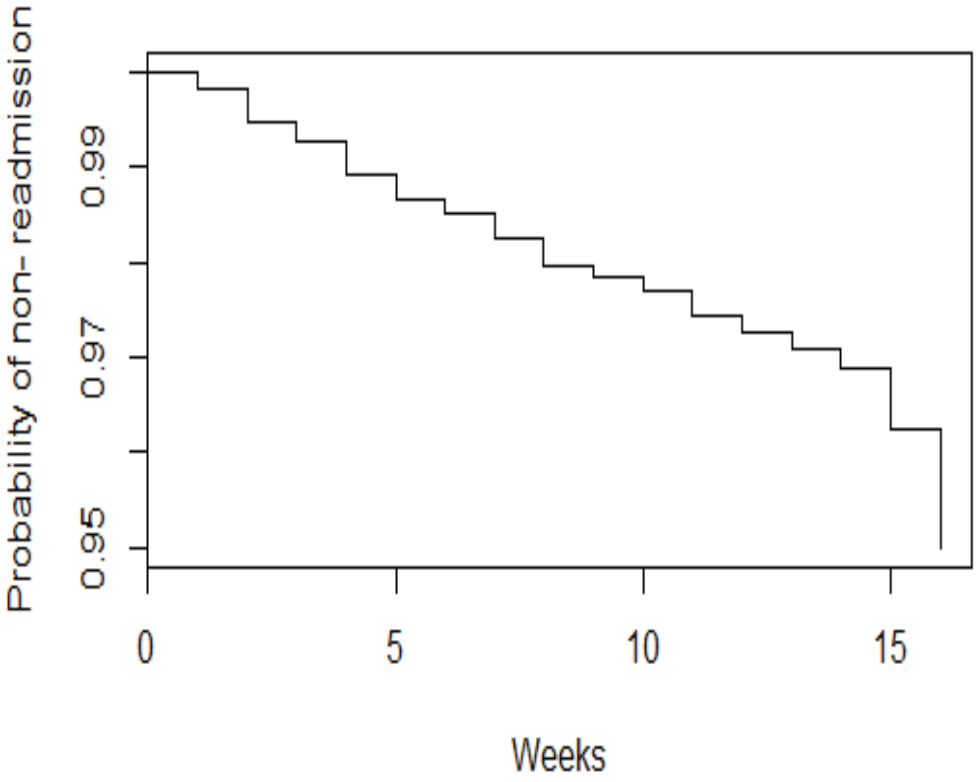

Figure 31 The Kaplan-Meier Survival Curve for Time to Readmission (16 weeks)

For comparing Model 1 and Model 2, the better model should fit well and not be too complex. The model with the smallest number of parameters, that is, Model 2 is preferred compared to Model 1 (as previous analysis Model1 is not significantly better than Model 2). In addition, by using AIC, the AIC is smaller for Model 2, providing evidence that Model 2 is much more suitable than Model 1. Therefore, Model 2 is the most appropriate model compared with the other models for investigating the time to readmission to hospital.

Thus, the multilevel logistic model for time to readmission of patient j admission i can be constructed without the other predictor variables as:

$$\log\left(\frac{P_{ij}}{1-P_{ij}}\right) = \beta_o \text{Const} + \beta_1 \text{Week}_{ij} + u_j \qquad (5.4)$$

where β_o, β_1 are coefficients and u_j is the random effect which is assumed to follow a normal distribution with zero mean and variance σ_u^2 (random parameter). The parameters in the Equation 5.4 can be estimated by $MLwiN$ as in the Table 5.3 below.

Table 5.1 Parameter estimates for the multilevel logistic model for binary response of bronchiectasis patients' readmission into Concord Hospital (within 16 weeks) since discharge date

Model 1 Dummy term (Ref: week1)

Variables	Estimate	Standard Error
Intercept	-0.6864	0.3202
week2	0.5742	0.4049
week3	-0.0380	0.4654
week4	0.5140	0.5140
week5	0.2350	0.4430
week6	0.4430	0.5527
week7	0.0755	0.4654
week8	-0.0180	0.4802
week9	-0.9896	0.6625
week10	-0.9802	0.6625
week11	-0.4536	0.5529
week12	-0.9548	0.6626
week13	-1.3538	0.7782
week14	-1.3473	0.7782
week15	-0.6410	0.5965
week16	-0.6277	0.5965

Table 5.2 Parameter estimates for the multilevel logistic model for binary response of bronchiectasis patient's readmission into Concord Hospital within 16 weeks since discharge date

Variables	Estimate	Standard Error
Model 2 Linear term		
Intercept	-3.1725	0.1687
week	-0.1005	0.0226
Model 3 Quadratic term		
Intercept	-3.1989	0.2623
week	- 0.0896	0.0857
$week^2$	- 0.0007	0.0055
Model 4 Cubic term		
Intercept		
week	-3.8141	0.4166
$week^2$	0.3351	0.2272
$week^3$	-0.0677	0.0333
	0.0028	0.0014

Table 5.3 Parameter estimates of Model 5.4 by using $MLwiN$

Parameters	Estimate	Standard Error
Fixed Parameters		
Constant	-3.7889	0.2311
Week	-0.0579	0.0255
Random Parameters		
σ_u^2	2.3343	0.5110

Table 5.4 Analysis of Deviance from Table 5.2

Model 1: Outcome ~ Dummy

Model 2: Outcome ~ Week

Model 3: Outcome ~ Week + $Week^2$

Model 4: Outcome ~ Week + $Week^2$+ $Week^3$

	Resid.Df	**Resid. Dev**	**Df**	**Deviance**	**Pr(>chi)**
Model 2	5451	1055.2			
Model 3	5450	1055.1	1	0.0174	0.89507
Model 4	5449	1050.9	1	4.2302	0.03971*
	Resid.Df	**Resid. Dev**	**Df**	**Deviance**	**Pr(>chi)**
Model 2	5451	1055.2			
Model 4	5449	1050.9	2	4.2476	0.1196

	Model1	**Model2**	**Model3**	**Model4**
	Dummy	Linear term	Quadratic term	Cubic term
Df	15	1	2	3
AIC	1073.9	1059.1	1061.1	1058.9

From Table 5.3, $Week$ provides a statistical significance with a negative parameter estimate (-0.0579). The intercept β_o is estimated to be -3.7789 (S.E. = 0.2311) and is interpreted as the log-odds of readmission in the average patient at time zero. The between-patient variance σ_u^2 is estimated as 2.3343 (S.E. = 0.5110). The results graph is shown in the Figure 32. Within increasing of time in weeks, the probability of readmission to hospital of bronchiectasis patients decreases. In addition, this study has been examined with the censored time at 13 weeks since patients leave hospital compared with 16 weeks for clarity purposes (Table 6.1). The choice of 13 weeks or 16 weeks did not change the basic conclusion relating to the choice of the baseline hazard.

The next part, additional influences on risk of readmission can be investigated by adding predictor variables to the initial discrete-time hazard model (Equation 5.4). These predictors were described in Section 5.4. Each of predictors was included to the model in Equation 5.4 one at the time. They were used to identify the factors associated with the LOS among bronchiectasis patients in the previous chapter. In the previous one, the ABR-registry factor provided a significant factor affecting to hospital ALOS and LOS. For hospital readmission, factors affecting to the readmission have been reported in the following Section 5.5.2.

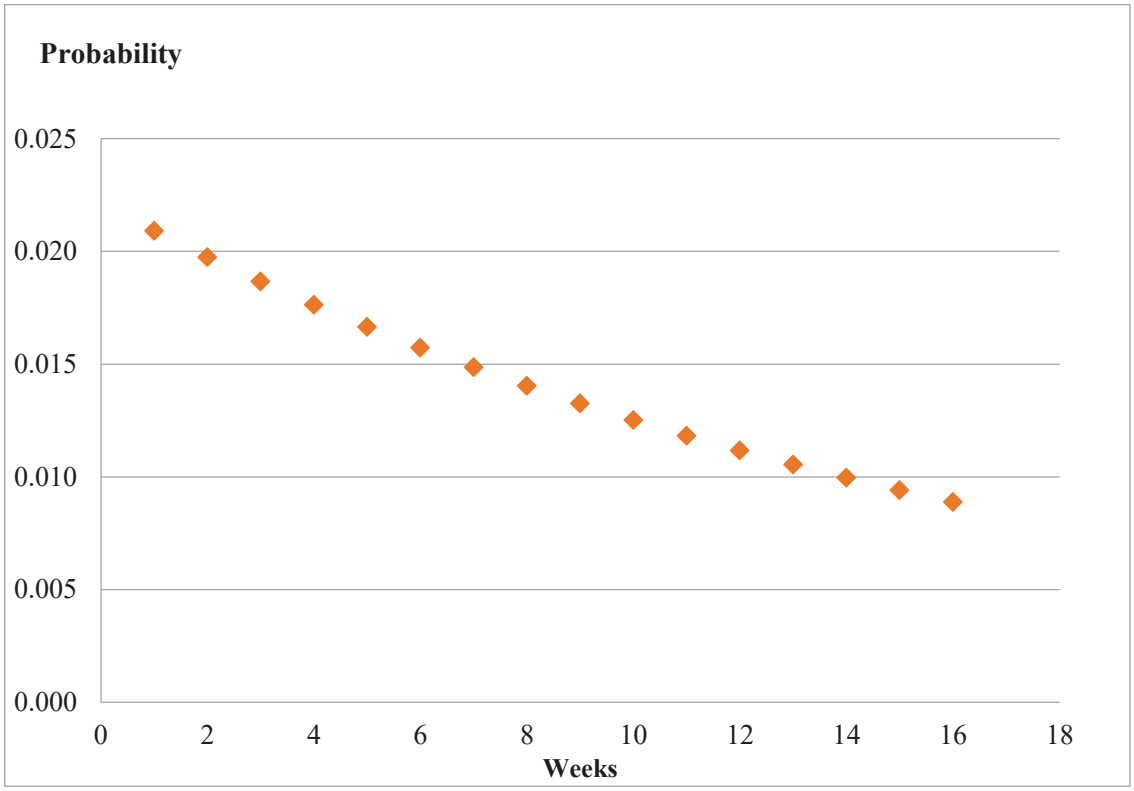

Figure 32 Probability for Time to Readmission within 16 weeks

5.5.2 Multilevel Logistic Model for investigating factors affecting to hospital readmission

Readmission into hospital is frequently indicated as an indicator of the quality of medical care. Although widely used, the lack of a standardized time frame might affect hospital management. In this case, bronchiectasis, which is a chronic lung disease, has unpredictable exacerbation. Patients with bronchiectasis may or may not return to hospital in 16 weeks since they leave the hospital. Such factors highlighted as contributors to patient readmission have been gender, age group and patient' smoking status, however, they may not affect readmission for bronchiectasis patients. In this study, the crucial factors have been investigated for bronchiectasis hospital readmission as described in the previous section. The predictor variables have been included to Model 5.4, such as gender, one at the time. The equation has been expanded as:

$$\log\left(\frac{P_{ij}}{1-P_{ij}}\right) = \beta_0 \text{Const} + \beta_1 \text{Week}_{ij} + \beta_2 \text{factor}_{j} + u_j \quad (5.5)$$

,where β_0, β_1, β_2 are called fixed parameters and u_j is the random parameters which is assumed to follow a normal distribution with zero mean and variance σ_u^2. The following predictor variables have been examined as the factors affecting to hospital readmission for bronchiectasis;

- Gender
- Age-groups
- Patient's smoking status
- ABR-Registry
- Season
- lnLOS

Additional influences on risk of readmission can be investigated by adding further predictors to the Model 5.4. The estimated parameters and its standard error are presented in Table 5.5-5.11.The effects of crucial predictors on the risk of readmission can be well displayed by plotting Kaplan-Meier curves (Kaplan and Meier, 1958) as the Figure 33-37. The important finding for the purpose of this study is that **Patient's smoking status** and **lnLOS** shows the statistical significance for the risk of hospital readmission. While, gender, age-groups, ABR-Registry and Season (at discharge date) were not statistically significant factors. The results for each predictor individually can be summarized as follow:

- **Gender**: Compared with females, males provided a positive coefficient shift (Table 5.5) over females although most of bronchiectasis patients in this cohort were females. This is shown in Figure 33 as males are prone to have higher readmission rate than females. However, Table 5.5 shows that the difference is not statistically significant.

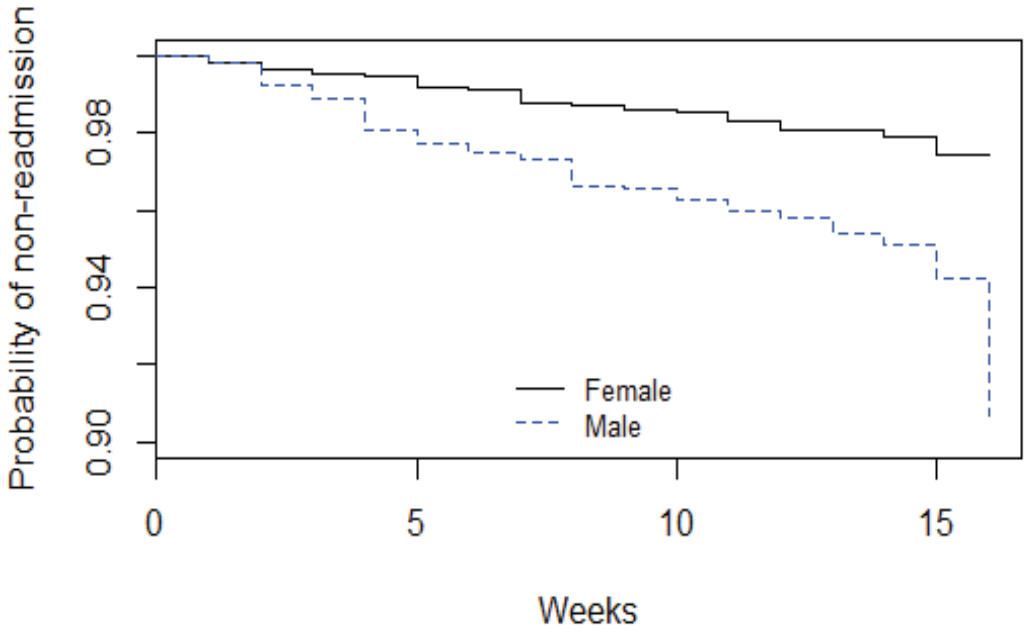

Figure 33 The Kaplan-Meier Survival Curve for Time to Readmission between males and females within 16 weeks

● **Age-groups**: Elderly bronchiectasis patients show higher readmission rates than younger aged-groups as shown in Figure 34. However, the results in Table 5.6 show that the age differentials are not significant.

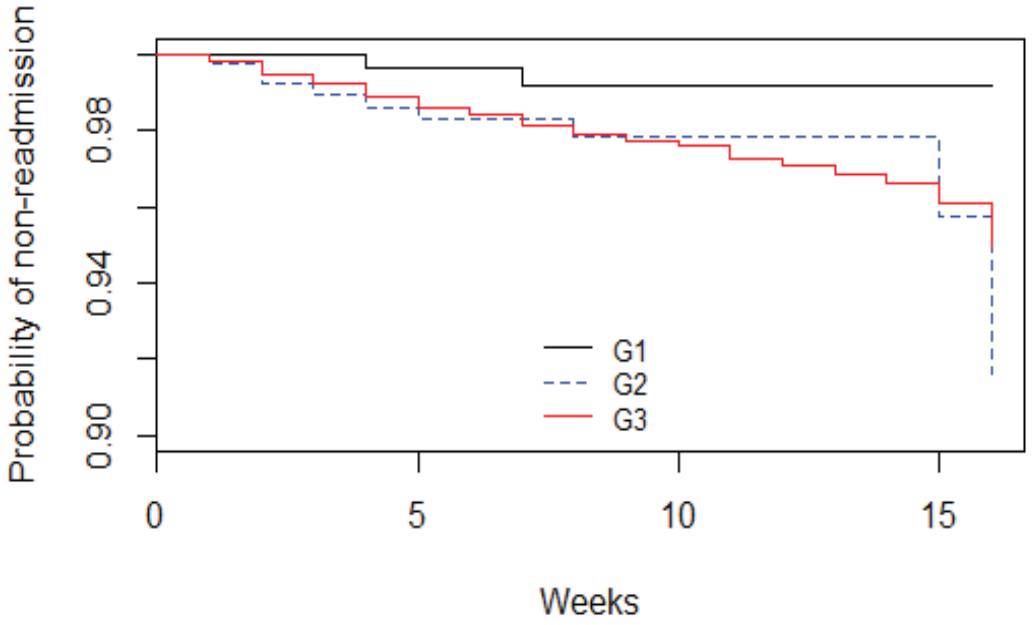

Figure 34 The Kaplan-Meier Survival Curve for Time to Readmission between aged-groups within 16 weeks (Note: Group1 (G1; 20-39), Group2 (G2; 40-59), Group3 (G3; ≥ 60)

● **Smoking status:** Figure 35 shows clearly that bronchiectasis patients who were smokers had a readmission rate higher than patients who were not smokers. Table 5.7 shows that this differential is significant.

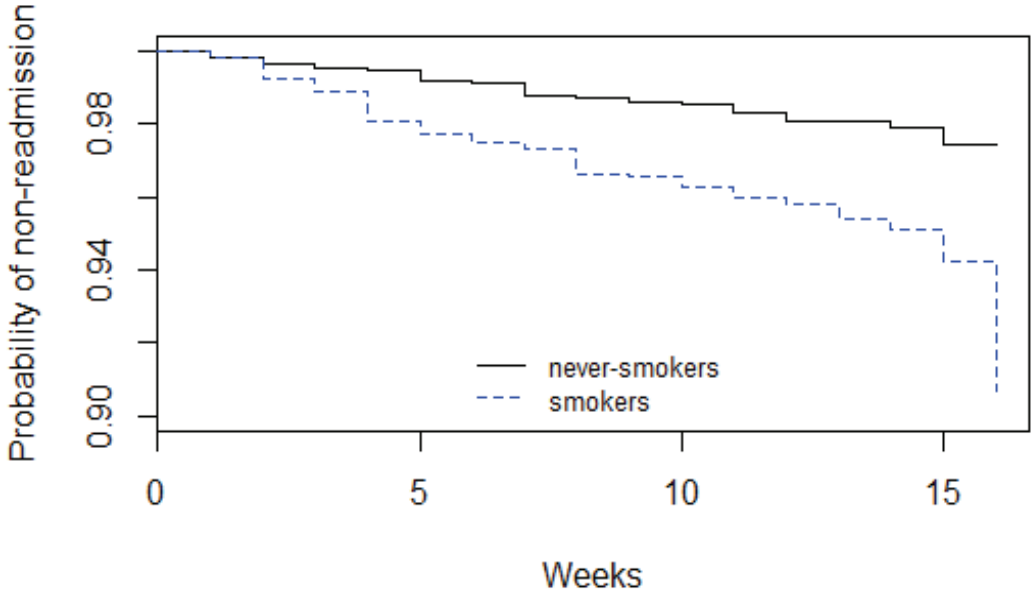

Figure 35 The Kaplan-Meier Survival Curve for Time to Hospital Readmission of patient smoking status within 16 week

● **ABR-Registry:** Bronchiectasis patients who participated with the ABR-registry show the higher readmission rate over the non- ABR registry group of bronchiectasis patients during 6 to 13 weeks as presented in Figure 36. Table 5.8 shows this factor differential is not significant.

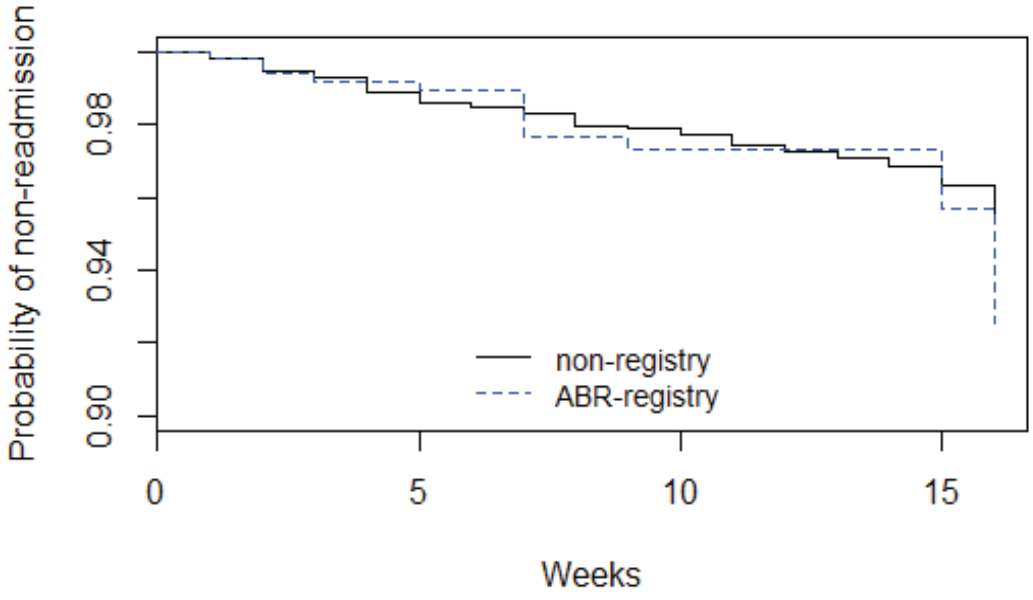

Figure 36 The Kaplan-Meier Survival Curve for Time to Readmission of patients' ABR-registry status within 16 weeks

● **Season:** If bronchiectasis patients were discharged in winter, summer is more likely the high season to readmission into hospital.

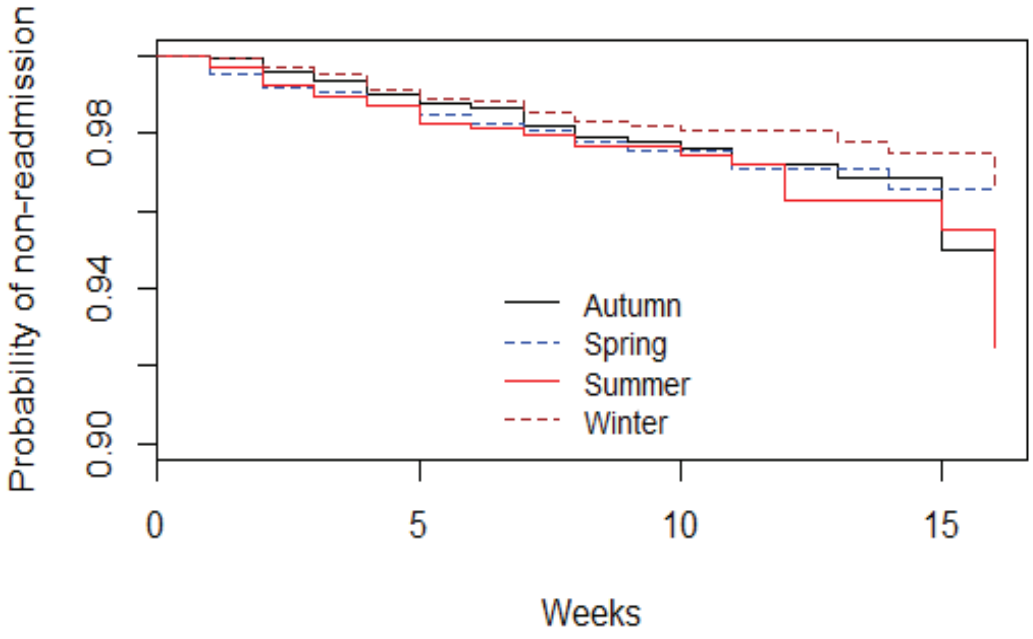

Figure 37 The Kaplan-Meier Survival Curve for Time to Hospital Readmission based on seasonality within 16 weeks

●lnLOS**:** length of stay in hospital (LOS) is a significant factor for readmission. A longer stay in hospital could reduce the readmission rate.

The estimated parameters and its standard error are presented of these factors have been represented in Table 5.5-5.10 as follow.

Table 5.5 Estimated Effects of **Gender** on the Probability of Readmission and Time to Readmission

Parameters	**Estimate**	**Standard Error**
Fixed Parameters		
Constant	-3.8923	0.2653
Week	-0.0583	0.0255
male	0.2472	0.2909
Random Parameters		
σ_u^2	2.2224	0.5011

Table 5.6 Estimated Effects of **Age-groups** on the Probability of Readmission and Time to Readmission

Parameters	**Estimate**	**Standard Error**
Fixed Parameters		
M2: Aged-group (Ref:Group1)		
Constant	-4.7608	0.8203
Week	-0.0581	0.0255
Age- Group 2	0.9638	0.9621
Age- Group 3	1.0264	0.8145
Random Parameters		
σ_u^2	2.2055	0.4983

Table 5.7 Estimated Effects of **Smoking-status** on the Probability of Readmission and Time to Readmission

Parameters	Estimate	Standard Error
Fixed Parameters		
Const	-4.0379	0.2611
Week	-0.0595	0.0253
smoker	0.6422*	0.2824
Random Parameters		
σ_u^2	1.7999	0.4603

(Note: * P< 0.05)

Table 5.8 Estimated Effects of **ABR-Registry** on the Probability of Readmission and Time to Readmission

Parameters	Estimate	Standard Error
Fixed Parameters		
Const	-3.8183	0.2376
Week	-0.0576	0.0255
ABR-registry	0.2379	0.4639
Random Parameters		
σ_u^2	2.3706	0.5146

Table 5.9 Estimated Effects of **Seasonality** on the Probability of Readmission and Time to Readmission

Parameters	Estimate	Standard Error
Fixed Parameters		
Const	-4.0044	0.3186
Week	-0.0578	0.0255
Spring	0.3270	0.3846
Summer	0.3677	0.3783
Autumn	0.2257	0.3686
Random Parameters		
σ_u^2	2.2968	0.5080

Table 5.10 Estimated Effects of **hospital LOS** on the Probability of Readmission and Time to Readmission

Parameters	Estimate	Standard Error
Fixed Parameters		
Const	-2.9011	0.4359
Week	-0.0523	0.0251
$lnLOS$	-0.4449*	0.1888
Random Parameters		
σ_u^2	2.0746	0.4832

(Note: * P< 0.05)

In conclusion, the crucial factors affecting hospital readmission (within 16 weeks) of bronchiectasis patient in Concord Hospital during July 2011- June 18 are patients' smoking status and length of stay in hospital. The model probability of readmission into hospital is presented as:

$$\log\left(\frac{P_{ij}}{1-P_{ij}}\right) = \beta_o \text{Const} + \beta_1 \text{Week}_{ij} + \beta_2 \text{Smoker}_j + \beta_3 \text{lnLOS}_j + u_j, \quad (5.6)$$

As before, β_0, $\beta_1, \beta_2, \beta_3$ are fixed parameters and u_{oj} refers to the random effects which is assumed to follow a normal distribution with zero mean and variance σ_u^2. The estimated parameters of the model have been shown in the Table 5.11. The results suggest that patients who were smokers had a higher readmission rate than patients were not smokers. The coefficient of smokers is positive and statistically significant ($P < 0.05$). While, the coefficient of lnLOS is negative statistical significant. It would indicate that the outcome is lower readmission with the longer stay or patients who had shorter stay in hospital before they were discharged were prone to have the higher risk of hospital readmission. This means that bronchiectasis patients who left hospital more quickly are tend to quicker readmission. The relationship between the lnLOS and readmission rate in this study could imply that the high cost of health care is associated with the longer stay in hospital ALOS as presented in Chapter 4.Thus, the new code (E77) with longer ALOS may facilitate the longer stays in hospital regarding to hospital costs.

Table 5.11 Parameter estimates of Model 5.6 (model with two significant factors: smoker, lnLOS)

Parameters	Estimate	Standard Error
Fixed Parameters		
Const	-3.2218	0.4451
Week	-0.0543	0.0250
Smoker	0.6070*	0.2905
lnLOS	-0.4050*	0.1816
Random Parameters		
σ_u^2	2.0746	0.4832

(Note: * P< 0.05)

The Model 5.6 (probability for time to readmission of bronchiectasis patient in Concord hospital within 16 weeks with two significant factors) can be illustrated as the Figure 38 below. The graph (by adding patients' smoking status and lnLOS) presents the probability of readmission between smoker and never smoker group. Clearly, smoker group has a higher rate of readmission than never-smoker.

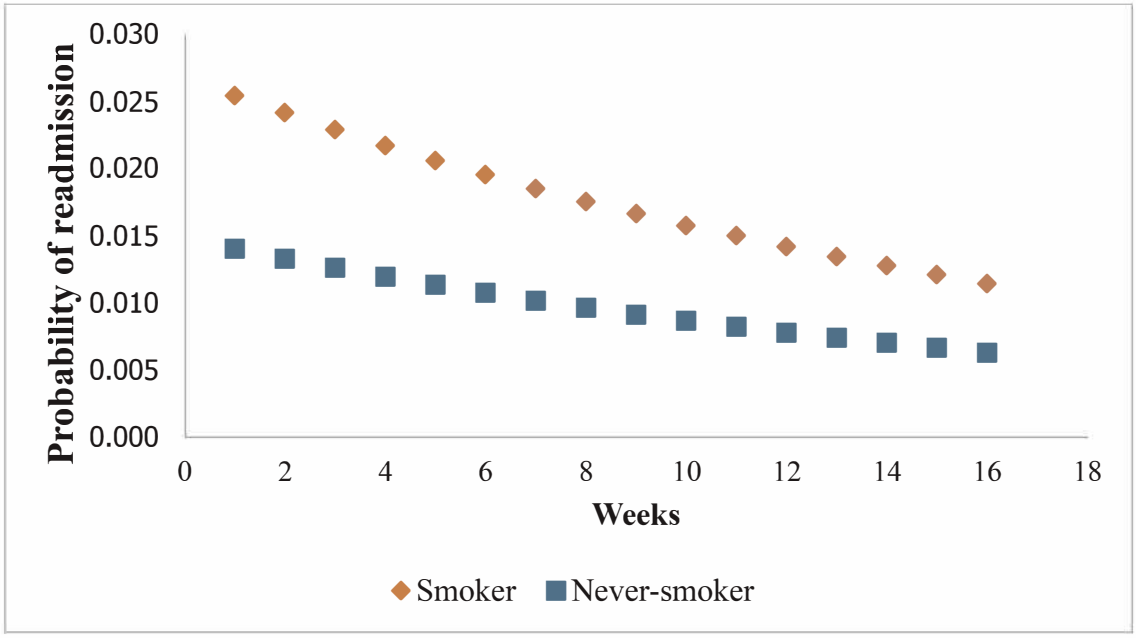

Figure 38 Probability for Time to Readmission of bronchiectasis patient in Concord hospital within 16 weeks by adding the couple significant factors: smoking status and lnLOS (mean of LOS =11.19)

Table 5.12 Probability of bronchiectasis readmission within 13 weeks and 16 weeks

Week	Probability to readmission (%)	
	13 weeks	16 weeks
1	2.2	2.1
2	2.1	2.0
3	2.0	1.9
4	1.9	1.8
5	1.7	1.7
6	1.7	1.6
7	1.6	1.5
8	1.5	1.4
9	1.4	1.3
10	1.3	1.3
11	1.2	1.2
12	1.2	1.1
13	1.1	1.1
14		1.0
15		0.9
16		0.9

As the table above, probability of bronchiectasis readmission within 13 weeks and 16 weeks is not much difference. The probability of bronchiectasis readmission is slightly decreasing within 13 or 16 weeks.

5.6 Conclusion

In this chapter, the multilevel model for binary outcome has been examined for analysis time to readmission to Concord hospital of bronchiectasis patients after they were discharged from hospital within 16 weeks. The results shows that time in week as the linear form is significant to predict time to be admitted to hospital after discharge. Another purpose in the study is to explore the potential factors such as patient characteristics or hospital LOS that may influence to hospital readmission as illustrated in Figure 29. The assumption is based on there is an association between patient characteristics, hospital LOS and the probability of patient readmission to the hospital. As stated previously, both patients' smoking status and hospital LOS are significantly factors supporting to the assumption of a link between patient characteristics, hospital LOS and hospital readmission of bronchiectasis patient. Due to the results, this identifies that patient characteristics (patient smoking status) have not affected to

hospital LOS significantly but not for hospital readmission. For hospital LOS, this indicator plays important role related to hospital performance. In this study indicates that the longer days in hospital can reduce the probability of readmission to hospital of bronchiectasis patients. For this particular cohort, the relationship between these factors and readmission can be demonstrated as the Figure 39 below. Smoking status and hospital LOS have directly an impact on bronchiectasis readmission. While, the ABR-registry status may be indirect influencing the readmission since the ABR-registry status is a crucial factor resulting in the hospital LOS. However, to ensure valid link between hospital readmission patent characteristics and hospital LOS may be worth considering for further study by addressing the hospital level in the multilevel model.

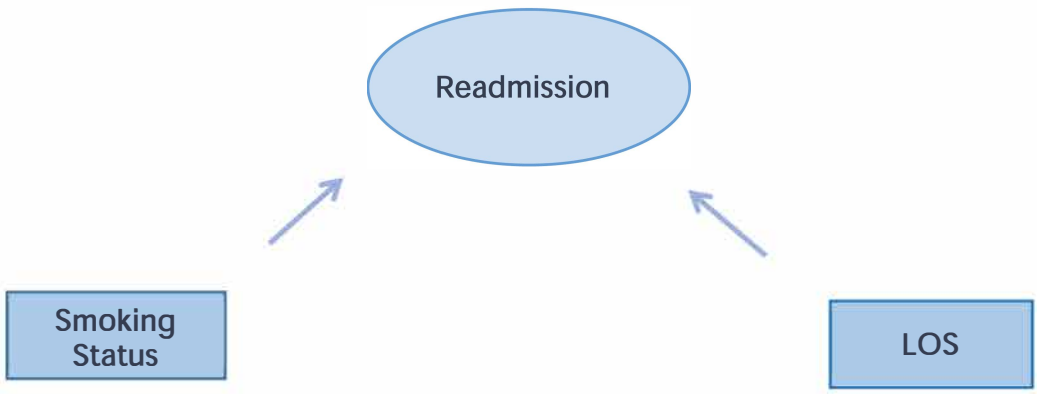

Figure 39 The relationship between LOS, patient smoking status and readmission

CHAPTER 6

Conclusion and Discussion

This chapter summarizes the contributions of the thesis results and discusses its findings. Furthermore, the limitations of the current work and the possibility for future work complete this chapter

6.1 Summary of thesis contributions

The body of this work originated from anecdote. The clinicians involved in the Australian Bronchiectasis Registry (ABR) recognized that patients who needed admission to hospital with bronchiectasis stayed longer than patients with other similar underlying lung problems. Additionally, there was no specific group of disease in the AR- DRG classification system to accurately describe and fund these complex admissions in Australia's current casemix/ activity based hospital funding system.

The idea of this project began with the study of the relationship between the actual length of stay (LOS) of bronchiectasis patients and the average length of stay (ALOS) that they were assigned to in a particular group of diseases in the AR-DRG classification system. It was clear that there was a gap of many days between LOS and ALOS for bronchiectasis. ***The first part*** of the work of this thesis contributed to the successful application for a bronchiectasis specific code (E77A and E77B) and was integrated into the 2016 version of the AR-DRG. Version 9 came into effect in 2018. This was expanded to explore the financial impact of this change in coding. An admission that prior to 2018 would have been coded to E65a and attracted an ALOS of 6.70 days, under the new code of E77A, attracted an ALOS of 8.10days. Despite this increase in ALOS, the actual LOS for our cohort was still 13 days, reflecting ongoing disparity between the complexity of admission for these patients and the funding received by the hospitals that care for them.

The second part of this project explored the time between episodes of in -hospital care or time to readmission and, consistent with other work, identified that older patients and winter season were associated with short time between admissions. The data used in this study have a multilevel structure in the sense that episodes are nested within patients, thus leading to episodes in the same patients exhibiting some similarities. These similarities might be due to patients exposed to the same characteristics or environments. Multilevel models were applied to analyze this dataset as the shown in the representative results shown in the section below. There were two parts for each level; a fixed part and a random part. The fixed part comprises

the individually recorded information such as gender, date of birth, admission date, discharge date, smoking status, etc. It can be interpreted as intercept and slope. The random part is the differences between the observed value and the fixed part (residual of each of patient). These can be used to estimate the unexplained variation in the model. For the first study, the multilevel model was examined to extend the relationship between LOS and ALOS by adding the crucial factors possibly affecting the LOS. A multilevel model (binary outcome) for investigating hospital readmission was then established to analyze the time until readmission. The factors as mentioned earlier were also addressed to analyze as influencing factors for hospital readmission. In this study, a Cox proportional hazards model was applied to predict the time until a new episode occurred. The latter approach, known as survival or event history analysis, is useful because the models predict whether or not the event occurs as well as the timing of the event.

6.2 Summary of the results

This project has three main purposes. **The *first*** aim is to investigate whether or not the actual length of stay (LOS) of bronchiectasis patients is consistent with the average length of stay (ALOS) based on the AR-DRG group they were assigned to when they were discharged from hospital. For this part, at first, a simple linear regression was used to investigate the relationship between ALOS and LOS. They were assumed to be in a linear relationship as $Y = \beta_0 + \beta_1 x$ where Y was the expected length of stay with each values of predictor x and β_o, β_1 were supposed to be 0, 1 respectively. Although, the results indicated that the model had statistical significance in predicting the length of stay in hospital (LOS) of bronchiectasis patients by a significant predictor ALOS and there was a significant linear correlation, the residuals plot in Figure22 was not supportive of the normality assumption. In addition, the Q-Q plot in Figure24 demonstrated that the points were not close enough to a straight line. Both suggested that the normality assumption seemed implausible. For this reason, the log-log transformed model was applied with the simple linear regression with the assumption as $\ln(Y) = \beta_0 + \beta_1 \ln x$ or $Y = e^{\beta_0} x^{\beta_1}$ where β_0 , β_1 are supposed to be 0 and 1 respectively. It can be written with the error term as $\ln(Y) = \beta_0 + \beta_1 \ln(x) + \varepsilon$. The results suggested that the log transformed model is statistically significant in predicting the length of stay LOS by a significant predictor ALOS and there was a significant linear relationship between the predictor and the response variables. The residual plots against fitted values for the log-log linear regression model in Figure 23 suggest that the zero mean assumption was suitable for comparing the residuals plots of the simple linear regression model in Figure 22. Furthermore, the Q-Q plot of the log-log linear regression model in Figure 25 indicated that the points were close to the line, supporting the normally distributed assumption, while the Q-Q plot of the simple linear regression model in

Figure 24 throws some doubt on the normality assumption. Thus, the log-log linear regression model (the log-log transformed model) was more appropriate to demonstrate the relationship between the LOS and ALOS. Based on 299 patients with 505 episodes of bronchiectasis in Concord hospital during July 2011- June 2018, most episodes were equal or less than 15 days, as shown in the Figure17. By two to fifteen days period, the observed or actual length of stay (LOS) for bronchiectasis patients was shifted significantly higher than the average length of stay (ALOS) associated with the AR-DRG classification system as shown in the Figure26 (Kingkam et al., 2017). This is an evidence to support the conclusion that bronchiectasis patients are prone to having the length of stay (LOS) in hospital higher than their expected length of stay when they had been assigned to the AR-DRG group of diseases. In particular, the length of stay (LOS) has equal and less than 15 days for most of patients (75%). By implication, patients admitted for bronchiectasis stay longer in hospital than predicted based on the ARDRGs available. In financial year 2018, bronchiectasis has had a specific code in the AR-DRG classification system as E77. This system has recorded the ALOS for bronchiectasis (major complexity) as 8.10 days. It indicates that the new code is related with the under-estimated the resources associated with patients' length of stay in hospital (LOS). This leads to the conclusion that the cost of the treatment for each episode of care for a bronchiectasis patient may be higher than the cost determined based on their AR-DRG assignment.

The *second* aim is to explore the long-term treatment of bronchiectasis patients recorded in the Australian Bronchiectasis Registry (ABR) and Concord hospital in the period July 2011-June2018 and to investigate the patient characteristics and environmental factors which may have an effect on their length of stay in hospital (LOS). The relationship between hospital LOS and ALOS was conducted as a multilevel model as $\ln LOS_{ij} = \beta_0 + \beta_1 \ln ALOS_{ij} + u_j + e_{ij}$ where β_0 , β_1 were the fixed parameters. The random part u_j, e_{ij} refers to group level residual $u_j \sim N(0,\sigma_u^2)$ and individual level residual $e_{ij} \sim N(0,\sigma_e^2)$. The results indicated that lnALOS is significant predictor of hospital LOS, on average one unit increases in lnALOS increases lnLOS by 0.7549 units. The estimated variance within-patients is 0.3586 (SD. = 0.0315) and the estimated variance between-patients is 0.0791 (SD. = 0.0291). The correlation in hospital LOS between two episodes from the same patient is about 0.18, which showed that the unexplained variability in hospital LOS between two episodes from the same patient decreased by accounting for adding lnALOS to the *null* Model 2.1.To analyze factors influencing the hospital LOS, there were five factors have been addressed for this analysis; 1) *Gender*: male and female, 2) *Age-groups*: patients' age on admission date were categorized into three groups which were Group 1 (20-39), Group 2 (40-60) and Group 3 ($\geq$ 60), 3). *Smoking status*: patients were distinguished into two categories; patients who were smokers, patients who had never smoked

during the time period (July 2011- June2018), 4) *ABR-Register status*: some patients in this cohort were participants in the ABR registry but most of them in this cohort were not members of the ABR- registry and 5) *Seasonality*: summer (December- February), autumn (March-May), winter (June-August) and spring (September-November). A multilevel model was used to examine whether or not these factors influenced the length of stay in hospital as represented in Section 4.3.

The results of the study indicated that these factors did not affect the length of stay at a significant level except for the non ABR-registry factor. "Patients who were not enrolled in the ABR-registry" was a statistically factor for length of stay in hospital. In addition, patients who were enrolled in the ABR-registry are prone to have longer stays in hospital compared with patients who did not participate in the ABR registry. This result may lead to changes in hospital funding, supporting the idea that the enrolled bronchiectasis patients in the ABR-registry is necessary both for patients and the healthcare system. For other factors, this analysis found that males, patient age-group 2 and patients who had never smoked were associated with a longer hospital LOS. As expected, winter and spring seem to be the crucial season for longer hospital ALOS for the bronchiectasis patient in this cohort. As above, the correlation in hospital LOS between two episodes from the same patient for the *null* Model 2.1 is about 0.26. This means that 26% of the unexplained variability in episodes is due to variation between patients. However, by adding these factors to the *null* Model 2.1 one at the time, overall, the variances for each factor did not decrease as much as expected as when the model was augmented by a covariate. For example, by adding gender to the *null* Model 2.1, the correlation in hospital LOS between two episodes from the same patient is about $\frac{0.1557}{0.5917} = 0.26$. This possibly reflects how the factors were statistically non-significant in influencing the lnLOS.

The *third* aim was to explore whether or not patient characteristics result in time to the next episode of care or hospital readmission for the cohort of 299 bronchiectasis patients in Concord hospital during the period July 2011-June 2018. The effect of *time* (week) on the hazard of hospital readmission was modeled by treating time as covariate and dummy variables. The discrete-time hazard model included only the time predictor (*week)* and showed that time as the quadratic term, cubic term and dummy variable were not statistically significant except for the linear term. In chapter 5, the model of time to readmission has been represented as the linear term which was a significantly better fit than the other time variable forms by considering censored time at week 16^{th}. The results in Table 5.17 indicated that changes of readmission to Concord Hospital dropped almost 2 % for every additional time in week by16 weeks as represented in Figure 32. The risk factors for hospital readmission were considered by adding

five factors; gender, age-groups, patients' smoking status, ABR-registry status and hospital LOS. The multilevel logistic model was conducted as below:

$$\log\left(\frac{P_{ij}}{1-P_{ij}}\right) = \beta_0\ \mathrm{Const} + \beta_1 \mathrm{Week}_{ij} + \beta_2 \mathrm{factor}_{ij} + u_j$$

, where $\beta_o, \beta_1, \beta_3$ are coefficients and u_j is the random effects which is assumed to follow a normal distribution with zero mean and variance σ_u^2. The results suggest that bronchiectasis patients who were smokers, and hospital LOS, both had a statistical significance for readmission while the others did not (Table 5.11). The probability of readmission by including both significant factors is represented i Table 6.1 below. Smoking is a factor known to worsen the condition and symptoms of bronchiectasis. The significant relationships between patients who smoke and hospital readmission can be related to that evidence. Considering hospital LOS, this factor provided a negative significant coefficient for this study, suggesting that longer stays in hospital can reduce readmission risk. The reduction of readmission can reduce the costs related to inpatients care. Overall, the probability of bronchiectasis readmission within 16 weeks increases slightly by adding smoker and hospital LOS as presented in Table 6.1. The probability of readmission between the ever-smoker group and never-smoker group is also illustrated in Figure 38.

Table 6.1 Probability of bronchiectasis readmission within 16 weeks

Week	Probability (%)	Probability (%) by adding significant factors
2	2.0	2.4
4	1.8	2.2
6	1.6	1.9
8	1.4	1.8
10	1.3	1.6
12	1.1	1.4
14	1.0	1.3
16	0.9	1.1

In brief, the two crucial indicators in the healthcare system; length of stay in hospital and readmission of bronchiectasis patients have been evaluated in this research. Length of stay, which is an important determinant of hospital performance and resource use, has been examined in three main ways in this research; **1)** the relationship between LOS and ALOS based on the AR-DRG classification system, **2)** patients characteristics and factors related to bronchiectasis influencing the LOS and **3)** LOS and patient characteristics affecting readmission into hospital. The results indicate that the LOS tends to be higher than the assigned ALOS in the AR-DRG classification system affecting inpatient costs. Patients who were not participants with the ABR-registry have had a significant impact on LOS, that is, patients who participated with the ABR-Registry are tend to have hospital LOS shorter than patients who were not. Moreover, patients who were smokers and hospital lnLOS have a statistical significance for hospital readmission, namely longer stays in hospital reduce the probability of readmission. This relates with the previous results that ABR- participants are prone to have hospital readmission more than non ABR-participants. In 2019, the report from the Australian Commission on Safety and Quality in Health Care has highlighted that high rates of hospital readmission indicate low-quality care. The low probability of readmission for bronchiectasis patients (during the observed period) may indicate the quality of Concord Hospital management performance. Moreover, this research is helpful for clinical practice, healthcare services and hospital planning purposes.

6.3 Limitations

It is clear that the projects that make up this thesis are nested in a single centre (Concord Hospital) and hence it is possible that the results are not representative of national or international cohorts. The Concord cohort has a similar gender and age distribution to the Australian Bronchiectasis Registry cohort as published by (Visser et al., 2019). Bronchiectasis has particularly high prevalence in Indigenous Australians (Blackall et al., 2018). No patients in the Concord cohort identify as Aboriginal or Torres Strait Islander. At the time of data analysis, only 10% of patients admitted to Concord Hospital for bronchiectasis were enrolled in the ABR. The Concord Hospital ABR enrolled bronchiectasis cohort is much larger (n=380) but only a small number required hospital admission during this time period. It could be those who were admitted were more complex but it is more likely that the two cohorts (the ABR and the Concord admissions) only overlapped by 18 months. It would be very worthwhile to run the modeling again over a time period when enrollment to the ABR was more complete. This could then be rolled out over the more than 20 sites in Australia contributing data to the ABR (n ~ 1500 at time of submission) to more accurately match National Australian ALOS with LOS for

bronchiectasis and to tease outpatient specific and hospital specific factors that might affect these. The admission data is limited only to Concord Hospital. The electronic medical record system in NSW does not allow one to track a patient across local health districts or admissions to other hospitals (*Note that*: Hospital readmissions could be identified using data linkage). It is possible that patients could have had extra admissions to other hospitals, could have changed address or died and this information might have been missed.

6.4 Further works

The ABR offers many opportunities for future statistical and mathematical modeling. Concord Hospital has no paediatric admissions but the ABR collects data on children with bronchiectasis many of whom are admitted to hospital for treatment of exacerbations. It remains unknown whether age and seasonality have the same effect on admissions in children, or whether the AR-DRG for bronchiectasis underfunds these admissions to the same degree. The admission data from a single hospital gave us a glimpse of one part of the journey of illness for a group of patients with this chronic lung disease. Most patients continue to carry a heavy burden of disease outside of the hospital environment. The AR DRG system does not capture the cost of this out of hospital burden. The ABR has data linkage capacity to the PBS (Pharmaceutical Benefits Scheme) and MBS (Medicare Benefits Schedule). This big data set is collated but as yet unexplored modeling opportunity for future collaborations. The mathematical modeling methods I used were relatively simple. I was limited by the availability of covariate data within the hospital records in terms of the complexity of predictors. It was also clear that we are not sure with re-admission whether a patient is still at risk of re-admission to that hospital. Future analysis utilizing the ABR, once it has multiple years of data, will tackle both of those weaknesses. In terms of modelling approaches, the next extension would be created a complete event history connecting time in and out of hospital. That would allow for testing the impact of health behaviors managing bronchiectasis on both time between and in hospital by using the MBS and PBS data to pick-up connections with primary health outside of hospital. In this analysis, I have already shown that smoking and hospital LOS impact time to re-admission once a patient is experiencing a hospital episode. There is the potential to treat interactions with primary health and those with the hospital system as a joint process, with hospital episodes driving primary health connections and the reverse as well. Patients often transfer between hospitals so tracking these hospital transfers also needs investigation. Factors and patient characteristics such as comorbidity and type of treatments within the studied timeframe may have an impact on hospital transfer and/or readmission. I have learnt that bronchiectasis is a relatively common condition with multiple factors that potentially contribute to clinical complexity. Two composite score systems (Bronchiectasis Severity Score BSI and FACED)

have been validated to stratify severity and risk of death. BMI have a tendency for assessment of severity of bronchiectasis comparing to FACED score (Costa et al., 2018). These scores could be used to refine the funding for bronchiectasis admissions to more accurately reflect ALOS in future versions of the AR-DRG system. Nesting this modeling in a cohort of patients from one hospital had some advantages. As a mathematician based in a School of Mathematical and Physical Sciences, I did not know very much about chronic lung disease and less about how mathematics and statistics might overlap and help clinicians to deliver effective clinical care or how to fund this care. I had the opportunity to spend time with the specialist doctor and learn about how she treats these patients, and came to understand better exactly why modeling could change the way the hospital system works for the patient and the doctor. This project truly was an example of the potential for interdisciplinary collaboration and opened my mind to the potential for applied medical mathematics.

REFERENCES

AGHAJANI, S. & KARGARI, M. 2016. Determining Factors Influencing Length of Stay and Predicting Length of Stay Using Data Mining in the General Surgery Department. *Hospital Practices and Research,* 1**,** 53-58.

AIHW. 2018. *Admitted patient care 2016–17: Australian hospital statistics* [Online]. Available: https://www.aihw.gov.au/reports/hospitals/ahs-2016-17-admitted-patient-care/contents/table-of-contents [Accessed].

AIHW. 2019. *Admitted patient care 2017–18* [Online]. Available: https://www.aihw.gov.au/reports/hospitals/admitted-patient-care-2017-18/contents/table-of-contents [Accessed].

ALIBERTI, S., MASEFIELD, S., POLVERINO, E., DE SOYZA, A., LOEBINGER, M. R., MENENDEZ, R., RINGSHAUSEN, F. C., VENDRELL, M., POWELL, P. & CHALMERS, J. D. 2016. Research priorities in bronchiectasis: a consensus statement from the EMBARC Clinical Research Collaboration. *European Respiratory Journal,* 48**,** 632-647.

ALLAIRE, J. 2012. RStudio: integrated development environment for R. *Boston, MA,* 537**,** 538.

ALLISON, P. D. 1982. Discrete-Time Methods for the Analysis of Event Histories. *Sociological Methodology,* 13**,** 61-98.

ANTIOCH, K. M. & WALSH, M. K. 2004. The risk-adjusted vision beyond casemix (DRG) funding in Australia. *The European Journal of Health Economics, formerly: HEPAC,* 5**,** 95-109.

ARGHA, A., SAVKIN, A., LIAW, S.-T. & CELLER, B. G. 2018. Effect of Seasonal Variation on Clinical Outcome in Patients with Chronic Conditions: Analysis of the Commonwealth Scientific and Industrial Research Organization (CSIRO) National Telehealth Trial. *JMIR medical informatics,* 6**,** e16.

ARRAM, E. O. & ELRAKHAWY, M. M. 2012. Bronchiectasis in COPD patients. *Egyptian Journal of Chest Diseases and Tuberculosis,* 61**,** 307-312.

ATTARAN, D., TOWHIDI, M. & ASNAASHARI, A. H. 2006. Sulfur mustard induced bronchiectasis 15-20 years After exposure, review of 34 cases. *Iranian Journal of Otorhinolaryngology,* 18**,** 21-25.

AU, P. O. 2018. Recent developments in federal government funding for public hospitals.

AUSTIN, P. C., GHALI, W. A. & TU, J. V. 2003. A comparison of several regression models for analysing cost of CABG surgery. *Statistics in medicine,* 22**,** 2799-2815.

AUSTRALIA, P. O. 2018. Recent developments in federal government funding for public hospitals.

BADGAL, A. 2015. Factors affecting the average length of stay of the patients in the inpatient department in a tertiary care centre in North India. *Journal of Evolution of Medical and Dental Sciences,* 4**,** 150-156.

BANJAR, H. H. 2007. Clinical profile of Saudi children with bronchiectasis. *Indian journal of pediatrics,* 74**,** 149.

BARKER, A. F. 2002. Bronchiectasis. *New England Journal of Medicine,* 346**,** 1383-1393.

BARTON, J., SCOTT, L. & MAGUIRE, G. 2018. Bronchiectasis in the Kimberley region of Western Australia. *Australian Journal of Rural Health,* 26**,** 238-244.

BASNAYAKE, T. L., MORGAN, L. C. & CHANG, A. B. 2017. The global burden of respiratory infections in indigenous children and adults: a review. *Respirology,* 22**,** 1518-1528.

BEIDAS, R. S. & KENDALL, P. C. 2010. Training therapists in evidence‐based practice: A critical review of studies from a systems‐contextual perspective. *Clinical Psychology: Science and Practice,* 17**,** 1-30.

BELL, S. C., ELBORN, J. S. & BYRNES, C. A. 2018. Bronchiectasis: Treatment decisions for pulmonary exacerbations and their prevention. *Respirology,* 23**,** 1006-1022.

BIBBY, S., MILNE, R. & BEASLEY, R. 2015. Hospital admissions for non-cystic fibrosis bronchiectasis in New Zealand. *New Zealand Med J,* 128**,** 30-8.

BLACKALL, S. R., HONG, J. B., KING, P., WONG, C., EINSIEDEL, L., RÉMOND, M. G., WOODS, C. & MAGUIRE, G. P. 2018. Bronchiectasis in indigenous and non‐indigenous residents of Australia and New Zealand. *Respirology,* 23**,** 743-749.

BROWN, M. P., STURMAN, M. C. & SIMMERING, M. J. 2003. Compensation policy and organizational performance: The efficiency, operational, and financial implications of pay levels and pay structure. *Academy of management Journal,* 46**,** 752-762.

BUENO, H., ROSS, J. S., WANG, Y., CHEN, J., VIDÁN, M. T., NORMAND, S.-L. T., CURTIS, J. P., DRYE, E. E., LICHTMAN, J. H. & KEENAN, P. S. 2010. Trends in length of stay and short-term outcomes among Medicare patients hospitalized for heart failure, 1993-2006. *Jama,* 303**,** 2141-2147.

BURSTEIN, L., FISCHER, K. B. & MILLER, M. D. 1980. The multilevel effects of background on science achievement: A cross-national comparison. *Sociology of Education***,** 215-225.

BUSSE, R., SCHREYÖGG, J. & SMITH, P. C. 2006. Hospital case payment systems in Europe. *Health care management science,* 9**,** 211-213.

CADILHAC, D. A., DEWEY, H. M., DENISENKO, S., BLADIN, C. F. & MERETOJA, A. 2019. Changes in acute hospital costs after employing clinical facilitators to improve stroke care in Victoria, Australia. *BMC health services research,* 19**,** 41.

CHALMERS, J. D., ALIBERTI, S., POLVERINO, E., VENDRELL, M., CRICHTON, M., LOEBINGER, M., DIMAKOU, K., CLIFTON, I., VAN DER EERDEN, M. & ROHDE, G. 2016. The EMBARC European Bronchiectasis Registry: protocol for an international observational study. *ERJ open research,* 2**,** 00081-2015.

CHALMERS, J. D., GOEMINNE, P., ALIBERTI, S., MCDONNELL, M. J., LONNI, S., DAVIDSON, J., POPPELWELL, L., SALIH, W., PESCI, A. & DUPONT, L. J. 2014. The bronchiectasis severity index. An international derivation and validation study. *American journal of respiratory and critical care medicine,* 189**,** 576-585.

CHALMERS, J. D., LOEBINGER, M. & ALIBERTI, S. 2015. Challenges in the development of new therapies for bronchiectasis. *Expert opinion on pharmacotherapy,* 16**,** 833-850.

CHALMERS, J. D., SMITH, M. P., MCHUGH, B. J., DOHERTY, C., GOVAN, J. R. & HILL, A. T. 2012. Short-and long-term antibiotic treatment reduces airway and systemic inflammation in non–cystic fibrosis bronchiectasis. *American journal of respiratory and critical care medicine,* 186**,** 657-665.

CHAN‐YEUNG, M., LAI, C. K., CHAN, K. S., CHEUNG, A. H., YAO, T. J., HO, A. S., KO, F. W., YAM, L. Y., WONG, P. C. & TSANG, K. W. 2008. The burden of lung disease in Hong Kong: a report from the Hong Kong Thoracic Society. *Respirology,* 13.

CHANDRASEKARAN, R., MAC AOGÁIN, M., CHALMERS, J. D., ELBORN, S. J. & CHOTIRMALL, S. H. 2018. Geographic variation in the aetiology, epidemiology and microbiology of bronchiectasis. *BMC pulmonary medicine,* 18**,** 83.

CHANG, A., REDDING, G. & EVERARD, M. 2008. Chronic wet cough: protracted bronchitis, chronic suppurative lung disease and bronchiectasis. *Pediatric pulmonology,* 43**,** 519-531.

CHANG, A. B., BELL, S. C., BYRNES, C. A., GRIMWOOD, K., HOLMES, P. W., KING, P. T., KOLBE, J., LANDAU, L. I., MAGUIRE, G. P. & MCDONALD, M. I. 2010. Chronic suppurative lung disease and bronchiectasis in children and adults in Australia and New Zealand. *Medical Journal of Australia,* 193**,** 356-365.

CHOTIRMALL, S. H. & CHALMERS, J. D. 2018. Bronchiectasis: an emerging global epidemic. Springer.

CLARKE, A. 2002. Length of in-hospital stay and its relationship to quality of care. *BMJ Quality & Safety,* 11**,** 209-210.

COLTMAN, C., DUDLEY, G., LANE, M., COSTANZI, J., HAUT, A. & GEHAN, E. 1971. Further clinical studies of combination chemotherapy using cyclophosphamide, vincristine, methotrexate and 5-flourouracil in solid tumors. *The American journal of the medical sciences,* 261**,** 73-78.

COMBES, C., KADRI, F. & CHAABANE, S. Predicting hospital length of stay using regression models: application to emergency department. 10ème Conférence Francophone de Modélisation, Optimisation et Simulation-MOSIM'14, 2014.

COMMISSION, A. 2019. The state of patient safety and quality in Australian hospitals.

COSTA, J., MACHADO, J., FERREIRA, C., GAMA, J. & RODRIGUES, C. 2018. The Bronchiectasis Severity Index and FACED score for assessment of the severity of bronchiectasis. *Pulmonology,* 24**,** 149-154.

COTS, F., MERCADÉ, L., CASTELLS, X. & SALVADOR, X. 2004. Relationship between hospital structural level and length of stay outliers: Implications for hospital payment systems. *Health policy,* 68**,** 159-168.

COX, D. R. & OAKES, D. 1984. *Analysis of survival data*, CRC Press.

CURTIS, K., MITCHELL, R., DICKSON, C., BLACK, D. & LAM, M. 2011. Do AR-DRGs adequately describe the trauma patient episode in New South Wales, Australia? *Health Information Management Journal,* 40**,** 7-13.

DE LA ROSA CARRILLO, D., ROLON, A. N., MORENO, R. M. G., VEIGA, B. M., FUSTER, C. O., GALO, A. P., SÁNCHEZ, C. P., GALLEGO, E. Q., VIDAL, O. S. & JIMÉNEZ, N. C. 2018. Cost of hospitalizations due to exacerbation in patients with non-cystic fibrosis bronchiectasis. *Respiration***,** 1-11.

DUCKETT, S. 2000. The development of Australian refined diagnosis related groups: the Australian inpatient casemix classification. *Casemix Quarterly,* 2**,** 115-20.

DUCKETT, S. & AGIUS, P. 2002. Performance of diagnosis‐based risk adjustment measures in a population of sick Australians. *Australian and New Zealand journal of public health,* 26**,** 500-507.

ECKERT, M., SCHEL, S. H., KENNEDY, H. G. & BULTEN, B. H. 2017. Patient characteristics related to length of stay in Dutch forensic psychiatric care. *The Journal of Forensic Psychiatry & Psychology,* 28**,** 863-880.

EDWARDS, E., ASHER, M. & BYRNES, C. 2003. Paediatric bronchiectasis in the twenty‐first century: Experience of a tertiary children's hospital in New Zealand. *Journal of paediatrics and child health,* 39**,** 111-117.

ERS 2018. Bronchiectasis. *Breathe (Sheff),* 14**,** 73-80.

ETIKAN, İ., ABUBAKAR, S. & ALKASSIM, R. 2017. The Kaplan-Meier estimate in survival analysis. *Biom Biostatistics Int J,* 5**,** 00128.

EVANS, D. J., BARA, A. & GREENSTONE, M. 2007. Prolonged antibiotics for purulent bronchiectasis in children and adults. *Cochrane Database of Systematic Reviews*.

EVANS, J., KOBEWKA, D., THAVORN, K., D'EGIDIO, G., ROSENBERG, E. & KYEREMANTENG, K. 2018. The impact of reducing intensive care unit length of stay on hospital costs: evidence from a tertiary care hospital in Canada. *Canadian Journal of Anesthesia/Journal canadien d'anesthésie,* 65**,** 627-635.

FAN, L.-C., LIANG, S., LU, H.-W., FEI, K. & XU, J.-F. 2015. Efficiency and safety of surgical intervention to patients with non-cystic fibrosis bronchiectasis: a meta-analysis. *Scientific reports,* 5**,** 17382.

FETTER, R. B. 1999. Casemix classification systems. *Australian Health Review,* 22**,** 16-38.

FINCH, S., MCDONNELL, M. J., ABO-LEYAH, H., ALIBERTI, S. & CHALMERS, J. D. 2015. A comprehensive analysis of the impact of Pseudomonas aeruginosa colonization on prognosis in adult bronchiectasis. *Annals of the American Thoracic Society,* 12**,** 1602-1611.

FORD, E. S. 2015. Hospital discharges, readmissions, and ED visits for COPD or bronchiectasis among US adults: findings from the nationwide inpatient sample 2001-2012 and Nationwide Emergency Department Sample 2006-2011. *CHEST Journal,* 147**,** 989-998.

GARBARINO, L. J., GOLD, P. A., SODHI, N., ANIS, H. K., EHIOROBO, J. O., BORAIAH, S., DANOFF, J. R., RASQUINHA, V. J., HIGUERA-RUEDA, C. A. & MONT, M. A. 2019. The effect of operative time on in-hospital length of stay in revision total knee arthroplasty. *Annals of translational medicine,* 7.

GARCÍA-CLEMENTE, M., ENRÍQUEZ-RODRÍGUEZ, A. I., ISCAR-URRUTIA, M., ESCOBAR-MALLADA, B., ARIAS-GUILLÉN, M., LÓPEZ-GONZÁLEZ, F. J., MADRID-CARBAJAL, C., PÉREZ-MARTÍNEZ, L. & GONZALEZ-BUDIÑO, T. 2019. Severe asthma and bronchiectasis. *Journal of Asthma***,** 1-5.

GOEMINNE, P. & DUPONT, L. 2010. Non-cystic fibrosis bronchiectasis: diagnosis and management in 21st century. *Postgraduate Medical Journal,* 86**,** 493-501.

GOLDFIELD, N. 2010. The evolution of diagnosis-related groups (DRGs): from its beginnings in case-mix and resource use theory, to its implementation for payment and now for its current utilization for quality within and outside the hospital. *Quality Management in Healthcare,* 19**,** 3-16.

GRIFFITHS, P. L., BROWN, J. J. & SMITH, P. W. 2004. A comparison of univariate and multivariate multilevel models for repeated measures of use of antenatal care in Uttar Pradesh. *Journal of the Royal Statistical Society: Series A (Statistics in Society),* 167**,** 597-611.

HILL, S., MORRISON, H., BURNETT, D. & STOCKLEY, R. 1986. Short term response of patients with bronchiectasis to treatment with amoxycillin given in standard or high doses orally or by inhalation. *Thorax,* 41**,** 559-565.

HOFOSS, D., VEENSTRA, M. & KROGSTAD, U. 2003. Multilevel analysis in health services research: a tutorial. *ANNALI-ISTITUTO SUPERIORE DI SANITA,* 39**,** 213-222.

HPA 2013. Analysis of hospital-acquired diagnoses and their effect on case complexity and resource use – Final report.

HU, X., LEE, J. S., PIANOSI, P. T. & RYU, J. H. 2015. Aspiration-related pulmonary syndromes. *Chest,* 147**,** 815-823.

IHPA 2016. Australian Consortium for Classification Development.

IHPA. 2019. *AR-DRG classification system* [Online].
Available: https://www.ihpa.gov.au/what-we-do/products/AR-DRG-classification-system [Accessed].

JACKSON, T. 2001. Using computerised patient-level costing data for setting DRG weights: the Victorian (Australia) cost weight studies. *Health Policy,* 56**,** 149-163.

JACOBS, D. M., NOYES, K., ZHAO, J., GIBSON, W., MURPHY, T. F., SETHI, S. & OCHS-BALCOM, H. M. 2018. Early hospital readmissions after an acute exacerbation of chronic obstructive pulmonary disease in the Nationwide Readmissions Database. *Annals of the American Thoracic Society,* 15**,** 837-845.

JONES, K. & MOON, G. 1993. Medical geography: taking space seriously. *Progress in human geography,* 17**,** 515-524.

KAPLAN, E. L. & MEIER, P. 1958. Nonparametric estimation from incomplete observations. *Journal of the American statistical association,* 53**,** 457-481.

KELLY, C., CHALMERS, J. D., CROSSINGHAM, I., RELPH, N., FELIX, L. M., EVANS, D. J., MILAN, S. J. & SPENCER, S. 2018. Macrolide antibiotics for bronchiectasis. *Cochrane Database of Systematic Reviews*.

KHALIFA, M. Reducing Length of Stay by Enhancing Patients' Discharge: A Practical Approach to Improve Hospital Efficiency. ICIMTH, 2017. 157-160.

KHOO, J. K., VENNING, V., WONG, C. & JAYARAM, L. 2016. Bronchiectasis in the last five years: new developments. *Journal of clinical medicine,* 5**,** 115.

KING, P. T., HOLDSWORTH, S. R., FREEZER, N. J., VILLANUEVA, E., FARMER, M. W., GUY, P. & HOLMES, P. W. 2010. Lung diffusing capacity in adult bronchiectasis: a longitudinal study. *Respiratory care,* 55**,** 1686-1692.

KING, P. T., HOLDSWORTH, S. R., FREEZER, N. J., VILLANUEVA, E. & HOLMES, P. W. 2006. Characterisation of the onset and presenting clinical features of adult bronchiectasis. *Respiratory Medicine,* 100**,** 2183-2189.

KINGKAM, P., VISSER, S., BROWN, J., WOODCOCK, S., BAIRD, T., JACKSON, D. & MORGAN, L. 2017. THE ARGUMENT FOR A BRONCHIECTASIS SPECIFIC AR-DRG: ANALYSIS OF HOSPITAL DISCHARGE DATA (2012-2016) FOR PATIENTS REGISTERED TO THE AUSTRALIAN BRONCHIECTASIS REGISTRY. *Respirology,* 22**,** 206-207.

KUTLAY, H., CANGIR, A. K., ENONENÖN, S., SAHINŞAHIN, E., AKAL, M., GÜNGÖR, A., ÖZDEMIR, N. & KAVUKCUKAVUKÇU, Ş. 2002. Surgical treatment in bronchiectasis: analysis of 166 patients. *European journal of cardio-thoracic surgery,* 21**,** 634-637.

LANGLAND-ORBAN, B., GAPENSKI, L. C. & VOGEL, W. B. 1996. Differences in characteristics of hospitals with sustained high and sustained low profitability. *Hospital & Health Services Administration,* 41**,** 385-401.

LAVE, J. R. & FRANK, R. G. 1988. Factors affecting Medicaid patients' length of stay in psychiatric units. *Health Care Financing Review,* 10**,** 57.

LEE, A. L., HILL, C. J., CECINS, N., JENKINS, S., MCDONALD, C. F., BURGE, A. T., RAUTELA, L., STIRLING, R. G., THOMPSON, P. J. & HOLLAND, A. E. 2014. The short and long term effects of exercise training in non-cystic fibrosis bronchiectasis–a randomised controlled trial. *Respiratory research,* 15**,** 44.

LISK, R., UDDIN, M., PARBHOO, A., YEONG, K., FLUCK, D., SHARMA, P., LEAN, M. E. & HAN, T. S. 2019. Predictive model of length of stay in hospital among older patients. *Aging clinical and experimental research,* 31**,** 993-999.

LIU, Y., PHILLIPS, M. & CODDE, J. 2001. Factors influencing patients' length of stay. *Australian Health Review,* 24**,** 63-70.

LOEBINGER, M., WELLS, A., HANSELL, D., CHINYANGANYA, N., DEVARAJ, A., MEISTER, M. & WILSON, R. 2009. Mortality in bronchiectasis: a long-term study assessing the factors influencing survival. *European Respiratory Journal,* 34**,** 843-849.

MAGUIRE, G. 2012. Bronchiectasis: A guide for primary care. *Australian family physician,* 41**,** 842.

MANDAL, P., SIDHU, M., KOPE, L., POLLOCK, W., STEVENSON, L., PENTLAND, J., TURNBULL, K., MAC QUARRIE, S. & HILL, A. 2012. A pilot study of pulmonary rehabilitation and chest physiotherapy versus chest physiotherapy alone in bronchiectasis. *Respiratory medicine,* 106**,** 1647-1654.

MARSH, H. W., BYRNE, B. M. & YEUNG, A. S. 1999. Causal ordering of academic self-concept and achievement: Reanalysis of a pioneering study and. *Educational psychologist,* 34**,** 155-167.

MARTIN, J. 1979. The Unit of Analysis Problem in Teacher Effectiveness Research.

MARTÍNEZ-GARCÍA, M.-A., DE LA ROSA CARRILLO, D., SOLER-CATALUÑA, J.-J., DONAT-SANZ, Y., SERRA, P. C., LERMA, M. A., BALLESTÍN, J., SÁNCHEZ, I. V., SELMA FERRER, M. J. & DALFO, A. R. 2013. Prognostic value of bronchiectasis in patients with moderate-to-severe chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine,* 187**,** 823-831.

MARTÍNEZ-GARCÍA, M. Á., DE GRACIA, J., RELAT, M. V., GIRÓN, R.-M., CARRO, L. M., DE LA ROSA CARRILLO, D. & OLVEIRA, C. 2014. Multidimensional approach to non-cystic fibrosis bronchiectasis: the FACED score. *European Respiratory Journal,* 43**,** 1357-1367.

MENÉNDEZ, R., MÉNDEZ, R., POLVERINO, E., ROSALES-MAYOR, E., AMARA-ELORI, I., REYES, S., POSADAS, T., FERNÁNDEZ-BARAT, L. & TORRES, A. 2017. Factors associated with hospitalization in bronchiectasis exacerbations: a one-year follow-up study. *Respiratory research,* 18**,** 176.

MIHAILOVIC, N., KOCIC, S. & JAKOVLJEVIC, M. 2016. Review of diagnosis-related group-based financing of hospital care. *Health services research and managerial epidemiology,* 3**,** 2333392816647892.

MOELLER, A. & KANTAR, A. 2018. An Overview of Bronchiectasis in Children. *Bronchiectasis.* Springer.

MORRISSEY, B. M. & HARPER, R. W. 2004. Bronchiectasis: sex and gender considerations. *Clinics in chest medicine,* 25**,** 361-372.

MOSS, T. R. 2018. Hospital length of stay and healthcare costs among African American women due to obesity and diabetic conditions in United States: A model for

correlation studies comparing ethnicity, co-morbidities and hospital resources. *Chronic diseases and translational medicine,* 4**,** 244-253.

MUNRO, K. A., REED, P. W., JOYCE, H., PERRY, D., TWISS, J., BYRNES, C. A. & EDWARDS, E. A. 2011. Do New Zealand children with non‐cystic fibrosis bronchiectasis show disease progression? *Pediatric pulmonology,* 46**,** 131-138.

MURRAY, M. P., PENTLAND, J. L. & HILL, A. T. 2009. A randomised crossover trial of chest physiotherapy in non-cystic fibrosis bronchiectasis. *European Respiratory Journal*.

MUSHLIN, A. I., BLACK, E. R., CONNOLLY, C. A., BUONACCORSO, K. M. & EBERLY, S. W. 1991. The necessary length of hospital stay for chronic pulmonary disease. *Jama,* 266**,** 80-83.

NAKAGAWA, Y., YOSHIHARA, H. & NAKAGAWA, Y. 2011. New indicators based on personnel cost for management efficiency in a hospital. *Journal of medical systems,* 35**,** 625-637.

NEWMAN, L., HARRIS, V., EVANS, L. J. & BECK, A. 2018. Factors associated with length of stay in psychiatric inpatient services in London, UK. *Psychiatric Quarterly,* 89**,** 33-43.

NHS. 2018. *Bronchiectasis* [Online].
Available: https://www.nhs.uk/conditions/bronchiectasis/causes/ [Accessed].

OECD 2011. Health at a Glance 2011. *OECD, OECD Publishing, Paris.,* 15.

PALWATWICHAI, A., CHAOPRASONG, C., VATTANATHUM, A., WONGSA, A. & JATAKANON, A. 2002. Clinical, laboratory findings and microbiologic characterization of bronchiectasis in Thai patients. *Respirology,* 7**,** 63-66.

PARK, S. & LAKE, E. T. 2005. Multilevel modeling of a clustered continuous outcome: nurses' work hours and burnout. *Nursing research,* 54**,** 406.

PERRY, K. M. & KING, D. S. 1940. Bronchiectasis: a study of prognosis based on a follow-up of 400 patients. *American Review of Tuberculosis,* 41**,** 531-548.

PLEIL, J. D., WALLACE, M. A. G., STIEGEL, M. A. & FUNK, W. E. 2018. Human biomarker interpretation: the importance of intra-class correlation coefficients (ICC) and their calculations based on mixed models, ANOVA, and variance estimates. *Journal of Toxicology and Environmental Health, Part B,* 21**,** 161-180.

POLVERINO, E., GOEMINNE, P. C., MCDONNELL, M. J., ALIBERTI, S., MARSHALL, S. E., LOEBINGER, M. R., MURRIS, M., CANTÓN, R., TORRES, A., DIMAKOU, K., DE SOYZA, A., HILL, A. T., HAWORTH, C. S., VENDRELL, M., RINGSHAUSEN, F. C., SUBOTIC, D., WILSON, R., VILARÓ, J., STALLBERG, B., WELTE, T., ROHDE, G., BLASI, F., ELBORN, S., ALMAGRO, M., TIMOTHY, A., RUDDY, T., TONIA, T., RIGAU, D. & CHALMERS, JAMES D. 2017. European Respiratory Society guidelines for the management of adult bronchiectasis. *European Respiratory Journal,* 50**,** 1700629.

PULLICINO, G., SCIORTINO, P., CAMILLERI, L., SCHÄFER, W. & BOERMA, W. 2016. The influence of patient characteristics on healthcare-seeking behavior: a multilevel analysis of 70 primary care practices in urban-suburban regions in Malta. *Quality in primary care,* 24**,** 106-110.

QI, Q., WANG, W., LI, T., ZHANG, Y. & LI, Y. 2015. Aetiology and clinical characteristics of patients with bronchiectasis in a Chinese Han population: a prospective study. *Respirology,* 20**,** 917-924.

RASBASH, J., CHARLTON, C., BROWNE, W. J., HEALY, M. & CAMERON, B. 2009. MLwiN Version 2.1. *Centre for multilevel modelling, University of Bristol*.

RASBASH, J., STEELE, F., BROWNE, W. J., GOLDSTEIN, H. & CHARLTON, C. 2017. A user's guide to MLwiN.

REA, H., MCAULEY, S., JAYARAM, L., GARRETT, J., HOCKEY, H., STOREY, L., O'DONNELL, G., HARU, L., PAYTON, M. & O'DONNELL, K. 2010. The clinical utility of long-term humidification therapy in chronic airway disease. *Respiratory medicine,* 104**,** 525-533.

REDONDO, M., KEYT, H., DHAR, R. & CHALMERS, J. D. 2016. Global impact of bronchiectasis and cystic fibrosis. *Breathe,* 12**,** 222.

RICO, F., LIU, Y., MARTINEZ, D. A., HUANG, S., ZAYAS-CASTRO, J. L. & FABRI, P. J. 2016. Preventable readmission risk factors for patients with chronic conditions. *The Journal for Healthcare Quality (JHQ),* 38**,** 127-142.

RINGSHAUSEN, F. C., DE ROUX, A., PLETZ, M. W., HÄMÄLÄINEN, N., WELTE, T. & RADEMACHER, J. 2013. Bronchiectasis-associated hospitalizations in Germany, 2005–2011: a population-based study of disease burden and trends. *PloS one,* 8**,** e71109.

ROBERTS, M., LOWNDES, L., MILNE, D. & WONG, C. 2012. Socioeconomic deprivation, readmissions, mortality and acute exacerbations of bronchiectasis. *Internal medicine journal,* 42**,** e129-e136.

ROSENFELD, M., DAVIS, R., FITZSIMMONS, S., PEPE, M. & RAMSEY, B. 1997. Gender gap in cystic fibrosis mortality. *American journal of epidemiology,* 145**,** 794-803.

ROTTER, T., KINSMAN, L., JAMES, E. L., MACHOTTA, A., GOTHE, H., WILLIS, J., SNOW, P. & KUGLER, J. 2010. Clinical pathways: effects on professional practice, patient outcomes, length of stay and hospital costs. *Cochrane database of systematic reviews*.

SÁNCHEZ-MUÑOZ, G., DE ANDRÉS, A. L., JIMÉNEZ-GARCÍA, R., CARRASCO-GARRIDO, P., HERNÁNDEZ-BARRERA, V., PEDRAZA-SERRANO, F., PUENTE-MAESTU, L. & DE MIGUEL-DÍEZ, J. 2016. Time trends in hospital admissions for bronchiectasis: analysis of the Spanish national hospital discharge data (2004 to 2013). *PloS one,* 11**,** e0162282.

SCHNEIDER, A., HOMMEL, G. & BLETTNER, M. 2010. Linear regression analysis: part 14 of a series on evaluation of scientific publications. *Deutsches Ärzteblatt International,* 107**,** 776.

SCHOOVAERTS, K., LORENT, N., GOEMINNE, P., ALIBERTI, S. & DUPONT, L. 2019. National Survey on the Management of Adult Bronchiectasis in Belgium. *COPD: Journal of Chronic Obstructive Pulmonary Disease***,** 1-3.

SCHREYÖGG, J., TIEMANN, O. & BUSSE, R. 2006. Cost accounting to determine prices: how well do prices reflect costs in the German DRG-system? *Health Care Management Science,* 9**,** 269-279.

SERISIER, D. J., MARTIN, M. L., MCGUCKIN, M. A., LOURIE, R., CHEN, A. C., BRAIN, B., BIGA, S., SCHLEBUSCH, S., DASH, P. & BOWLER, S. D. 2013. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non–cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. *Jama,* 309**,** 1260-1267.

SHI, L. 1996. Patient and hospital characteristics associated with average length of stay. *Health care management review,* 21**,** 46-61.

SHROUT, P. E. & FLEISS, J. L. 1979. Intraclass correlations: uses in assessing rater reliability. *Psychological bulletin,* 86**,** 420.

SINGLETON, R., MORRIS, A., REDDING, G., POLL, J., HOLCK, P., MARTINEZ, P., KRUSE, D., BULKOW, L. R., PETERSEN, K. M. & LEWIS, C. 2000. Bronchiectasis in Alaska Native Children: Causes and. *Pediatric pulmonology,* 29**,** 182-187.

SKREPNEK, G. H., OLVEY, E. L. & SAHAI, A. 2012. Econometric approaches in evaluating costs and outcomes within pharmacoeconomic analyses. *Pharmaceuticals Policy and Law,* 14**,** 105-122.

SMITH, K. R. & MORRIS, J. F. 1962. Reversible Bronchial Dilatation*: Report of a Case. *Diseases of the Chest,* 42**,** 652-656.

SOUTHAM-GEROW, M. A., SILVERMAN, W. K. & KENDALL, P. C. 2006. Client similarities and differences in two childhood anxiety disorders research clinics. *Journal of Clinical Child and Adolescent Psychology,* 35**,** 528-538.

STALPERS, L. J. & KAPLAN, E. L. 2018. Edward L. Kaplan and the Kaplan-Meier Survival Curve. *BSHM Bulletin: Journal of the British Society for the History of Mathematics,* 33**,** 109-135.

STEINFORT, D. P., BRADY, S., WEISINGER, H. S. & EINSIEDEL, L. 2008. Bronchiectasis in Central Australia: a young face to an old disease. *Respiratory medicine,* 102**,** 574-578.

SUD, M., YU, B., WIJEYSUNDERA, H. C., AUSTIN, P. C., KO, D. T., BRAGA, J., CRAM, P., SPERTUS, J. A., DOMANSKI, M. & LEE, D. S. 2017. Associations between short or long length of stay and 30-day readmission and mortality in hospitalized patients with heart failure. *JACC: Heart Failure,* 5**,** 578-588.

TAHERI, P. A., BUTZ, D. A. & GREENFIELD, L. J. 2000. Length of stay has minimal impact on the cost of hospital admission. *Journal of the American College of Surgeons,* 191**,** 123-130.

TAN, W. C., SEALE, P., IP, M., SHIM, Y. S., CHIANG, C. H., NG, T. P., ABISHEGANADAN, J., CHAROENRATANAKUL, S., DEGUIA, T. & MAHAYIDDIN, A. 2009. Trends in COPD mortality and hospitalizations in countries and regions of Asia‐Pacific. *Respirology,* 14**,** 90-97.

TEN HACKEN, N. H., WIJKSTRA, P. J. & KERSTJENS, H. A. 2007. Treatment of bronchiectasis in adults. *Bmj,* 335**,** 1089-1093.

TSANG, K., HO, P., CHAN, K., IP, M., LAM, W., HO, C., YUEN, K., OOI, G., AMITANI, R. & TANAKA, E. 1999. A pilot study of low-dose erythromycin in bronchiectasis. *European Respiratory Journal,* 13**,** 361-364.

VENNING, V., BARTLETT, J. & JAYARAM, L. 2017. Patients hospitalized with an infective exacerbation of bronchiectasis unrelated to cystic fibrosis: C linical, physiological and sputum characteristics. *Respirology,* 22**,** 922-927.

VIDAILLAC, C., YONG, V. F., JAGGI, T. K., SOH, M.-M. & CHOTIRMALL, S. H. 2018a. Gender differences in bronchiectasis: a real issue? *Breathe,* 14**,** 108-121.

VIDAILLAC, C., YONG, V. F. L., JAGGI, T. K., SOH, M.-M. & CHOTIRMALL, S. H. 2018b. Gender differences in bronchiectasis: a real issue? *Breathe,* 14**,** 108-121.

VISSER, S. K., BYE, P. & MORGAN, L. 2018. Management of bronchiectasis in adults. *Medical Journal of Australia,* 209**,** 177-183.

VISSER, S. K., BYE, P. T., FOX, G. J., BURR, L. D., CHANG, A. B., HOLMES-LIEW, C.-L., KING, P., MIDDLETON, P. G., MAGUIRE, G. P. & SMITH, D. 2019. Australian adults with bronchiectasis: The first report from the Australian Bronchiectasis Registry. *Respiratory medicine*.

VON MACKENSEN, S., HOEPPE, P., MAAROUF, A., TOURIGNY, P. & NOWAK, D. 2005. Prevalence of weather sensitivity in Germany and Canada. *International journal of biometeorology,* 49**,** 156-166.

WHITWELL, F. 1952. A study of the pathology and pathogenesis of bronchiectasis. *Thorax,* 7**,** 213.

WINSLOW, C., BODE, R. K., FELTON, D., CHEN, D. & MEYER JR, P. R. 2002. Impact of respiratory complications on length of stay and hospital costs in acute cervical spine injury. *Chest,* 121**,** 1548-1554.

WONG, C., JAYARAM, L., KARALUS, N., EATON, T., TONG, C., HOCKEY, H., MILNE, D., FERGUSSON, W., TUFFERY, C. & SEXTON, P. 2012. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. *The Lancet,* 380**,** 660-667.

XU, L., ZHANG, F., DU, S., YU, Q., CHEN, L., LONG, L.-H., LI, Y.-M. & JIA, A.-H. 2016. Inhaled antibiotics in non-cystic fibrosis bronchiectasis: A meta-analysis. *Die Pharmazie-An International Journal of Pharmaceutical Sciences,* 71**,** 491-498.

ZANINI, A., AIELLO, M., ADAMO, D., CHERUBINO, F., ZAMPOGNA, E., SOTGIU, G., CHETTA, A. & SPANEVELLO, A. 2015. Effects of pulmonary rehabilitation in patients with non-cystic fibrosis bronchiectasis: a retrospective analysis of clinical and functional predictors of efficacy. *Respiration,* 89**,** 525-533.