Chronic Obstructive Pulmonary Disease Exacerbations – Cost, Risk Factors and Impact of Long-Acting Muscarinic Antagonists

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ABSTRACT

Health care resource utilisation (HCRU) data for chronic obstructive pulmonary disease (COPD) exacerbation-related hospitalisations can be used to drive the introduction of long-acting muscarinic antagonists (LAMAs) in the Maltese National Health Service (NHS). An understanding of the predictors for COPD exacerbations leading to hospitalisation may assist in developing guidelines for LAMA use, which prioritise patients who would benefit most from this therapy. A data collection proforma was designed and validated. All the hospital admissions during February-April 2017 were screened and a total of 148 COPD exacerbation-related admissions were identified. The cost estimates for these admissions were computed using an activity-based costing (ABC) approach. A case-control study was used to identify the predictors for COPD exacerbation-related hospitalisation. A total of 81 cases were recruited by convenience sampling from the identified admissions. Another 81 patients were recruited from respiratory outpatients as control subjects, during the same time frame. Control patients had to be clinically stable without a COPD exacerbation-related hospitalisation during the previous year. The data collection proforma was completed for recruited cases and control patients. Data was gathered from patients' medical records and via patient self-report. Pre-validated tools (COPD assessment test (CAT), EQ-5D-3L, inhaler adherence scale, inhaler technique scores) were completed through a semi-structured interview. The total estimated hospitalisation cost amounted to €225,000. Parsimonious logistic regression identified six significant predictors for hospitalisation. CAT scores above 18.9 (OR 1.193; 95% CI 1.096-1.299), a history of at least 2 past COPD exacerbation-related hospitalisations (OR 1.702; 95% CI 1.238-2.339), and at least 3 concomitant comorbidities (OR 1.593; 95% CI 1.025-2.474), were positively associated with the occurrence of a hospitalisation. Lack of inhaled long-acting beta agonists (LABA)

therapy (OR 6.494; 95% CI 0.041-0.587), emergency nebuliser use in the last 3-months (OR 4.537; 95% CI 1.209-17.039) and intravenous (IV) antibiotic use in the last 3-months (OR 8.545; 95% CI 1.093-66.827), were also positively associated with the occurrence of a hospitalisation. The identified predictors for COPD exacerbation-related hospitalisation may be used to prioritise patient access to LAMA therapy.

Keywords: chronic obstructive pulmonary disease, exacerbation-related hospitalisation, health care resource utilisation, long-acting muscarinic antagonists, predictors for hospitalisation

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List of Abbreviations

ABC	Activity-Based Costing
ABGs	Arterial Blood Gases
ACOS	Asthma-COPD Overlap Syndrome
AECOPD	Acute Exacerbation of Chronic Obstructive Pulmonary Disease
A&E	Accident and Emergency
ATTAIN Study	Aclidinium To Treat Airway obstruction In COPD patieNts
AUDIPOC Study	Clinical Audit of COPD Patients Requiring Hospital Admissions in Spain
CAT	COPD Assessment Test
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
DPI	Dry Powder Inhaler
ECLIPSE Study	Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints
ECS	Electronic Case Summary
EFRAM Study	Estudi dels Factors de Risc d'Agudització de la MPOC (Risk Factors of COPD Exacerbation Study)

EQ-5D	EuroQuol five dimensions questionnaire
FEV_1	Forced Expiratory Volume in One Second
GOLD	Global Initiative for Obstructive Lung Disease
GLOBE Study	Gemifloxacin Long-Term Outcomes in Bronchitis Exacerbations
GSK	GlaxoSmithKline
HCRU	Health Care Resource Utilisation
HDU	High Dependency Unit
HrQoL	Health-related Quality-of-Life
ICS	Inhaled Corticosteroids
INVIGORATE study	Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease
ITU	Intensive Therapy Unit
IV	Intravenous
LABAs	Long-Acting Beta Agonists
LAMAs	Long-Acting Muscarinic Antagonists
LoS	Length of Stay

LTOT	Long-Term Oxygen Therapy
LVRS	Lung Volume Reduction Surgery
MDH	Mater Dei Hospital
MDI	Metered Dose Inhaler
NHS	National Health Service
NIV	Non-Invasive Ventilation
OR	Odds Ratio
POET	Prevention of Exacerbations with Tiotropium in COPD
QOL	Quality-of-Life
SABAs	Short-Acting Beta Agonists
SAMA	Short-Acting Muscarinic Antagonists
SD	Standard Deviation
SPARK Study	Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium
TORCH Study	TOwards a Revolution in COPD Health
USA	United States of America
VAS	Visual Analog Scale
WHO	World Health Organisation

CHAPTER 1

INTRODUCTION

1.1 BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease which is characterised by persistent airflow limitation. It is associated with an enhanced chronic inflammatory response to noxious particles or gases in the airways and the lung (Tabet et al., 2013). Smoking is the single most important risk factor for COPD. Whilst none of the available pharmacological agents are disease-modifying, smoking cessation is a disease-modifying intervention (Menn et al., 2012). The progressive nature of the disease leads to significant limitations in daily life with dyspnoea, reduced exercise capacity, comorbid conditions, exacerbations and hospitalisations becoming a frequent occurrence (Donner et al., 2011; Molinari et al., 2015). The occurrence of exacerbations and presence of comorbidities play a role in the overall severity of individual patients (Tabet et al., 2013).

Mapel and Roberts (2012) point out that although the prevalence of COPD is higher in the geriatric population, it is not uncommon among middle-aged adults. Given that middle-aged adults are still in the workforce, this presents indirect cost consequences, such as absences from work (Mapel and Roberts, 2012). Apart from being a leading cause of work disability, COPD also generates a significant burden on health care systems (Casas et al., 2006). It is estimated that more than 3 million people die from COPD every year, accounting for 5% of all deaths globally (Mapel and Roberts, 2012). The World Health Organisation (WHO) forecasts that COPD will become the third leading cause of death worldwide by 2030 (Oba and Lone, 2015). As a result, this condition is gaining importance in the field of public health (Tabet et al., 2016).

1.2 MULTIMORBIDITY AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is not only a disease of airflow limitation but a heterogeneous disease with extra-pulmonary manifestations, such that it is now being considered as part of the metabolic syndrome (Agusti et al., 2010; Molinari et al., 2015). This is also confirmed by the Global Initiative for Obstructive Lung Disease (GOLD) guidelines which state that concomitant chronic diseases including cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, anxiety and lung cancer, occur frequently in COPD patients.[1] GOLD guidelines recommend that these comorbidities should be actively sought and treated appropriately when present as they can influence mortality and hospitalisations independently.[1]

Although it is well-known that smoking may lead to concomitant comorbidities, it is also increasingly recognised that COPD patients have a high burden of comorbidities which may be independent of smoking (Putcha et al., 2015).

1.2.1 Comorbidity Clusters

Coexisting comorbidities among COPD patients are a widespread problem and their occurrence has been studied by several researchers (Putcha et al., 2015). Vanfleteren et al., (2013) studied the most common comorbidities in a COPD cohort of 213 patients and identified the following comorbidity clusters: cardiovascular cluster, cachectic cluster, metabolic cluster and psychological cluster (Vanfleteren et al., 2013).

[1] Global initiative for chronic Obstructive Lung Disease (GOLD). Pocket guide to COPD diagnosis, management, and prevention: a guide for health care professionals. [Online]. GOLD Inc.; 2017. [cited 2017 Jan 10]. Available from: URL: http://goldcopd.org/wp-content/uploads/2016/12/wms-GOLD-2017-Pocket-Guide.pdf.

1.2.2 Implications of Comorbidities

Several studies have assessed the implication of comorbidities on hospitalisation risk, length of stay and hospital-related mortality. These studies have shown that comorbidities contribute to worse patient-centred outcomes as well as increased health care resource utilisation (HCRU) and mortality (Kinnunen et al., 2003; Lin et al., 2010; Almagro et al., 2012; Baty et al., 2013).

1.3 PARADIGM SHIFT IN COPD MANAGEMENT

The newer pharmacological agents namely the long-acting bronchodilators, improve long-term prognosis, reduce respiratory symptoms and improve the patients' quality-of-life (QOL) (Mapel and Roberts, 2012). Throughout these last two decades, there have been several large clinical trials which have not only investigated pharmacological agents but also pulmonary rehabilitation and lung volume reduction surgery (LVRS) (Donner et al., 2011). This has led to a radical shift in the management of COPD where the previously adopted palliative approach was replaced by a more active approach (Mapel et al., 2010; Donner et al., 2011).

A better understanding of the different pathophysiology mechanisms is thought to improve COPD management (Alagha et al., 2014). Innate immunity and remodelling of the bronchial epithelium and smooth muscle cells play a role in disease management. COPD endotypes which result from different pathophysiology mechanisms, give rise to clinical heterogeneity (Alagha et al., 2014). Vanfleteren et al., (2014) call for a personalised approach to airway diseases. A better understanding of the endotypes that lie behind chronic airway disease is likely to shift the current health care from treating diseases to the so-called P4 medicine. The P4 medicine is a new type of medicine that is predictive, preventive, personalised and participatory (Vanfleteren et al., 2014).

1.4 COPD EXACERBATIONS

COPD is characterised by exacerbations (Hurst et al., 2010). Symptoms of an exacerbation range from increased breathlessness accompanied by cough and sputum production in mild COPD, to life-threatening respiratory failure in severe COPD (Devine, 2008). The consensus definition of an exacerbation proposed by Rodriguez-Roisin (2000) is, "a sustained worsening of a patient's condition from the stable state and beyond normal day-to-day variations that is acute in onset, and that may also require a change in medication and/or hospitalisation in a patient with underlying COPD".

Many exacerbations are unreported, and this not only underestimates their incidence but may also lead to under-treatment and poor recovery (Pavord et al., 2016). In a study on a COPD patient cohort who had received instruction on reporting worsening symptoms, only 50% of exacerbations were reported to the clinical team (Seemungal et al., 1998).

Traditionally, exacerbations were thought to be of viral or bacterial origin, however recent research has indicated otherwise. Bafadhel et al., (2011) proposed that exacerbations may be subdivided into 4 distinct clusters: bacterial, viral, eosinophilic, and pauci-inflammatory (Bafadhel et al., 2011). Similar to the disease itself, exacerbations are heterogeneous, as they vary in severity and phenotype. Differences in the biologic basis, prognosis and response to therapy give rise to exacerbation-phenotypes (Pavord et al., 2016).

1.4.1 Incidence and Determinants of COPD Exacerbations

There is minimal information pertaining to exacerbation incidence, and this could be partly due to unreported exacerbations (Hurst et al., 2010; Jones 2015). Seasonality is known to affect the exacerbation incidence. The higher incidence of exacerbations during the fall-winter season is mirrored by the seasonal variations in viral loads in the atmosphere (Molinari et al., 2015).

The observational cohort study by Hurst et al., (2010) confirms the previously observed trend by Donaldson and Wedzicha, (2006) namely that with increasing disease severity, exacerbations become more frequent (Donaldson and Wedzicha, 2006; Hurst et al., 2010). As indicated by the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study, the most reliable predictor of exacerbations in an individual patient is the exacerbation history (Hurst et al., 2010).

1.4.2 Frequent Exacerbation-Phenotypes

Individuals with a frequent exacerbation-phenotype are prone to exacerbations as a result of intrinsic susceptibility and have exacerbations on exposure to particular triggers, such as respiratory viral infection (Hurst et al., 2010). Data from an observational cohort study by Hurst et al., (2010) suggests that the frequent-exacerbation phenotype can be identified on the basis of a history of exacerbations (Hurst et al., 2010). This makes it possible to selectively recruit patients for clinical trials and allows for appropriate targeting of patients for interventions (Hurst et al., 2010).

1.4.3 Exacerbation Trends

A long-term follow-up study carried out by Suissa et al., (2012) suggested that the course of COPD has two phases after the first hospitalised exacerbation. A period of stable risk (generally less than 2 years) has been identified between the first and second hospitalised exacerbation. After the second hospitalised exacerbation, severe exacerbations tend to recur progressively. This pattern creates a window of opportunity to intervene in the stable phase, with the aim of preventing a subsequent severe exacerbation (Suissa et al., 2012). Evidence has also shown that COPD exacerbations tend to cluster together and a high-risk period for recurrence has been identified in the first 8-weeks following an initial event (Hurst et al., 2009).

1.4.4 Interventions to Reduce Exacerbation Risk

Apart from the available pharmacotherapeutic agents, there are several non-pharmacologic interventions which can reduce exacerbation risk (Marchetti et al., 2013). As shown in a large-scale observational study, smoking cessation is an important non-pharmacologic intervention (Au et al., 2009). The efficacy of pulmonary rehabilitation in exacerbation reduction has also been demonstrated in small-scale clinical studies (Seymour et al., 2009; Puhan et al., 2011). Pneumococcal and annual influenza vaccinations reduce the risk of exacerbation and hospitalisation in patients with COPD, and it is recommended that these are offered to patients with COPD (Poole et al., 2000; Walters et al., 2010).[2] In the local scenario, this is an intervention that could be emphasised by the community pharmacist who has regular contact with the patient when collecting chronic treatments.

[2]National Institute for Health and Clinical Excellence (NICE). Chronic obstructive pulmonary disease: management of chronic pulmonary obstructive disease in adults in primary and secondary care. [Online]. NICE; 2010. [cited 2017 Oct 14]. Available from: URL: https://www.nice.org.uk/guidance/cg101/resources/chronic-obstructive-pulmonary-disease-in-over-16s-diagnosis-and-management-3510932393158.

1.5 THE IMPACT OF COPD EXACERBATIONS

COPD exacerbations have a negative impact on the patients' general health status (Spencer and Jones, 2003). The burden of these exacerbations on healthcare systems and society has been highlighted in the literature (Molinari et al., 2015; Halpin et al., 2016). COPD exacerbations are often emphasised since they not only impact the patient, but also impinge on patient carers, and healthcare systems.

1.5.1 Effect on the Patient

Exacerbations may result in permanent loss of lung function after which patients never fully recover to their pre-hospitalisation status (Mapel and Roberts, 2012). Their cumulative effect on lung function makes them critical to disease progression (Pavord et al., 2016). This cumulative effect on lung function was demonstrated in the Gemifloxacin Long-Term Outcomes in Bronchitis Exacerbations (GLOBE) study, where the extent of recovery was negatively affected by the occurrence of subsequent exacerbations. The GLOBE study also highlights that following an initial exacerbation, the patients' improvement in health status reaches a plateau after four weeks post-exacerbation, where there is a long phase of slow improvement (Spencer and Jones, 2003).

The weeks following every Acute Exacerbation of COPD (AECOPD) mark a high risk of mortality (Hurst et al., 2010; Suissa et al., 2012; Jones, 2015). Suissa et al., (2012) also observe that the mortality rate rises with every new exacerbation (Suissa et al., 2012). The patients' QOL may also be seriously impaired after the occurrence of an acute exacerbation (Menn et al., 2012). Studies have captured the impact of COPD exacerbations on patients (Table 1.1).

Table 1.1 The impact of COPD exacerbations on patients

Study	Study objectives	Study outcomes
Donaldson et al., 2005	To assess the likelihood of patients with COPD becoming housebound	Patients with exacerbations spent a significantly lower time outdoors (-0.16 hour/day/year; $P<0.001$). A significantly more rapid decline in time spent outdoors was evident in patients with frequent exacerbations ($P=0.011$).
Cote et al., 2007	To examine the short- and long- term impact of exacerbations on exercise capacity	The presence of exacerbations resulted in progressive worsening of the 6-minute walking distance over time, with a loss of 74 metres reported after 2 years. The control group, consisting of patients who did not experience exacerbations during the study period, showed no significant change from baseline.
Celli et al., 2008 **TORCH study**	To assess the effect of pharmacotherapy on rate of decline of lung function in COPD	Patients who experienced 0-1.0 moderate to severe exacerbations per year had a 37% faster decline in lung function than those with no exacerbations ($P<0.001$). Among those patients who experienced >1.0 moderate to severe exacerbation, the rate of decline in forced expiratory volume in one second (FEV_1) was 65% faster ($P<0.001$).

The studies demonstrate that exacerbations impact negatively not only on lung function but have a statistically significant impact on exercise capacity and QOL.

1.5.2 Effect on Health Care Resource Utilisation

COPD exacerbations frequently result in an increase in HCRU (Geitona et al., 2011; Jones, 2015; Pavord et al., 2016). Whilst mild and moderate exacerbations necessitate a change in treatment, severe exacerbations often require hospitalisation for advanced monitoring and assisted ventilation (Pavord et al., 2016). In keeping with this view, clinical trials of COPD treatments commonly assess exacerbations based on HCRU and changes in therapy (Jones, 2015). Acute exacerbations absorb around 50% of direct costs for COPD (Mantero et al., 2017). The costs resulting from exacerbations are mainly attributed to hospitalisation (Anzueto, 2010; Mapel et al., 2010; Toy et al., 2010).

1.6 EXACERBATION-RELATED HOSPITALISATION

COPD patients have an annual risk for hospitalisation that is two or three times that of age- and gender-matched controls without COPD (Mapel and Roberts, 2012). Most COPD hospitalisations result from exacerbations (Oba and Lone, 2015). Hospital admissions due to exacerbations are a major problem in the management of the disease due to their negative impact on health-related quality of life (HrQoL) and prognosis (Casas et al., 2006; Bahadori and FitzGerald, 2007). The study by Suissa et al., (2012) demonstrated that 50% of patients died within 3.6 years of their first hospitalisation for COPD exacerbation (Suissa et al., 2012).

The exacerbations leading to hospitalisation are the most expensive events affecting COPD medical costs (Mapel et al., 2010). Geitona et al., (2011) and Oba and Lone (2015) recognise that prevention of COPD exacerbations is key to cost-containment of COPD management (Geitona et al., 2011; Oba and Lone, 2015). The research being presented in this dissertation was undertaken with a focus on identifying the factors that increase the risk for COPD exacerbation-related hospitalisation.

1.6.1 Predictors for COPD Hospitalisation and Poor Outcome

In a systematic review evaluating 17 studies, variables including long-term oxygen therapy (LTOT) use, a poor HrQoL and lack of routine physical activity were all associated with an increased risk for COPD admissions and readmission to hospital (Bahadori and FitzGerald, 2007). A multicentre, prospective observational study showed that the most relevant risk factor for a composite event (new ambulatory exacerbation, hospitalisation or death) is the history of frequent exacerbations (Miravitlles et al., 2015). The study by Miravitlles et al., (2015) also showed that a COPD assessment test (CAT) score ≥13.5 was also a significant risk factor for the composite event (Miravitlles et al., 2015). In a retrospective population-based cohort study it was concluded that a history of severe exacerbations was associated with new hospitalised exacerbations and mortality (Santibanez et al., 2016).

1.6.2 Non-Pharmacological Approaches to Hospitalisation Prevention

The prospective controlled trial by Casas et al., (2006) showed that a standardised integrated care intervention effectively prevents hospitalisations due to exacerbations in COPD patients (Casas et al., 2006). The economic analysis in conjunction with a multicentre randomised clinical trial by Bourbeau et al., (2006) showed that self-management education is cost effective mainly through reductions in exacerbation-related hospitalisations (Bourbeau et al., 2006).

1.7 ROLE OF LAMAs IN COPD

The efficacy of inhaled long-acting muscarinic antagonists (LAMAs) in reducing the annual exacerbation rate has been demonstrated in the POET, SPARK and ATTAIN studies (Vogelmeier et al., 2011; Wedzicha et al., 2013; Jones et al., 2014).

In a systematic review, Wedzicha et al., (2017) identified two clinical trials comparing exacerbation reduction in stable COPD with long-acting beta agonists (LABAs) versus LAMAs (Wedzicha et al., 2017). The INVIGORATE trial compared once-daily tiotropium (LAMA) with once daily indacaterol (LABA) and the POET trial compared once-daily tiotropium (LAMA) with twice-daily treatment with salmeterol (LABA) (Vogelmeier et al., 2011; Decramer et al., 2013). A meta-analysis of these two clinical trials, showed that LAMAs had a number of benefits over LABAs (Wedzicha et al., 2017). Table 1.2 summarises the results of this meta-analysis.

Table 1.2 Summary of meta-analysis results

Benefits of LAMAs over LABAs	Statistical analysis
▪ Lower likelihood to have one or more moderate to severe COPD exacerbation in patients receiving LAMAs	30.9% versus 34.6%; risk ratio 0.89, 95% CI 0.85-0.94
▪ Lower likelihood to have a severe exacerbation requiring hospitalisation in patients receiving LAMAs	7.1% versus 9.2%; risk ratio 0.77, 95% CI 0.66-0.90
▪ Greater improvement in FEV_1 in patients receiving LAMAs	Mean difference +19 mL, 95% CI +11.34 mL to + 28.66 mL

Adapted from: Wedzicha JA, Calverley PMA, Albert RK, Anzueto A, Criner GJ, Hurst JR et al. Prevention of COPD exacerbations: A European Respiratory Society/American Thoracic Society guideline. *Eur Respir J.* 2017; 50: 1-12.

The benefits of inhaled LAMA over LABA therapy are outlined. Of particular note is the effect of LAMAs on reducing the exacerbations requiring hospitalisation. Hospitalisations present a useful target to decrease the costs of this disease. Preventing exacerbation-related hospitalisations will also offer a prognostic benefit to the patient.

1.8 PHARMACOECONOMIC IMPLICATIONS OF INTRODUCING LAMAs

In a Monte Carlo simulation, Mapel et al., (2010) concluded that treatments that reduce the risk or severity of exacerbations are likely to be cost-effective among those patients who have frequent exacerbations and hospitalisations. Mapel et al., (2010) highlight that the major determinants of the cost-effectiveness of exacerbation reduction include treatment efficacy, the frequency of exacerbations, the cost and severity of exacerbations, and the cost of the new COPD medication (Mapel et al., 2010).

Tiotropium has been evaluated in various health care settings. In a cost-effectiveness analysis developed for the Swiss public health insurance system the use of tiotropium bromide, salmeterol and standard care were compared over a 12-month period. The results showed that tiotropium was dominant over the competing strategies since the higher acquisition cost of tiotropium bromide was fully offset by the fewer number of exacerbations (Schramm et al., 2005). Similar overall cost reduction was indicated by a budget impact model adapted to Singapore (Lee et al., 2006).

Oostenbrink et al., (2005) employed a Markov model to evaluate tiotropium bromide and compare its cost-effectiveness with ipratropium and salmeterol in the Netherlands and Canada. Probabilistic sensitivity analysis led to the following outcomes; the probability of LAMA being cost-effective or dominant was 95% and 60% in Canada and the Netherlands respectively (Oostenbrink et al., 2005).

1.9 STUDY SETTING

The setting for this study was the national health service (NHS) in Malta encompassing the access to LAMAs in the hospital scenario including acute management and the community scenario in terms of chronic management.

1.10 RATIONALE FOR THE STUDY

Within the NHS in Malta, the use of LAMAs is not widespread among COPD patients, due to formulary restrictions. Treatment offered by the local NHS is limited to LABAs, and ipratropium (a short-acting anti-muscarinic agent). This is in conflict with the latest clinical practice guidelines, which recommend LAMAs as first-line maintenance bronchodilator therapy in patients with stable COPD who have a high risk of exacerbations or in highly symptomatic patients.[3]

The cost estimation of COPD exacerbation-related hospitalisations gives the opportunity of measuring their impact on health care resource use. This data can be used to drive the introduction of LAMAs on local formularies, especially since no previous study has addressed this to-date. An understanding of the predictors of exacerbation-related hospitalisation may have important implications for implementing health care policies. The latter deliverable from this study can be extrapolated to other health care systems beyond the Maltese NHS.

[3]Global initiative for chronic Obstructive Lung Disease (GOLD). Pocket guide to COPD diagnosis, management, and prevention: a guide for health care professionals. [Online]. GOLD Inc.; 2017. [cited 2017 Jan 10]. Available from: URL: http://goldcopd.org/wp-content/uploads/2016/12/wms-GOLD-2017-Pocket-Guide.pdf.

1.11 AIMS AND OBJECTIVES

The aim of the study was to estimate the burden associated with COPD exacerbation-related hospitalisation and putting forward a protocol for LAMA use. The objectives of the research were to:

i. Identify COPD exacerbations leading to hospitalisation
ii. Estimate the resulting costs of hospitalisation
iii. Determine the predictors for COPD exacerbation-related hospitalisation, to identify patients who would benefit most from LAMA therapy

CHAPTER 2

METHODOLOGY

2.1 STUDY DESIGN

The study consisted of three phases. In phase 1 a thorough literature review was conducted and a data collection proforma was designed. The second phase consisted of a prospective study where the number of hospital admissions to Mater Dei Hospital (MDH) due to COPD exacerbation, over a 3-month period were identified. The resulting costs from these admissions were estimated. The third phase consisted of a case-control study to identify the predictors for hospitalisation. This phase involved a comparison between two groups of patients: those admitted to hospital as a result of an exacerbation (cases) and those reviewed at outpatients who have not been hospitalised with COPD in the past year (control patients).

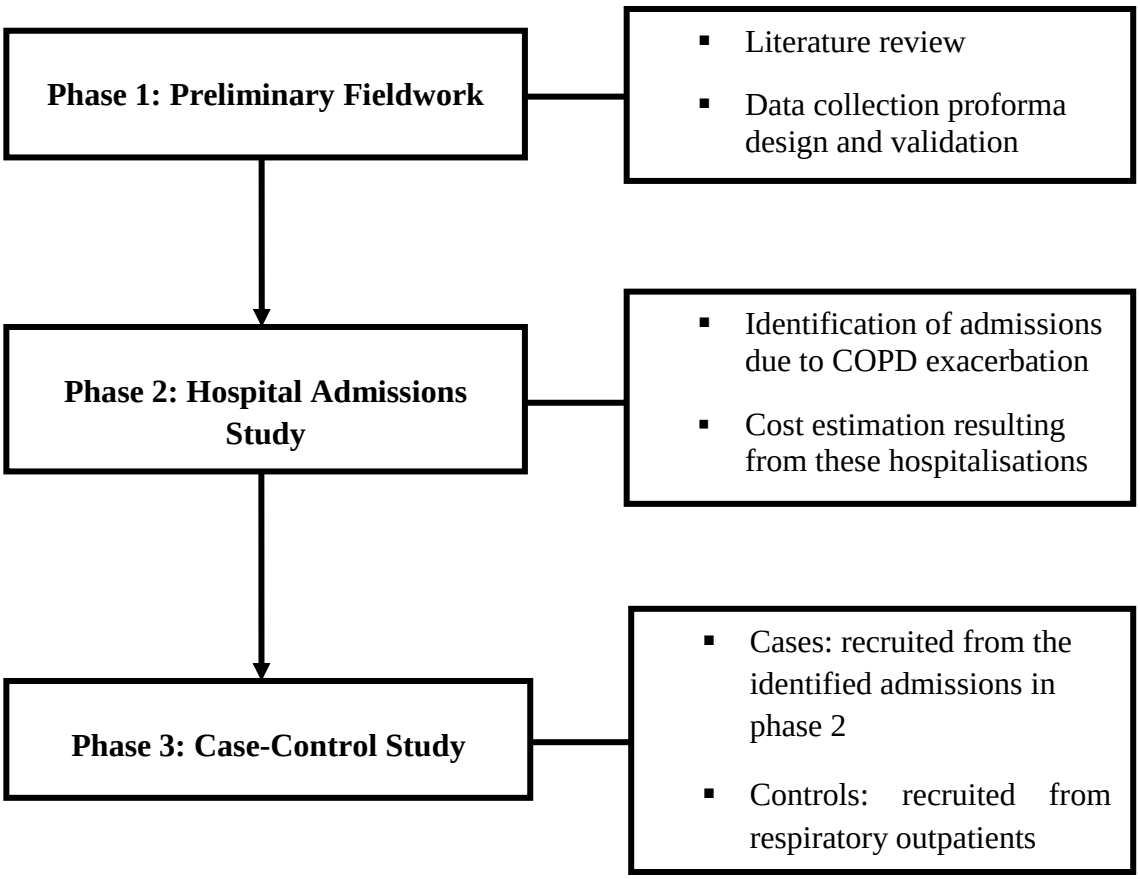

Figure 2.1 Outline of the study

2.2 PHASE 1 – PRELIMINARY FIELDWORK

A data collection proforma (Appendix 1) was designed and tailored for both the hospital admissions study and case-control study. This proforma was adapted from the Risk Factors of COPD Exacerbation (EFRAM) study (Garcia-Aymerich et al., 2001), which aims to identify the risk factors for COPD hospitalisations and was considered well-suited for the purpose of this research. The data fields in the compiled proforma included: Sociodemographic Variables, Symptomatology and Health Status, Medical Care, Clinical Variables. A section on the Use of Hospital Resources was included for the purpose of the hospital admissions study.

Pre-validated tools, namely: EuroQuol five dimensions three-level version questionnaire (EQ-5D-3L), COPD assessment test (CAT), inhaler adherence scale, and inhaler technique scores were identified for use in this study (Appendix 2).

2.2.1 EQ-5D-3L and CAT Instruments

The EQ-5D-3L measures the patients' overall health status and the CAT assesses the impact of COPD on the patients' daily routine (Jones et al., 2009; Mapel and Roberts, 2012). Permission to use these tools was granted from EuroQol Research Foundation and GlaxoSmithKline (GSK) respectively (Appendix 2).

The EQ-5D-3L instrument is readily available in the English and Maltese languages. The CAT is only available in the English version. For the purpose of this research the CAT was translated to the Maltese language. The back-translation method was used to ensure consistency in the translated tool. A summary of these tools with their rationale for use is outlined in Table 2.1.

Table 2.1 EQ-5D-3L and CAT

Name of tool	Rationale for use	Description of tool
EQ-5D-3L	Well-validated for use in COPD Self-administered Brief and easy to conduct	In the descriptive section respondents are asked to select a level (no problems, some problems and severe problems) for each of the five dimensions in the tool. In the visual analogue scale (VAS) respondents value their HrQoL on a rating scale from 0 (worst imaginable health state) to 100 (best imaginable health state).
CAT	Short and simple Good repeatability Good discriminative properties among stable and exacerbated COPD	Consists of eight items with scores ranging from 0 to 5 (0= no impairment, 5= greatest impairment). The scores from each item are added to calculate an overall score, ranging from 0 to 40. Higher scores are indicative of a poorer control of COPD.

Adapted from: Jones et al., 2009; Menn et al., 2010; Mapel and Roberts, 2012; Miravitlles et al., 2015; Nolan et al., 2016

2.2.2 Inhaler Adherence Scale and Inhaler Technique Scores

The Inhaler Adherence Scale, and Inhaler Technique Scores for both metered dose inhaler (MDI) and dry powder inhaler (DPI) were identified to measure the patients' adherence to inhaled medication and to assess inhaler technique. Since these tools are only available in the English version, they were translated to the Maltese language. The back-translation method was used in order to ensure consistency in the translation. A summary of these tools with their rationale for use is outlined in Table 2.2.

Table 2.2 Inhaler adherence scale and inhaler technique scores

Name of tool	**Rationale for use**	**Description of tool**
Inhaler Adherence Scale (core scale items)	Easy to use and completed in less than 5 minutes Adequate reliability Selected in preference to the expanded scale items due to higher internal consistency	4-item scale, leading to a 'Yes' or 'No' answer One point is assigned for each question answered as 'No', with the total score ranging from 0-4 Higher scores indicate better adherence to inhaled medication
Inhaler Technique Scores	Validated standardised checklists specific to MDI and DPI	Scored on an 8-point and 7-point scale for MDI and DPI respectively Higher scores indicate a better technique

Adapted from: Brooks et al., 1994 and Roy et al., 2011

2.3 FACE AND CONTENT VALIDITY

Face and content validity of the data collection proforma was carried out by a panel of six experts consisting of three physicians (consultant respiratory specialist, specialist trainee in general medicine, public health trainee) and three pharmacists (academic pharmacist, clinical pharmacist and hospital pharmacist). A validation form (Appendix 3) was designed and distributed to the expert panel by hand or via e-mail as preferred by each expert. The data collection proforma was well-received amongst the panel of experts and the suggested changes were taken on board (Appendix 3).

2.4 ETHICAL APPROVAL

Approval of the research protocol was obtained from the University Research and Ethics Committee (Appendix 4). Patient consent forms and patient information sheets outlining the purpose of the study were prepared in English and Maltese (Appendix 4).

2.5 PHASE 2 – HOSPITAL ADMISSIONS STUDY

The study was undertaken at the local acute general hospital (MDH). The COPD exacerbation-related admissions to MDH during a pre-determined time frame (February-April 2017) were identified. The resulting hospitalisation costs were computed.

2.5.1 Definitions and Exclusion Criteria

Hospitalisation was defined by an admission to a general medical ward, admission to a high-dependency unit (HDU) or intensive therapy unit (ITU). The study's exclusion criteria were patients without a prior diagnosis of COPD, patients with a history of asthma-COPD overlap syndrome (ACOS) and patients who were given an alternative diagnosis to COPD exacerbation.

2.5.2 Sampling Technique and Data Collection

Cluster sampling is a statistically accepted sampling technique and was employed for the purpose of this research. Data collection was done prospectively, throughout the months of February to April 2017. Within the time frame allocated for this research, a 3-month fieldwork period was identified as statistically robust.

The medical admissions booklet at the Accident and Emergency (A&E) department was screened and all admissions flagged as COPD exacerbations were noted. The working diagnosis of the caring medical firm was checked and those patients who were given an alternative diagnosis to COPD, such as exacerbation of congestive heart failure were excluded from the study group. Patients presenting with pneumonia but flagged as COPD exacerbation were identified by checking for the presence of consolidations on chest X-ray. This eliminated any classification bias in those patients who were initially flagged as COPD exacerbation but had a different underlying cause for their hospitalisation. The software used to screen the eligible patients included iSoft Clinical Manager[4] and Electronic Case Summary (ECS).[5]

The data collected for the identified cluster sample consisted of patient demographics including caring consultant, medication history of respiratory drugs used on a chronic basis, clinical variables (including number of comorbidities, recent spirometry results and BAP-65 scores) and use of hospital resources.

[4] iSOFT is an international supplier of software applications for the healthcare sector.

[5] Electronic Case Summary (ECS) System was developed 'in-house' in order to have a computerised system for compiling discharge letters and from which clinical data relating to each hospital discharge could be derived.

Data pertaining to the use of hospital resources included the duration of the patient's hospital stay, the use of non-invasive ventilation (NIV) on the medical ward (equivalent to HDU admission) and admission to ITU, together with their respective duration. Data acquisition was performed via patients' paper-based medical case notes.

2.5.3 Methodology for Calculating Costs

The activity-based costing (ABC) bottom-up approach was used to estimate hospitalisation costs. The main advantage of this methodology is that it provides a micro-economic analysis where all the resources directly employed for the provision of healthcare are taken into account (Geitona et al., 2011). Since this methodology is already adopted by the hospital's administrative and finance departments, it was also practical and feasible to employ for the purpose of this research. Indirect cost was not included in this research since the aim of this study was to estimate the impact of exacerbations on hospitalisation costs.

2.5.3.1 Estimating Hospitalisation Costs

Both admission costs and the bed night costs constitute the cost of an inpatient stay. These costs are calculated at a rate (minute^{-1}) and differ among a general medical ward and ITU/HDU.[6] Data pertaining to admission costs to a general medical ward or ITU/HDU and the bed night costs of general medical ward or ITU/HDU were obtained from the hospital's administrative and finance departments (Appendix 5).

[6] Personal communication. Mr. John Abela. Financial Consultant: Crowe Horwath; September 2017.

2.5.3.2 Estimating Length of Hospital Stay

Accuracy in the length of hospital stay is paramount to estimate hospitalisation cost. Ward bed counts are generally done by bed management personnel at 7am. With this methodology, a patient who is admitted on Day 1 at 11am and discharged on day 2 at 2pm, would result in 1 bed night cost.[7] Since the exact time that the patient is transferred to a ward is hard to tell, the length of hospital stay was calculated based on the patients' number of bed nights. This prevents cost overestimation and ensures that the total hospitalisation cost is as accurate as possible.

2.6 PHASE 3 - CASE-CONTROL STUDY

This phase of the study aimed at identifying the predictors for hospitalisation from COPD exacerbation. The case-control approach was employed in order to reach this objective.

2.6.1 Definitions and Exclusion Criteria

Cases were defined as patients who were hospitalised as a result of a COPD exacerbation. The same exclusion criteria as outlined in the hospital admissions study was used. Control patients were defined as known cases of COPD who were clinically stable and who had not sustained an exacerbation-related hospitalisation one year previous to the date of patient interview. Patients with ACOS were excluded from the study group. Variables relating to the use of corticosteroids in the previous 3-months and use of antibiotics (oral and IV) in the previous 3-months were marked as 'Yes' in the data collection proforma, only when administered for a respiratory cause.

[7] Personal communication. Mr. John Abela. Financial Consultant: Crowe Horwath; September 2017.

2.6.2 Sampling Technique and Patient Recruitment

The convenience sampling technique was employed and patient participation was voluntary. Cases and control subjects were recruited during the same time frame (February-April 2017), after being matched for age and gender. An overview of the case-control group formation is depicted in Figure 2.2.

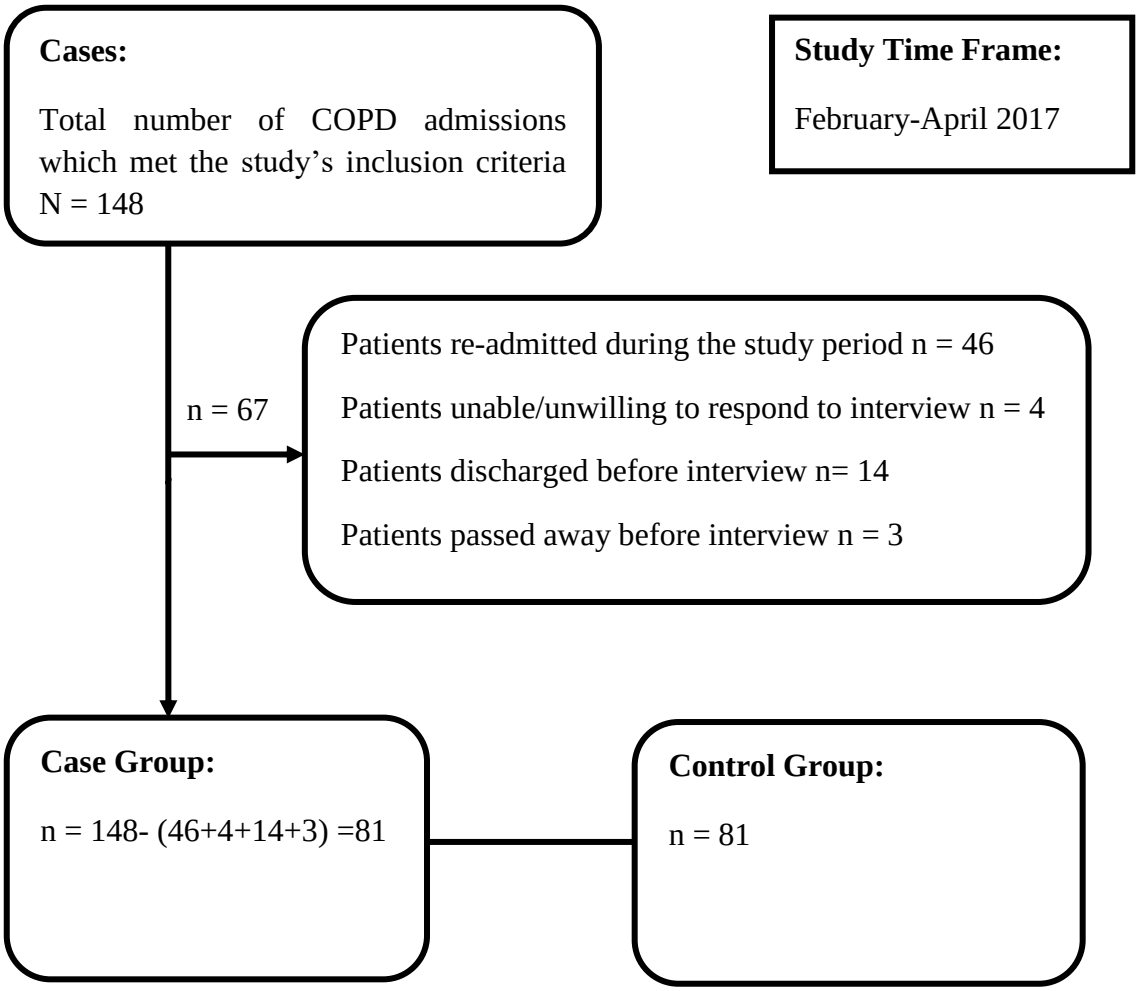

Figure 2.2 Flowchart of cases and control group formation

The case group was composed of 81 patients recruited by convenience from a pre-identified cluster sample of exacerbation-related hospitalisations. The same number of patients were subsequently recruited in the control group.

The case group was recruited from the identified hospital admissions in phase 2 of the study. Eligible patients were given the study information sheet (Appendix 4) while admitted at the ward and those willing to participate were asked to sign the consent form (Appendix 4).

The control group was recruited from the outpatient clinics of four respiratory physician consultants. The outpatients nurse preparing the files flagged those patients who attended for follow-up of COPD and who did not have a COPD hospitalisation in the previous year. These patients were given an information sheet (Appendix 4) while waiting to see the physician and those willing to participate were asked to sign the consent form (Appendix 4).

2.6.3 Data Collection

The data collection proforma (Appendix 1) was completed manually by the researcher for all cases and control subjects. The section on "*Use of Hospital Resources"* was only applicable to the hospitalised cases and was omitted for the control group.

Data was collected via patient self-report, and from patients' medical records. Both paper-based and electronic medical records are available at MDH. The software used to access the electronic medical records included iSoft and ECS. The described pre-validated tools were completed via semi-structured interview.

2.7 STATISTICAL ANALYSIS

The data collected from the hospital admissions study and case-control study was inputted into IBM SPSS® v24 and the data was analysed and interpreted. All statistical calculations were carried out using this software.

The descriptive statistics used to describe categorial (nominal) variables included absolute frequencies and percentages. The descriptive statistics used to describe continuous variables included the mean, standard deviation (SD) and median.

The Pearson correlation coefficient was employed to establish whether there is any correlation between two quantitative variables. The confidence interval (CI) was set at the 95% level of significance.

Univariate analysis was carried out to determine the variables which exhibited a statistically significant difference with respect to the dependent variable (case-control). The Chi-square test was used to compare the categorical variables. Continuous variables were first tested for normality using the Shapiro-Wilk test. The continuous variables which were parametric were compared with the Independent Samples *t*-test whilst those which were non-parametric were compared with the Mann-Whitney U test.

A logistic regression model was fitted to analyse collectively the impact of the predictors upon the dependent variable that they influence. A single predictor could be rendered a very important contributor in explaining variations in the dependent variable but would be rendered unimportant in the presence of other predictors. For this reason, a logistic regression model was employed. The rationale for using a logistic regression model is because the dependant variable is categorical.

The odds ratio (OR) was used as an association measure. In a case-control study, the OR is simply the odds of the event in the case group divided by the odds of the event in the control group. The ORs with their 95% CI were estimated by multinomial logistic regression. To analyse the data, a 0.05 level of significance (alpha) was adopted. All *p*-values were computed assuming two-tailed tests.

CHAPTER 3

RESULTS

3.1 DESCRIPTIVE STATISTICS FOR HOSPITAL ADMISSIONS STUDY

The hospital admissions satisfying the study's inclusion criteria resulted in the formation of a cluster sample of 148 patients. A total of 46 patients were readmitted over the 3-month study time frame, leading to a readmission rate of 31.1%.

Readmission rate for COPD exacerbation during a 3-month time frame
46/148 x 100% = 31.1%

3.1.1 Patient Demographics

The mean age of the study population (N=148) was 68.78 (SD 9.299). The age ranged from 44 years to 94 years. Out of a total of 148 COPD exacerbation-related admissions, 67.6% (n=100) were male and 32.4% (n=48) were female (Figure 3.1).

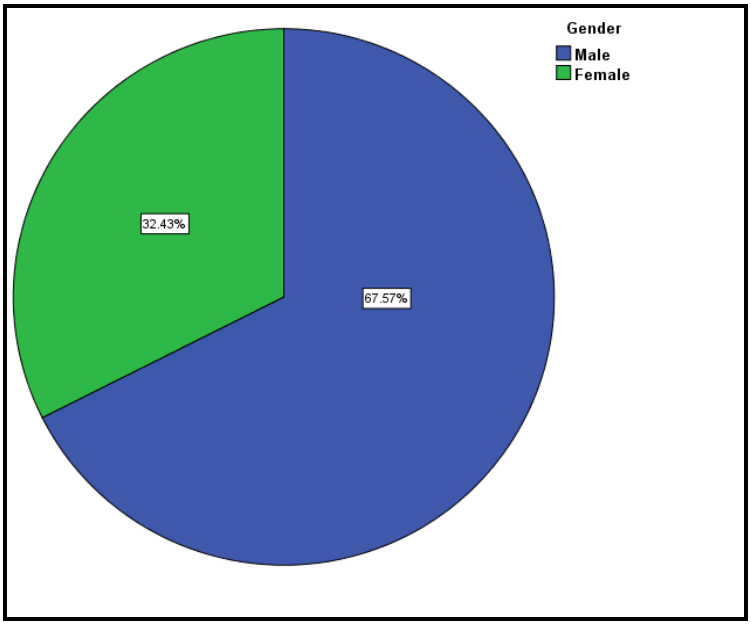

Figure 3.1 Gender distribution (N=148)

This pie chart depicts the gender distribution of the study population. The male gender was found to dominate in this study population. International data from various studies indicates that the overall prevalence and incidence of COPD are higher in men (Menezes et al., 2005; Buist et al., 2007; Van Durme et al., 2009).

Data pertaining to the study population (N=148) revealed that 32.4% (n=48) of patients were admitted under the care of a respiratory specialist whilst 67.6% (n=100) were admitted under general medical care. The decision of whether or not a patient hospitalised with COPD exacerbation was admitted under general medical care or specialist respiratory care depended on the local roster of on-call consultants admitting general medical care cases.

3.1.2 Drug History of Chronic Respiratory Medications

Among the different pharmacological classes of inhaled drugs are the short-acting beta agonists (SABA), short-acting muscarinic antagonists (SAMA), LABAs, LAMAs, and inhaled corticosteroids (ICS). Out of the population studied, only 16.9% (n=25) were making use of inhaled LAMA medication or inhaled LABA/LAMA combination (Table 3.1). With regards to oral agents, 4.1% (n=6) of the study population were prescribed theophylline for chronic use.

Table 3.1 Patients' drug history of inhaled medication (N=148)

Study sample N=148		**SABA**	**SAMA**	**LABA**	**LAMA**	**LABA/ LAMA**	**ICS**
Frequency	**Yes**	142	107	69	6	19	79
	No	6	41	79	142	129	69
Percentage	**Yes**	95.9	72.3	46.6	4.1	12.8	53.4
	No	4.1	27.7	53.4	95.9	87.2	46.6

SABA (short-acting beta agonist); SAMA (short-acting muscarinic antagonist); LABA (long-acting beta agonist); LAMA (long-acting muscarinic antagonist); ICS (inhaled corticosteroid)

Of note, is the high percentage of patients utilising reliever medication (SABA) and the low percentage of patients using LAMA therapy. This indicates that few patients are on optimum therapy whilst the majority of patients are poorly controlled as they are using the reliever medication on a chronic basis.

3.1.3 Clinical Variables

In this section, the results pertaining to the clinical variables namely concomitant comorbidities and BAP-65 scores are presented.

3.1.3.1 Concomitant Comorbidities

The mean number of comorbidities other than COPD was 2.55 (SD 1.86, N=148 patients). The number of comorbidities ranged from 0-11. About 7.4% (n=11) of patients had no other comorbidities apart from COPD, whilst 27.0% (n=40) had one additional comorbidity. The majority of patients (65.5%, n=97) had 2 or more underlying comorbidities in addition to COPD (Figure 3.2).

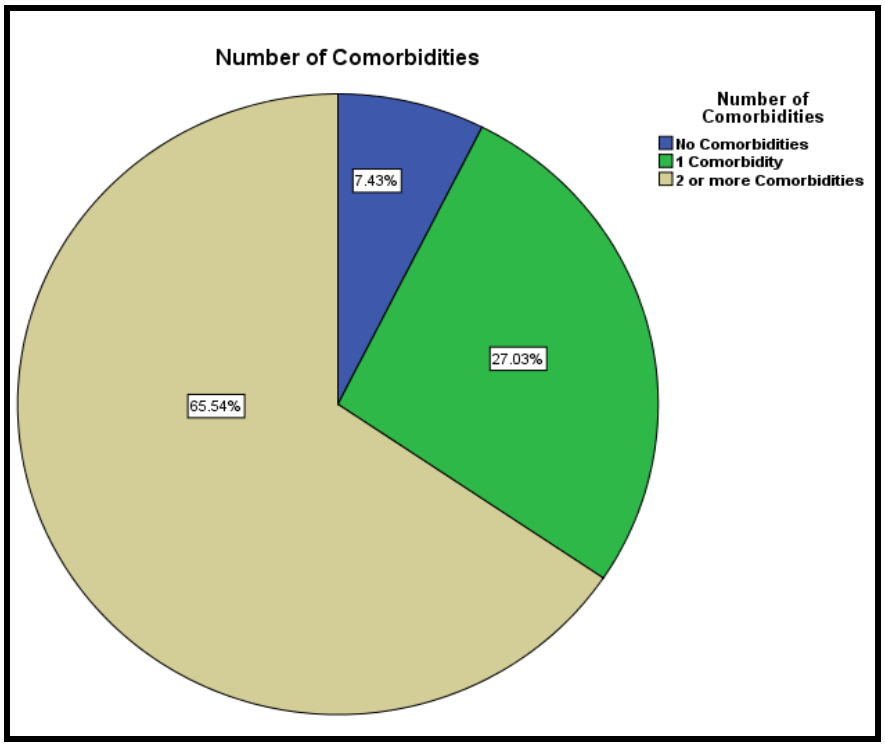

Figure 3.2 Comorbidities other than COPD (N=148)

The pie chart depicts the percentage of patients with no other comorbidities, those with one other comorbidity and those with two or more comorbidities in addition to COPD.

Among the COPD cohort of hospitalised patients, 60 different concomitant comorbidities were identified. Table 3.2 summarises the 11 most prevalent concomitant comorbidities in the study population.

Table 3.2 Prevalence of comorbidities in the study population (N=148)

Comorbidity	**Prevalence of comorbidity in the study population (N=148)**	
	n	**%**
Hypertension	72	48.6
Ischaemic heart disease	42	28.4
Congestive heart failure	41	27.7
Depression	36	24.3
Diabetes mellitus	24	16.2
Alcoholism	24	16.2
Atrial fibrillation	13	8.8
Benign prostatic hypertrophy	13	8.8
Hypothyroidism	9	6.1
Lung cancer	8	5.4
Anxiety	8	5.4

The 11 most prevalent comorbidities in the study population are presented. Cardiovascular disease is the most common group of comorbidities, followed by the psychological cluster and the metabolic cluster. Among the different types of malignancies, lung cancer showed the greatest prevalence in the studied COPD cohort. This may be related to the effect of cigarette smoke.

3.1.3.2 BAP-65 Score

The majority of patients (n=58) had a BAP-65 score of 3 or 4, implying high risk for intubation and/or mortality. The next most common BAP-65 score was that of two, implying intermediate risk. This was then followed by the low-risk category (BAP-65 score of 1) (Table 3.3).

Table 3.3 BAP-65 scores of study population (N=148)

Study population N=148		**Frequency**	**Percentage**
BAP-65 score	1 (low risk)	39	26.4
	2 (intermediate risk)	51	34.5
	3 or 4 (high risk)	58	39.2

This table summarises the frequency and percentages of the BAP-65 scores of the study population indicating that the majority of the patients are within the high-risk group.

BAP-65 system is a score composed of 4 variables: blood urea nitrogen (BUN), altered mental status, pulse, and age >65. The BAP-65 score is calculated based on the following criteria: BUN >25mg/dL; mental status - disoriented, stuporous, or comatose; pulse >109 beats/min; age >65 years. A point is gained for each variable, according to the explained criteria. Higher BAP-65 scores correlate with the need for mechanical ventilation and mortality (Tabet et al., 2016).

3.2 HEALTHCARE RESOURCE UTILISATION DATA

In the following section results pertaining to HCRU data and costings are presented.

3.2.1 Length of Hospital Stay and Level of Care

The length of hospital stay, ranged from 1-44 days with the median being 4 days. Out of a total of 148 hospitalised patients, 136 patients required acute medical care necessitating admission to a general medical ward. A total of 12 patients required intensified medical care, necessitating ITU or HDU admission. Out of these 12 patients, 9 patients required the use of NIV on a medical ward (equivalent to HDU admission) and 3 patients required ITU admission, further increasing the hospitalisation costs. The duration of use of NIV ranged from 1-7 days whilst length of stay in ITU ranged from 2-5 days.

3.2.2 Activity-Based Costing

The micro-economic analysis of hospitalisation costs attributed to COPD exacerbations throughout the months of February-April 2017 amounted to €222,878 (Table 3.4). The hospitalisation cost ranged from €331 - €10,049 per patient admission. The mean hospitalisation cost is €1506.

Table 3.4 Summary of hospitalisation costs

Cost of admissions in monetary terms (Euro) (N=148)	**% of total hospitalisation cost**
Cost for admissions to medical ward (n=136) = €176,096	79.0%
Cost for HDU admissions (n=9) = €32,494	14.6%
Cost for ITU admissions (n=3) = €14,288	6.4%
Total hospitalisation cost in 3-months (N=148) = €222,878	**100%**

A summary of the cost-breakdown for exacerbation-related hospitalisation is outlined. The hospitalisation cost ranged from €331 - €10,049 with average hospitalisation cost being €1506.

3.3 CORRELATIONS WITH MEASURES OF RESOURCE USE

The hospital admissions study has led to the identification of correlations with measures of resource use. The patients' length of stay (LoS) in hospital was used as a measure of resource use.

3.3.1 BAP-65 Scores

As shown in the scatter plot, the length of hospital stay correlates positively with the BAP-65 score (Figure 3.3).

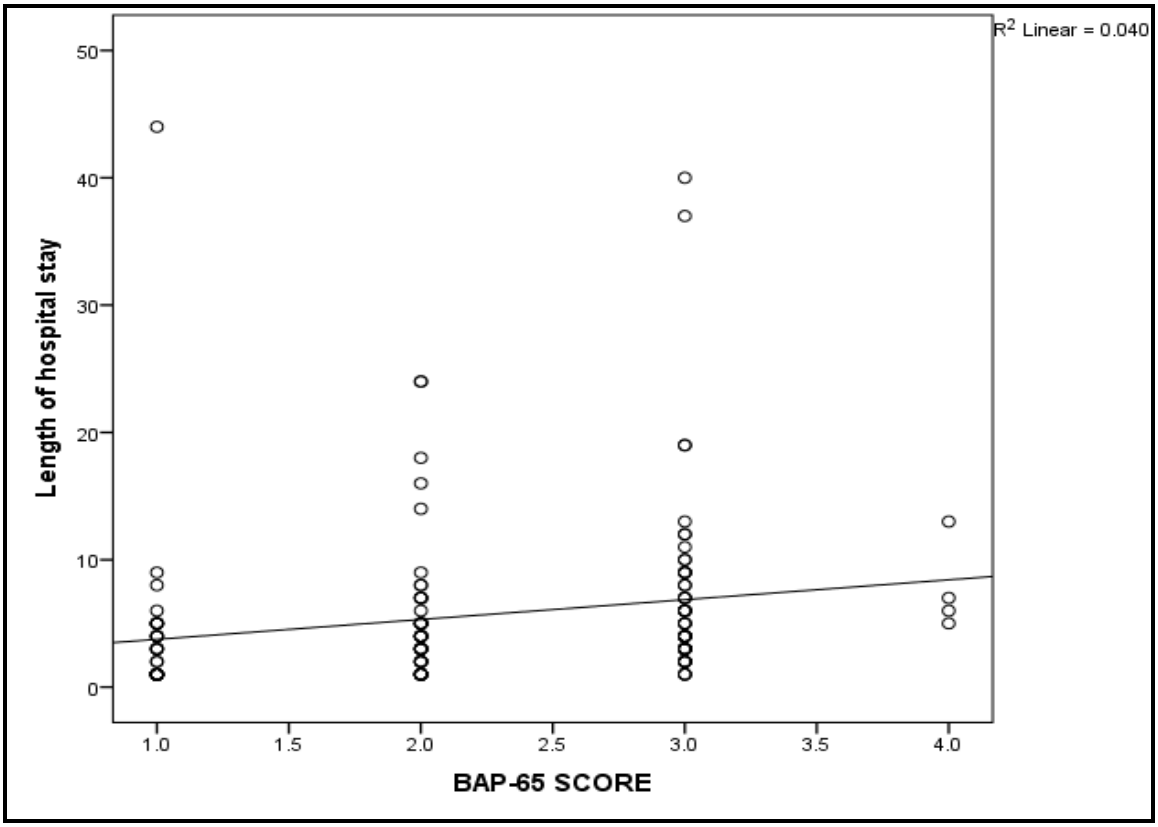

Figure 3.3 Scatter plot of length of hospital stay versus BAP-65 score

Among the cohort of hospitalised patients (N=148), the most common BAP-65 score was that of 3 or 4. Once the patients' BAP-65 score on admission is calculated, the expected length of hospital stay may be estimated by extrapolation from the above scatter plot.

The Pearson correlation coefficient (0.199) is positive indicating a positive relationship between length of hospital stay and BAP-65 scores. The *p*-value (0.015) is less than the 0.05 level of significance indicating that this positive relationship is significant and not attributed to chance. It can be generalised that patients with higher BAP-65 scores tend to stay longer in hospitals.

3.3.2 Number of Comorbidities

A statistically significant positive correlation was observed between the length of hospital stay and the number of comorbidities. The Pearson correlation coefficient (0.198) is positive indicating a positive relationship between length of hospital stay and the number of comorbidities. The *p*-value (0.016) is less than the 0.05 level of significance indicating that this positive relationship is significant and not attributed to chance. Patients with more comorbidities can be considered to stay longer in hospitals.

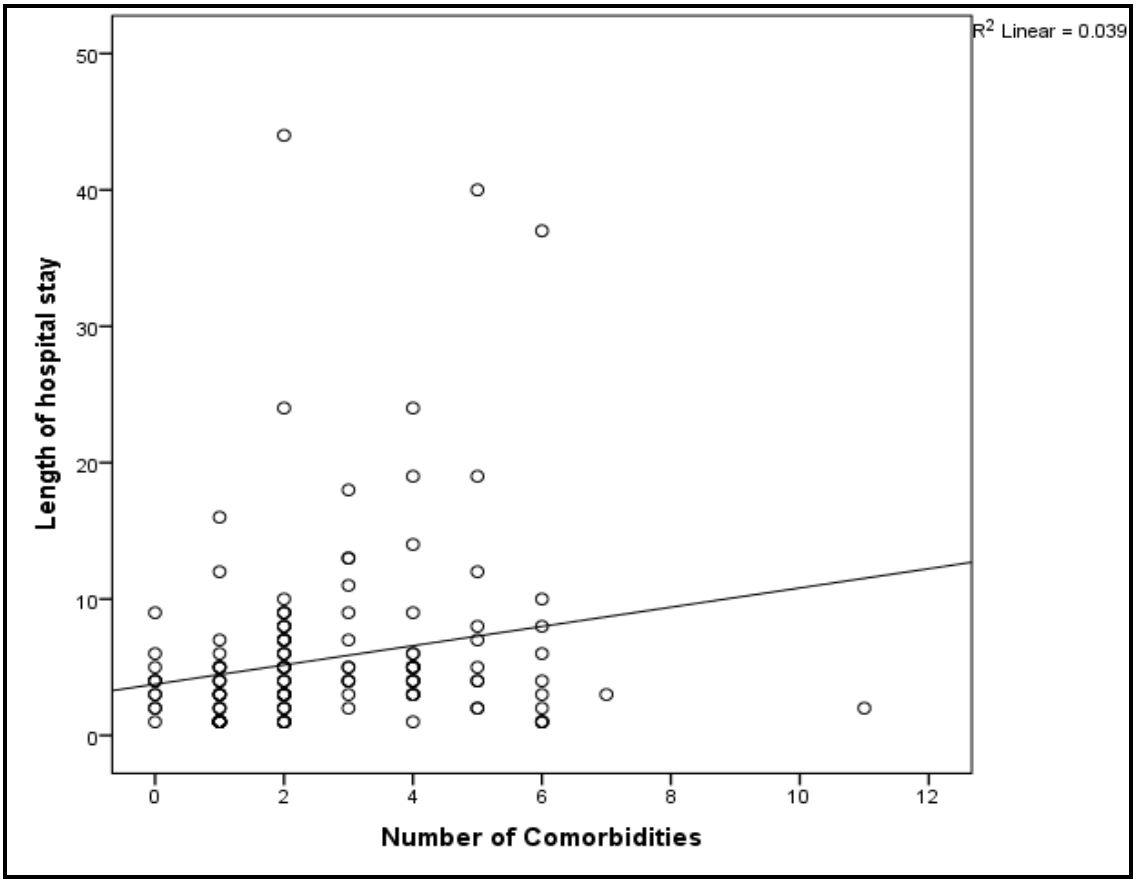

Figure 3.4 Scatter plot of LoS in hospital versus number of comorbidities

The mean number of comorbidities for the hospitalised COPD cohort was 2.55 (N=148). This scatter plot may also be utilised to estimate the length of hospital stay. The number of coexisting comorbidities may be obtained from the documented medical case notes and the length of hospital stay estimated via extrapolation.

3.4 CASE-CONTROL STUDY

The results of the case control study and the predictors for COPD exacerbations leading to hospitalisation are described in the following section.

3.4.1 Sample Size

The study sample for the case-control study is 162 divided equally between cases and control subjects; 81 in each group.

A sample of 162 patients selected from a total population of 350,000[8] individuals aged 16 years and over guarantees a maximum margin of error of 7.7%, assuming a 95% confidence level (Appendix 6).

3.4.2 Case-Control Matching

Case-control matching for age and gender was employed to avoid confounding.

Table 3.5 Age distribution among cases and control subjects

Study sample N=162		**Age-group**				
		40-49years	**50-59 years**	**60 -69 years**	**70 years or more**	**Total**
Group	**Case**	2	11	32	36	81
	Control	1	6	33	41	81
Total		3	17	65	77	162

$X^2(3) = 2.144$, $p = 0.543$

[8] National Statistics Office (NSO). World Population Day: 11 July 2018 [Online]. Malta; 2018 [cited 2018 July 30]. Available from: URL: https://nso.gov.mt/en/News_Releases/View_by_Unit/Unit_C5/Population_and_Migration_Statistics/Documents/2018/News2018_107.pdf.

The *p*-value (0.543) exceeds the 0.05 level of significance indicating that there is no age discrepancy between the case and control groups (Table 3.5).

Table 3.6 Gender distribution among cases and control subjects

Study sample N=162		**Gender**		**Total**
		Male	**Female**	
Group	**Case**	52	29	81
	Control	59	22	81
Total		111	51	162

$X^2(1) = 1.402$, $p = 0.236$

The *p*-value (0.236) exceeds the 0.05 level of significance indicating that there is no gender discrepancy between the case and control groups (Table 3.6).

3.5 STATISTICAL ANALYSIS FOR CASE-CONTROL STUDY

3.5.1 Univariate Analysis

Univariate analysis identified any association between the dependent variable (case-control) and a single predictor. The Chi-Square test was used to identify any association between the case-control group and any other categorical variable (Appendix 7). The association between the case-control group and any other continuous variable was identified with the Independent Samples *t*-test or Mann-Whitney U test, depending on the normality of the data (Appendix 7).

3.5.2 Multinomial Logistic Regression Modeling

The regression model analysed the impact of the predictors upon the dependent variable in a collective manner. The variables which were found to be significant in univariate analysis were fed into a logistic regression model, using the stepwise approach. The variables which retained statistical significance after being subject to the model were identified (Appendix 7).

The variables which were not statistically significant when analysed collectively, were eliminated by the model, leading to a reduced model. In this way, the predictors for COPD exacerbation-related hospitalisation were identified (Table 3.7). The extent to which this six-predictor model affects the total variability between cases and controls is explained by the Nagelkerke Pseudo R^2 value (0.677).

Table 3.7 Predictors for COPD exacerbation-related hospitalisation

	-2 log likelihood	**Chi-square**	**df**	***p*-value**
Inhaled LABA	87.029	8.762	1	0.003
IV antibiotic use in the last 3-months	83.473	5.206	1	0.023
Emergency nebuliser use in the last 3-months	83.572	5.304	1	0.021
CAT score	102.472	24.204	1	<0.001
Number of comorbidities	82.876	4.608	1	0.032
Number of previous COPD hospitalisations	93.642	15.375	1	<0.001

3.6 MEASURES OF ASSOCIATION

The ORs were used to measure the association between the identified predictors and their likelihood of influencing whether a patient is in the case group. The control group was thus used as reference category.

3.6.1 Odds Ratios

The ORs were computed through logistic regression (Table 3.8).

Table 3.8 Summary of odds ratio results

Predictor	**Odds ratio**	***p*-value**	**95% confidence interval**	
			Lower bound	**Upper bound**
Inhaled LABA=No	6.494	0.006	0.041	0.587
IV antibiotic use in the last 3-months=Yes	8.545	0.041	1.093	66.827
Emergency nebuliser use in the last 3-months=Yes	4.537	0.025	1.209	17.031
CAT score	1.193	<0.001	1.096	1.299
Number of comorbidities	1.593	0.038	1.025	2.474
Number of previous COPD hospitalisations	1.702	0.001	1.238	2.339

The OR for inhaled LABA use indicates that its use is actually a protective factor. All the other identified predictors are risk factors for COPD exacerbation-related hospitalisation. The narrower the CI, the higher the precision of the OR.

3.6.2 Interpretation of Odds Ratios

The OR for inhaled LABA (No) (6.494) is significantly different from 1 because the *p*-value (0.006) is less than the 0.05 criterion. This implies that lack of LABA use increases the odds for hospitalisation by 6.494 times. Inhaled LABA use is a significant protective factor. The ORs for IV antibiotic use (Yes) and emergency nebuliser use (Yes) in the last 3-months are also significantly different from one because the *p*-values are less than the 0.05 criterion (0.041, 0.025). This implies that both recent IV antibiotic use and emergency nebuliser use increase the odds for hospitalisation by 8.545 and 4.537 times respectively.

To interpret the ORs results for covariates, the following computation would need to be carried out [(OR – 1) x 100%]. The ORs for the CAT score, number of comorbidities and number of previous COPD hospitalisations are 1.193, 1.593 and 1.702 respectively. These are significantly different from 1 because the *p*-values are less than the 0.05 level of significance (<0.001, 0.038, 0.001). This implies that for every one unit increase in the CAT score the odds for hospitalisation increases by 19.3% [(1.193-1) x 100%]. Similarly, the odds for hospitalisation increase by 59.3% for every one unit increase in the number of comorbidities. In the same way, for every one unit increase in the number of previous hospitalisations, the odds for hospitalisation increases by 70.2%.

3.6.3 Probability curves for covariates

The graph shows that as the CAT score increases the probability of being in the case group increases while the probability of being in the control group decreases. This conforms to what we expect about higher CAT scores being a risk factor. The two probability curves intersect at CAT score = 18.9.

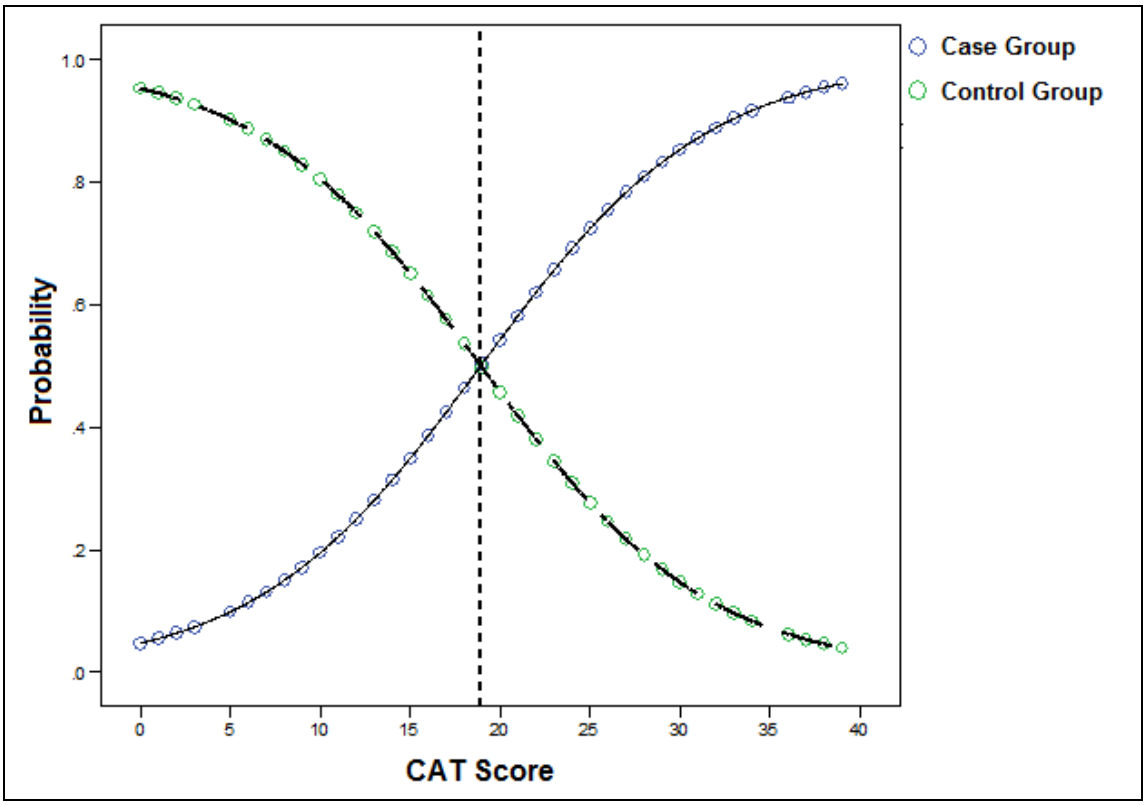

Figure 3.5 Probability curve for CAT Score

This implies that patients with a CAT score >18.9 are more likely to be in the case group while patients with a CAT score <18.9 are more likely to be in the control group.

The graph shows that an increase in the previous COPD hospitalisations increases the likelihood of being in the case group and decreases the likelihood of being in the control group. This confirms that the number of previous COPD hospitalisations is a significant risk factor. The two probability curves intersect at number of previous COPD hospitalisations = 1.65.

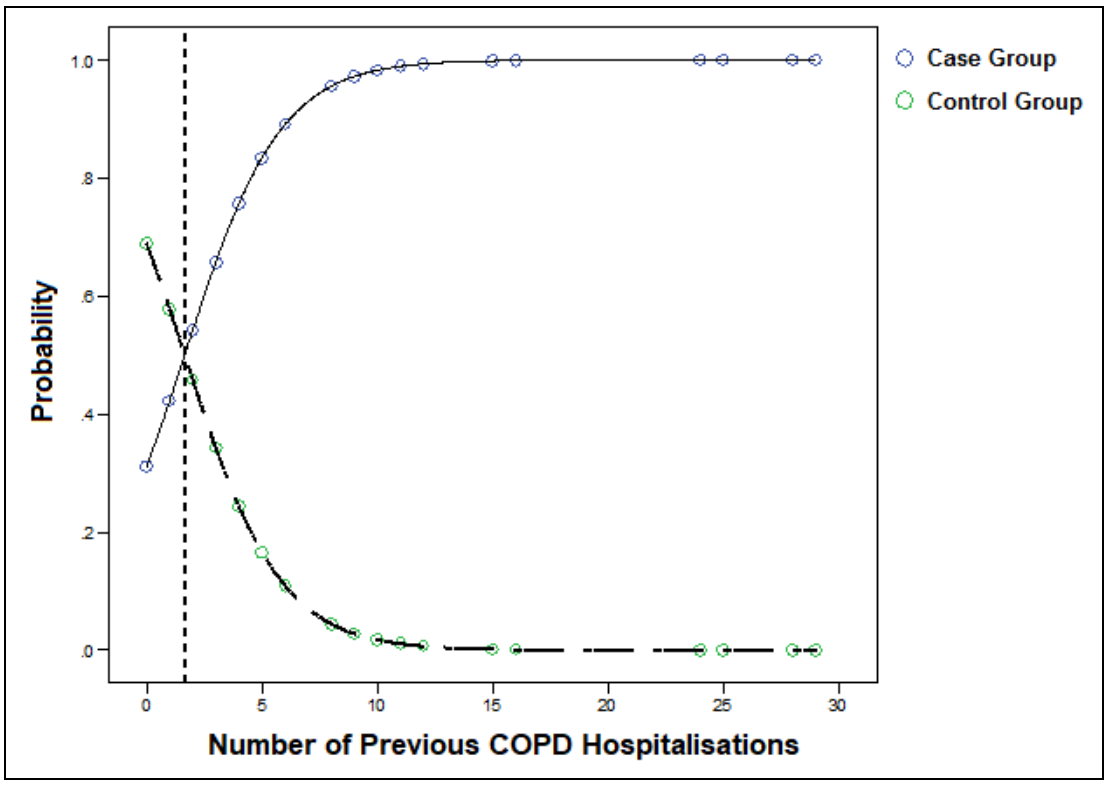

Figure 3.6 Probability curve for number of previous COPD hospitalisations

Patients with at least 2 previous COPD hospitalisations in a lifetime are more likely to be in the case group, while patients with at most 1 hospitalisation in a lifetime are more likely to be in the control group.

The graph shows that a larger number of concomitant comorbidities, increase the probability of being in the case group and decrease the probability of being in the control group. This confirms that the number of comorbidities is a significant risk factor. The two probability curves intersect at number of comorbidities = 2.2.

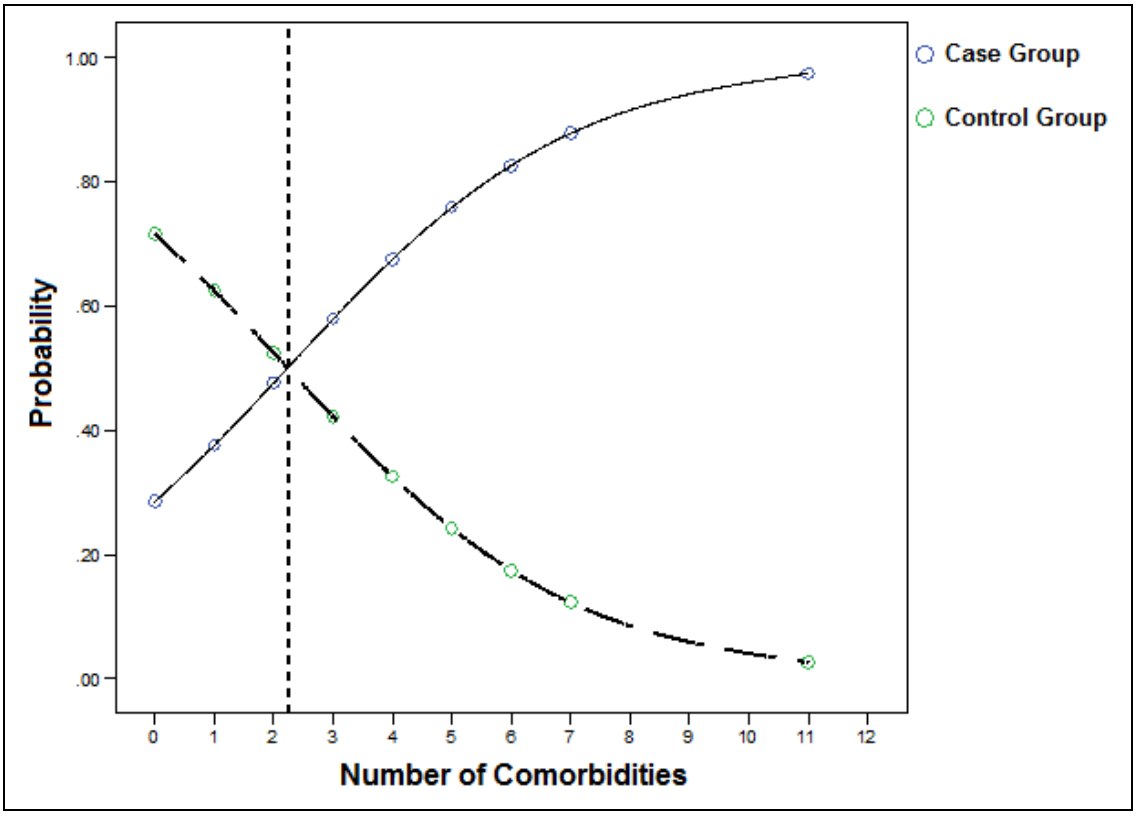

Figure 3.7 Probability curve for number of comorbidities

Patients with more 3 comorbidities or more are more likely to be in the case group whilst those patients with 2 comorbidities or less are more likely to be in the control group.

CHAPTER 4

DISCUSSION

4.1 THE SIGNIFICANCE OF THE STUDY IN THE LOCAL SETTING

In COPD management, exacerbations are an important clinical end-point and the newer treatment strategies are tested against this outcome (Scott et al., 2005; Agusti et al., 2014). Treatment modalities that impact on COPD exacerbations leading to hospitalisation have important implications both from a clinical and economic perspective. LAMAs have been shown to reduce COPD exacerbations and the associated hospitalisations (Jones, 2015).

From this study, it was revealed that only 16.9% (n=25) of patients admitted with COPD exacerbation were receiving LAMA therapy. The fact that patient access to LAMAs is restricted to those who are willing to purchase the drug, may explain this low percentage. Owing to the lack of availability of LAMAs in the local NHS, respiratory physicians are faced with a barrier when prescribing these drugs. The COPD exacerbation-related admissions captured during the 3-month time frame, may be attributed in part to lack of optimum therapy. This is to be interpreted with caution since only around half of the study sample (46.6%, n=69) were receiving LABA therapy. This is explained by the fact that the local protocols for LABA use in the Maltese NHS stipulate that this is to be solely prescribed by respiratory specialists. This precludes patients admitted under general medical care from LABA use.

Data from various international studies indicates that 35-54% of the total COPD treatment expenditures are attributed to hospitalisation (Ward et al., 2000; Rutten Van-Molken and Feenstra, 2001; Jansson et al., 2002; Britton, 2003; Masa et al., 2004). Hospital admissions are often utilised as a target to reduce the costs associated with COPD (Molinari et al., 2015). This study addresses the hospitalisation cost arising from COPD exacerbations as one the study objectives.

In this study, the total estimated hospitalisation cost resulting from COPD exacerbations in a 3-month time frame amounted to €225,000. When introducing new drugs onto formularies, it is necessary for health-policy makers to consider treatment efficacy in conjunction with a budget impact analysis (Mapel et al., 2010). A possible approach would be to compare the average cost per admission (€1506) to the cost of LAMA therapy over a 12-month period (Table 4.1).

Table 4.1 Summary of cost of LAMA therapy and hospitalisation cost

Locally available LAMAs in the retail sector	**Wholesale cost per pack**	**Cost of LAMA therapy per patient over a 12-month period***
Glycopyrronium (Seebri Breezhaler®)	€40 per 30 capsules	€480 per patient per year
Glycopyrronium/indacaterol (Ultibro Breezhaler®)	€57.38 per 30 capsules	€688.56 per patient per year
Umeclidinium/vilanterol (Anoro Ellipta®)	€43.74 per 30 capsules	€524.88 per patient per year

Total estimated hospitalisation cost during the 3-month study time frame €225,000
Extrapolated hospitalisation cost per year** €900, 000
Average cost per admission €1506

* The calculated cost of LAMA therapy per patient per year is based on local wholesale prices. LAMAs procured via tendering agreements through the NHS are generally cheaper than the wholesale prices.

** The extrapolated hospitalisation cost per year was based on the hospitalisation costs during the winter season. Since the rate of COPD exacerbations is seasonal, the number of COPD hospital admissions will vary throughout the year, and so will the hospitalisation costs.

Given that resources are finite, prioritisation of patient access to LAMAs is also key to the development of efficient healthcare policies. This study addressed this aspect by way of the objective to determine the predictors for COPD exacerbation-related hospitalisation. Based on these identified predictors a protocol for LAMA use can be drawn up, and this will serve as a tool in prioritising patient access to these agents.

4.2 IMPORTANT CONSIDERATIONS FOR THE INTRODUCTION OF LAMAs

When evaluating LAMA therapy for inclusion in the Maltese NHS, a holistic approach should be adopted. The effect of seasonality on exacerbation rate and total direct and indirect cost arising from exacerbations should be taken into consideration. Due consideration should also be given to LAMA efficacy in the real life setting and the choice of LAMA for inclusion in the local NHS.

The effect of seasonality on exacerbation rate has been reported in the POET trial where it was shown that the rate of exacerbations requiring treatment was about twice as high during the winter as during the summer.[9] The number of COPD exacerbation-related admissions is expected to vary with season and so will the hospitalisation costs. The study captured the peak season for exacerbations and this should be taken into consideration when extrapolating the hospitalisation costs to yearly cost estimates.

This study aimed at capturing the cost of exacerbations leading to hospitalisation. It should be pointed out that the hospitalisation costs represent part of the direct cost associated with COPD exacerbations. Other direct costs resulting from COPD exacerbations include the cost of the primary care provided by the Maltese NHS to treat

[9] American College of Emergency Physicians (ACEP). COPD exacerbations twice as common in winter. [Online] ACEP; 2011 [cited 2018 Jan 16]. Available from: URL: https://www.acep.org/MobileArticle.aspx?id=82226&coll_id=716&parentid=.

these exacerbations in the community. Indirect costs such as missed days from work were also not included in this research. Should a pharmacoeconomic model be employed to evaluate LAMA use, all costs arising from these exacerbations should be incorporated.

Mapel et al., (2010) explain that it is difficult to ascertain the reproducibility of the efficacy of LAMAs reported in clinical trials to real life settings (Mapel et al., 2010). Inter-patient variability such as differences in disease severity, comorbidities and demographics are likely to affect treatment efficacy. Patients in the general population are also less likely to be as compliant with treatment as those participating in closely monitored clinical trials (Mapel et al., 2010). In a narrative review Jones, (2015) concludes that LAMAs are broadly comparable in terms of preventing exacerbations (Jones 2015). This implies that the decision as regards to which LAMA to introduce in the local setting can be based on the procurement cost.

4.3 FACTORS AFFECTING LENGTH OF HOSPITAL STAY

In this study the median length of hospital stay was 4 days. The median length of hospital stay of patients admitted with AECOPD in the AUDIPOC study in Spain, is longer and is reported to be around 7 days (Pozo-Rodriguez et al., 2012). Pearson's correlation showed that both the BAP-65 scores and number of comorbidities were shown to correlate positively with length of hospital stay (*p*-values 0.015, 0.016). The factors affecting length of hospital stay will in turn impact HCRU.

In the hospital admissions study, the majority of patients (39.2%, n=58) had a BAP-65 score of 3 or 4, implying high risk for intubation and/or mortality as well as higher hospitalisation stay and costs. Shorr et al., (2011) showed that a rising BAP-65 score closely parallels the length of hospital stay and total hospital costs (Shorr et al., 2011). The implications of this finding and its reproducibility in the local setting make it a potentially useful system for economic risk stratification and benchmarking purposes. In addition, the simplicity of this tool encourages its use.

Within the identified cluster sample of hospitalised patients, 92.5% (n=137) had one or more comorbidities in addition to COPD. This data compares well with that of international studies from a wide range of COPD cohorts, where approximately 86-98% of individuals with COPD were found to have at least 1 comorbid condition (Putcha et al., 2015). The statistically significant positive correlation between length of hospital stay and number of comorbidities is in line with a Finnish analysis of administrative hospitalisation data (Kinnunen et al., 2003). This analysis also showed that patients hospitalised with COPD who had additional comorbidities spent a significantly longer time in hospital (Kinnunen et al., 2003).

4.4 PREDICTOR MODEL FOR COPD HOSPITALISATION

The first step in establishing an accurate predictor model for COPD hospitalisation was the identification and elimination of confounding variables. The patients recruited as control subjects needed to satisfy the criterion of not having had a COPD exacerbation-related hospitalisation in the previous year as per study design of this research. Since control patients were recruited from respiratory outpatients, these patients were likely to have had other follow-up appointments in the previous year as opposed to the hospitalised patients which may not have necessarily been followed up by respiratory specialists. The number of hospitalisations in the previous year and attendance to respiratory outpatients were excluded from the model as it was likely for these variables to be strong predictors as a result of the study's inclusion criteria and patient recruitment of control subjects.

The Parsimonious logistic regression model identified six significant predictors for hospitalisation. Using the Nagelkerke Pseudo R-Square value shows that this six-predictor logistic regression model explains 67.7% of the total variation between the cases and controls. The CAT score is the best predictor as it has the lowest *p*-value (approximately zero). This is followed by number of previous COPD hospitalisation (*p*-value <0.001), inhaled LABA therapy (*p*-value 0.003), emergency nebuliser use in the last 3-months (*p*-value 0.021), IV antibiotic use in the last 3-months (*p*-value 0.023), and number of comorbidities (*p*-value 0.032). A summary of the predictors which are continuous variables is presented in Table 4.2, where the results from this research are compared to international previous findings.

Table 4.2 Comparison of local research to prior international research

Local findings from this research	Findings from international research
A CAT score > 18.9 is positively associated with the occurrence of a hospitalisation (OR 1.193; 95% CI 1.096-1.299)	In a Spanish study by Miravittles et al., (2015) it was shown that a CAT score ≥13.5 points is a significant risk factor for hospitalisation (Miravittles et al., 2015)
The presence of at least 2 past exacerbation-related hospitalisations is positively associated with the occurrence of a hospitalisation (OR 1.702; 95% CI 1.238-2.339)	In a Spanish study by Santibanez et al., (2016) a history of at least 2 hospitalised exacerbations was positively associated with new severe exacerbations (Santibanez et al., 2016)
The presence of at least 3 concomitant comorbidities is positively associated with the occurrence of a hospitalisation (OR 1.593; 95% CI 1.025-2.474)	In an American study, Schwab et al., (2017) report an association between the presence of comorbidities and COPD-related hospitalisations (Schwab et al., 2017)

This table summarises the predictors which are continuous variables identified from this study and compares this to prior international research. The ORs together with the 95% CIs are presented. The cut-off point beyond which patients are likely to sustain an exacerbation leading to hospitalisation is also presented. In summary, the results of this study are generally consistent with prior research.

The predictors which are categorical variables are also outlined. The use of inhaled LABAs is a protective factor and lack of its use increases the risk for hospitalisation by 6.494 times (95% CI 0.041-0.587). This conforms to the available evidence from a systemic review by Kew et al., (2013) which shows that formoterol significantly improves FEV_1 and lung volumes, dyspnoea, health status, exacerbation rate and number of hospitalisations (Kew et al., 2013). Since the only LABA available on the

NHS for the adult population is formoterol, it can be generalised that most patients were utilising this drug in preference to other LABAs available for retail.

Recent use of emergency nebulisers in the community and recent IV antibiotic use increase the risk for hospitalisation by 4.537 times (95% CI 1.209-17.031) and 8.543 times (95% CI 1.093-66.827) respectively. IV antibiotics are normally prescribed in acute care settings and their recent use among the COPD cohort suggests a recent exacerbation or an infective component. The recent use of emergency nebulisers is also indicative of a recent acute exacerbation. It is local practice for physicians to opt for nebulised bronchodilators in preference to MDIs for AECOPD, despite evidence from Welniak et al., (2015) showing that they are equally effective when taken correctly (Welniak et al., 2015). The fact that both these variables are significant risk factors may be explained by treatment failure of the initial exacerbation or a frequent-exacerbation phenotype.

4.5 INNOVATIVE CONTRIBUTION OF THE STUDY

An exhaustive literature review, revealed that no study to date has combined the identification of the predictors for COPD exacerbation-related hospitalisation together with the costs resulting from these hospitalisations. This study also explores correlations with measures of resource use. The predictors for COPD hospitalisation may be used to identify the patients who are at the highest risk for sustaining an exacerbation leading to hospitalisation. The BAP-65 scores and the number of comorbidities may be utilised in order to predict the most expensive hospitalisations. The significant predictors for hospitalisation may lead to the establishment of a protocol for LAMA use, for inclusion in the Maltese NHS (Figure 4.1).

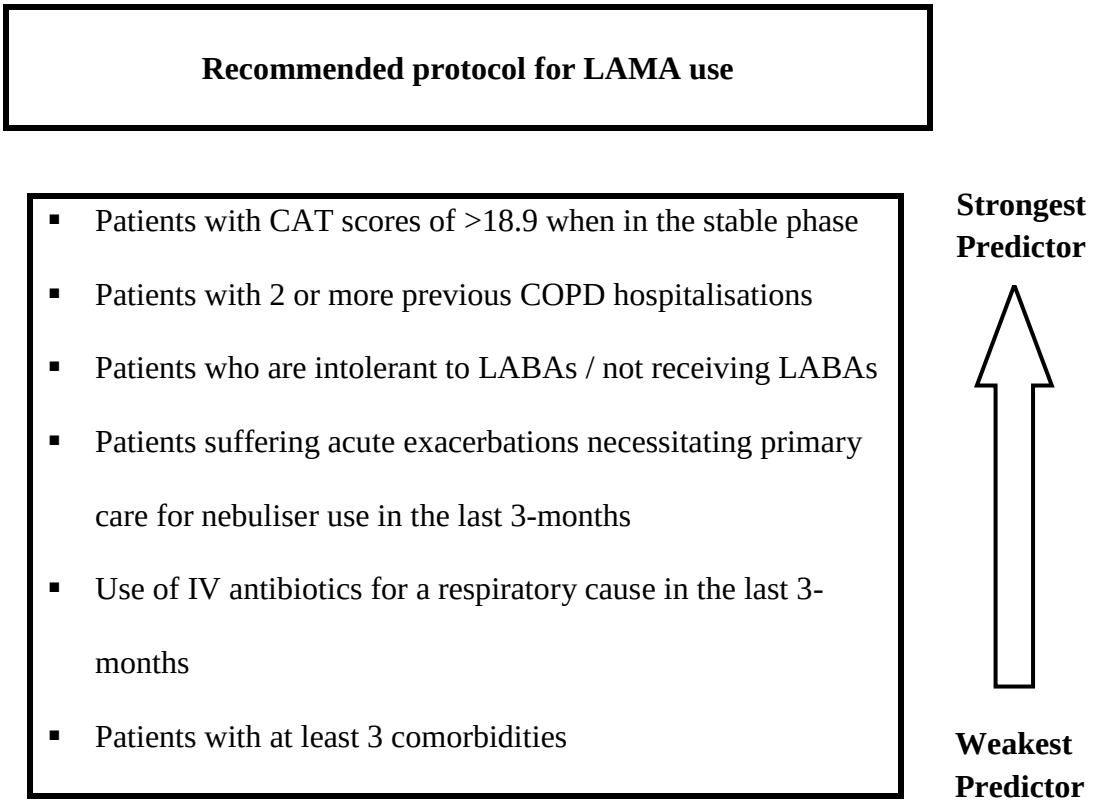

Figure 4.1 Recommended protocol for LAMA use

This figure highlights the patients who should be given priority to LAMA therapy. Although the developed protocol assists in identifying the patients at high risk for hospitalisation, it is not infallible and should only be used as a guide.

Despite that number of comorbidities is the least strong predictor for hospitalisation, its significance should not be undermined, given that it is also related with hospitalisations of a longer duration, which implies higher hospitalisation costs. Schwab et al., (2017) suggest that payers or providers should attempt to target COPD care management resources by assessing patients' comorbidity profiles. In this way, patients at greater risk of acute HCRU can be identified (Schwab et al., 2017).

The outcome measures from the hospital admissions study suggest that a holistic approach should be adopted for better management of COPD exacerbation-related hospitalisation. In agreement with this, Molinari et al., (2015) and Schwab et al., (2017) underline that a multidisciplinary approach to COPD management is the way forward to consolidate care while managing costs (Molinari et al., 2015; Schwab et al., 2017). The predictors for hospitalisation should be coupled with other factors which are associated with higher HCRU.

In this study, critical care admissions (ITU or HDU) accounted for 20% of the total estimated hospitalisation cost. The fact that only a relatively few patients (8.1%, n=12) required admissions to critical care units suggests that special attention is required to try and prevent these expensive hospitalisations. In this study, a significant number of patients (31.1%, n=46) were readmitted throughout the 3-month study time frame. Nantsupawat et al., (2012) and Baker et al., (2013) report an early readmission rate of 20% in a cohort of Medicare fee-for-service patients in the United States of America (USA) (Nantsupawat et al., 2012; Baker et al., 2013). The local readmission rate is higher than that reported in international studies. As explained by Mantero et al., (2017), early readmissions particularly those within 30 days of initial hospitalisation could be indicative of treatment failure and special attention should be given to try and reduce the readmission rate (Mantero et al., 2017).

4.6 LIMITATIONS

Recognising a study's limitations is an important aspect as it may create a niche for further study. It will also assist in interpreting the results with caution. Some of the confounders were recognised and tackled a priori when designing the methodology.

The larger the sample size the more representative and reproducible the results. Some of the admitted patients were lost to follow-up since they happened to be discharged prior to their interview being conducted. This happened since it was unfeasible for the researcher to be stationed at MDH on a 24/7 basis during the study time frame. The 3-month time frame used for the hospital admissions study is statistically representative, however a longer time frame would add significance to the study. Since the number of patients receiving LAMA therapy is low (16.9%, n=25), the effect of LAMA use on the LoS and admission to critical care units could not be established.

Clinical databases are not specifically designed for research objectives and any information obtained through this channel could be low in quality. In some instances, there may be insufficient completion of medical records or lack of agreement among different records. Hospitalisations prior to 2009 were only recorded on paper and thus could not be tracked down electronically. Since it was unfeasible to go through the patients' files for any older hospitalisations, the year 2009 was used as a cut-off point. The data which was based on patient self-report is subject to recall bias.

4.7 RECOMMENDATIONS FOR FURTHER STUDY

Determining the cost-effectiveness projections for LAMA therapy is a niche for further research. The lack of studies examining the potential cost-effectiveness of newer therapies in the area of exacerbation reduction has also been pointed out in the GOLD guidelines.[10] The outcome measures from the hospital admissions study provides the framework for further pharmacoeconomic research. Mapel et al., (2010) carried out a

[10] Global initiative for chronic Obstructive Lung Disease (GOLD). Pocket guide to COPD diagnosis, management, and prevention: a guide for health care professionals. [Online]. GOLD Inc.; 2017. [cited 2017 Jan 10]. Available from: URL: http://goldcopd.org/wp-content/uploads/2016/12/wms-GOLD-2017-Pocket-Guide.pdf.

Monte Carlo simulation in order to determine cost-effectiveness for a range of COPD controller medications but the analysis did not include LAMAs. The same methodology used by Mapel et al., (2010) may be used to determine the cost-effectiveness of LAMA therapy in the local scenario.

The high readmission rate in the identified cluster sample highlights the need for studying the characteristics of early readmissions. One could attempt to identify the risk factors for early readmission and whether lack of LAMA use increases the readmission risk. The literature also highlights an emerging need for the determination of the risk factors for early COPD readmission (Mantero et al., 2017). It is thought that identifying these risk factors may allow for a more precise approach with specific interventions targeting the individual needs of the patients. This could assist in reducing the readmission rate and may therefore have a key role in improving the management of COPD patients (Mantero et al., 2017).

4.8 CONCLUSION

COPD exacerbation-related hospitalisations during a 3-month period have been identified and the hospitalisation cost estimated. The high rate of readmissions warrants special attention given that this may be a sign of treatment failure. The BAP-65 score may not only assist in triage decision-making but also correlates positively with measures of resource use. A protocol for local LAMA use has been developed based on the identified predictors for hospitalisation. Multi-morbidity not only increases the risk for hospitalisation but is also associated with a higher HCRU.

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Appendix 1

Data collection proforma

Data Collection Proforma

COPD Exacerbations – Cost, Risk Factors and Impact of LAMAs

Case Number _____

Initials _____

ID Number _____

Section A: Sociodemographic Variables

i.) Age _____

ii.) Gender M F

iii.) Marital Status married separated /divorced widowed single

iv.) Employment status employed unemployed retired

v.) Occupation(s) (current or past) _____

vi.) Level of Education primary secondary post-secondary tertiary

vii.) Number of people living at home (excluding patient) _____

viii.) Smoking history Current Ex-smoker Never Passive

ix.) Number of packets daily (if relevant) _____

x.) Age started smoking (if relevant) _____

xi.) Age stopped smoking (if relevant) _____

xii.) Pack years smoked (if relevant) _____

Section B: Symptomatology and Health Status

i.) COPD assessment test score _____

ii.) EQ-5D-3L _____

iii.) EQ VAS _____

Section C: Medical Care

i.) Drug history of inhaled SABA Y N

ii.) Drug history of inhaled SAMA Y N

iii.) Drug history of Inhaled LABA Y N

iv.) Drug history of Inhaled LAMA Y N

v.) Drug history of inhaled LABA/LAMA combination Y N

vi.) Drug history of inhaled corticosteroids Y N

vii.) Drug history oral methylxanthines Y N

viii.) Oral corticosteroid use in the last 3-months Y N

ix.) Oral antibiotic use in the last 3-months Y N

x.) Intravenous antibiotic use in the last 3-months Y N

xi.) Home nebuliser use in the last 3-months Y N

xii.) Emergency nebuliser use in the last 3-months Y N

xiii.) Influenza vaccination during the past year Y N

xiv.) Pneumococcal vaccination ever Y N

xv.) Pulmonary rehab during the past year Y N

xvi.) Domiciliary use of oxygen (short burst) in the last 3-months Y N

xvii.) Domiciliary use of oxygen (concentrator) in the last 3-months Y N

xviii.) Compliance with LTOT (>15hrs/day) Y N

xix.) Inhaler Adherence Scale score (max 4) _____

xx.) Inhaler Technique Optimal score (max 8 for MDI, max 7 for DPI) _____

xxi.) Spacer use with MDI Y N

xxii.) Caring Consultant (Exacerbators only) Respiratory General Medicine

Section D: Clinical Variables

i.) Co-morbidities

_____

_____

_____

ii.) Number of previous COPD hospitalisations ____

iii.) Total COPD hospitalisations in past year ____

iv.) Total COPD exacerbations in past year ____

v.) Attendance to respiratory MOP in past year _____

vi.) Attendance to general medical MOP in past year _____

vii.) BMI _____ (most recent, only acceptable if in 2015-2017)

viii.) FEV_1 _____ (most recent, only acceptable if in 2015-2017)

ix.) FVC _____ (most recent, only acceptable if in 2015-2017)

x.) FEV_1/FVC _____ (most recent, only acceptable if in 2015-2017)

xi.) GOLD group _____

xii.) New Consolidation on Chest X-ray (exacerbators only) _____

xiii.) Serum urea level (exacerbators only) _____

xiv.) Mental Status (exacerbators only) _____

xv.) Pulse on presentation (exacerbators only) _____

xvi.) BAP-65 score (exacerbators only) _____

Section E: Use of Hospital Resources (exacerbators only)

i.) Length of hospital stay _____ days

ii.) Days in medical ward _____

iii.) Days on NIV in medical ward (equivalent to HDU) _____

iv.) Total days in ITU _____

Proforma tar-Ricerka

COPD Exacerbations – Cost, Risk Factors and the Impact of LAMAs

Numru tal-Kaz _____

Inizjali _____

Numru ta' l-ID _____

Sezzjoni A: Informazzjoni Socjo-demografika

i.) Eta' _____

ii.) Sess M F

iii.) Stat civili mizzewweg separat /divorzjat armel/a guvni/xebba

iv.) Impjieg Impjegat qieghed irtirat

v.) Tip ta' Impjieg(i) jew Professjoni (prezent jew passat) _____

vi.) Edukazzjoni primarja sekondarja post-sekondarja terzjarja

vii.) Numru ta' nies li jghixu fid-dar (minbarra l-pazjent) _____

viii.) Tipjip Npejjep Waqaft milli npejjep Qatt Passiv

ix.) Numru ta' pakketti ta' sigaretti kuljum (jekk tapplika) _____

x.) L-eta' meta bdejt tpejjep (jekk tapplika) _____

xi.) L-eta' meta waqaft tpejjep (jekk tapplika) _____

xii.) 'Pack years' tat-tipjip (jekk tapplika) _____

Sezzjoni B: Sintomi u Stat ta' Sahha

iv.) COPD assessment test _____

v.) EQ-5D-3L _____

vi.) EQ VAS _____

Sezzjoni C: Kura Medika

i.)	Uzu regolari ta' SABA f'forma ta' inhaler	Y	N		
ii.)	Uzu regolari ta' SAMA f'forma ta' inhaler	Y	N		
iii.)	Uzu regolari ta' LABA f'forma ta' inhaler	Y	N		
iv.)	Uzu regolari ta' LAMA f'forma ta' inhaler	Y	N		
v.)	Uzu regolari ta' LABA/LAMA f'forma ta' inhaler	Y	N		
vi.)	Uzu regolari ta' corticosteroids f'forma ta' inhaler	Y	N		
	Uzu regolari ta' Methylxanthines f'forma ta' pilloli	Y	N		
vii.)	Uzu ta' sterojdi f'forma ta' pilloli f'dawn l-ahhar 3-xhur	Y	N		
viii.)	Uzu ta' antibijotici f'forma ta' pilloli f'dawn l-ahhar 3-xhur	Y	N		
ix.)	Uzu ta' antibijotici fil-vina f'dawn l-ahhar 3-xhur	Y	N		
x.)	Uzu ta' 'nebulisers' id-dar f'dawn l-ahhar 3-xhur	Y	N		
xi.)	Uzu ta' 'nebulisers' b'emergenza f'dawn l-ahhar 3-xhur	Y	N		
xii.)	Tilqim kontra l-influenza is-sena li ghaddiet	Y	N		
xiii.)	Tilqim kontra n-Pneumococcus	Y	N		
xiv.)	Riabilitazzjoni tal-pulmun f'din l-ahhar sena	Y	N		
xv.)	Uzu ta' l-ossignu d-dar (Cilindru) f'dawn l-ahhar 3-xhur	Y	N		
xvi.)	Uzu ta' l-ossignu d-dar 'Concentrator' f'dawn l-ahhar 3-xhur	Y	N		
xvii.)	Hin fuq l-ossignu >15 siegha tul il-gurnata	Y	N		
xviii.)	Inhaler Adherence Scale	Puntegg (mas. 4) _____			
xix.)	Teknika ta' l-inhaler	Puntegg (mas. 8 ghall-MDI, mas. 7 ghall- DPI)____			
xx.)	Uzu ta' l-ispacer mal-iMDI	Y	N		
xxi.)	Konsulent (ghal min jidhol l-isptar b'attakk)	Tan-nifs	Tal-medicina		

Sezzjoni D: Parametri Klinici

i.) Mard iehor

_____

_____

_____

ii.) Numru ta' drabi li dhalt l-isptar minhabba is-COPD ____

iii.) Numru ta' drabi li dhalt l-isptar minhabba is-COPD matul l-ahhar sena ____

iv.) Numru ta' attakki tas-COPD matul l-ahhar sena ____

v.) Attendenza ghall-Outpatients tal-Pulmun matul l-ahhar sena ____

vi.) Attendenza ghall-Outpatients tal-Medicina Generali matul l-ahhar sena ____

vii.) BMI _____ (l-iktar ricenti, accettabli jekk bejn 2015 u 2017)

viii.) FEV_1 _____ (l-iktar ricenti, accettabli jekk bejn 2015 u 2017)

ix.) FVC _____ (l-iktar ricenti, accettabli jekk bejn 2015 u 2017)

x.) FEV_1/FVC _____ (l-iktar ricenti, accettabli jekk bejn 2015 u 2017)

xi.) GOLD group _____

xii.) Konsolidazzjoni f'X-ray tal-Pulmun (ghal min jidhol l-isptar b'attakk) _____

xiii.) Livell ta'urea fid-demm (ghal min jidhol l-isptar b'attakk) _____

xiv.) Stat mentali (ghal min jidhol l-isptar b'attakk) _____

xv.) Il-polz ta' meta pazjent jidhol l-isptar (ghal min jidhol l-isptar b'attakk) _____

xvi.) BAP-65 score (ghal min jidhol l-isptar b'attakk) _____

Sezzjoni E: Uzu ta' rizorsi ta'l-isptar (ghal min jidhol l-isptar b'attakk tas-COPD)

i.) Tul ta' zmien fl-isptar _____ granet

ii.) Numru ta' granet fis-swali tal-medicina _____

iii.) Numru ta' granet fejn sar uzu mill-NIV go sala tal-medicina _____

iv.) Numru ta' granet fl-ITU _____

Appendix 2

Pre-validated tools

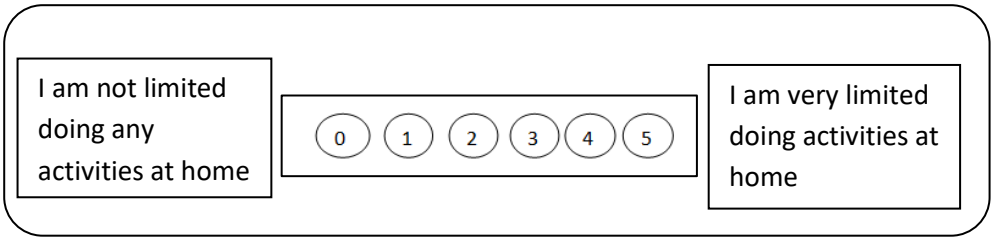
COPD Assessment Test

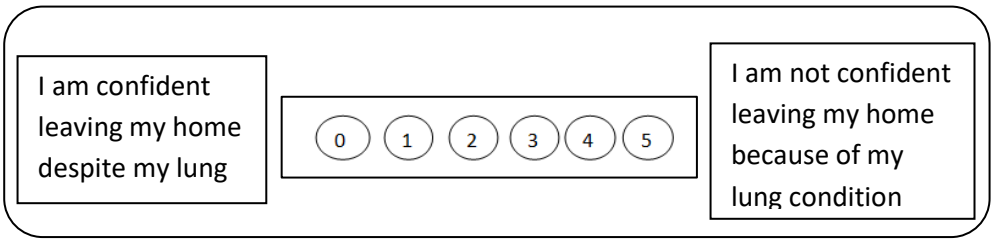
This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

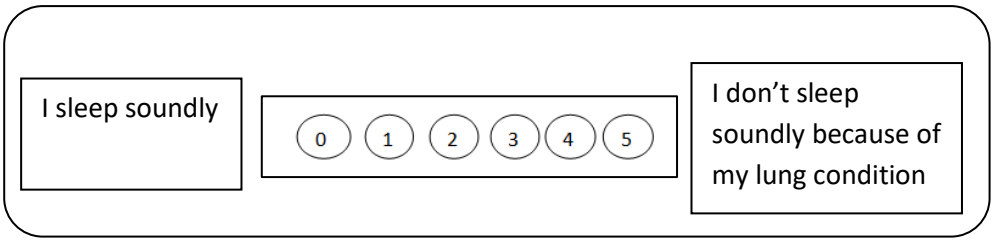
For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

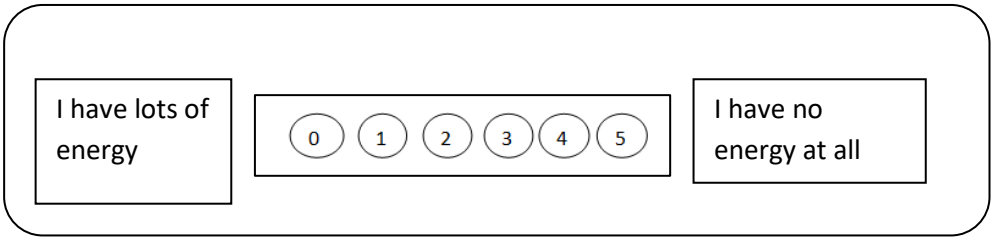
Example: I am very happy 0 1 2 3 4 5 I am very sad

I never cough	0 1 2 3 4 5	I cough all the time
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless


I am not limited doing any activities at home
0 1 2 3 4 5
I am very limited doing activities at home


I am confident leaving my home despite my lung
0 1 2 3 4 5
I am not confident leaving my home because of my lung condition


I sleep soundly
0 1 2 3 4 5
I don't sleep soundly because of my lung condition


I have lots of energy
0 1 2 3 4 5
I have no energy at all

Total Score: _____

EQ-5D-3L

By placing a mark in one box in each group below, please indicate which statements best describes your state of health today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain / Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety / Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

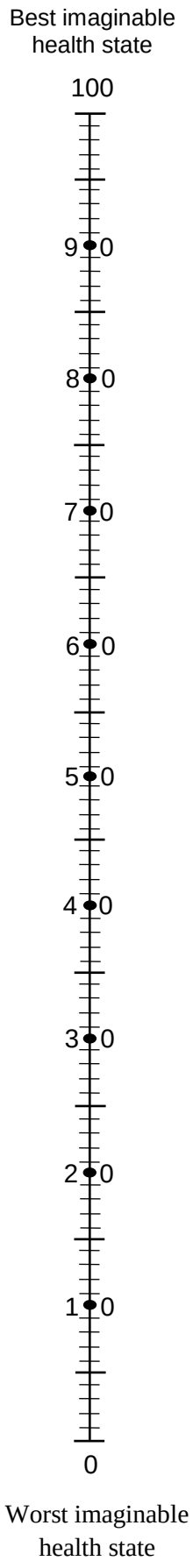
I am extremely anxious or depressed ❑

EQ VAS (Visual Analog Scale)

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point to the scale indicates how good or bad your health state is today.

Your own health state today



Inhaler Adherence Scale

1. During the last 3 months, have you at times been careless about using your inhaler or nebuliser?

Yes No

2. During the last 3 months, have you ever forgotten to use your inhaler or nebulizer?

Yes No

3. During the last 3 months, have you ever stopped using your inhaler because you felt better?

Yes No

4. During the last 3 months, have you ever used your inhaler or nebuliser less than the doctor prescribed because you felt better?

Yes No

No = 1 point

Total score (maximum 4): _____

Inhaler Technique

Metered Dose Inhaler	Dry Powder Inhaler
1. Shake the inhaler and remove protective cap	1. Prepare the inhaler before usage
2. Hold inhaler upright	2. Keep inhaler horizontal
3. Exhale to residual volume	3. Exhale to residual volume
4. Place mouthpiece between lips and teeth	4. Place mouthpiece between lips and teeth
5. Inhale slowly and simultaneously activate the cannister	5. Inhale forcefully and deeply
6. Continue slow and deep inhalation	6. Take the inhaler out of the mouth
7. Hold breath for 5–10 s	7. Hold breath for 5 s
8. Take inhaler out of mouth and hold breath for 5–10 s	
Score (max 8): _____	Score (max 7): _____

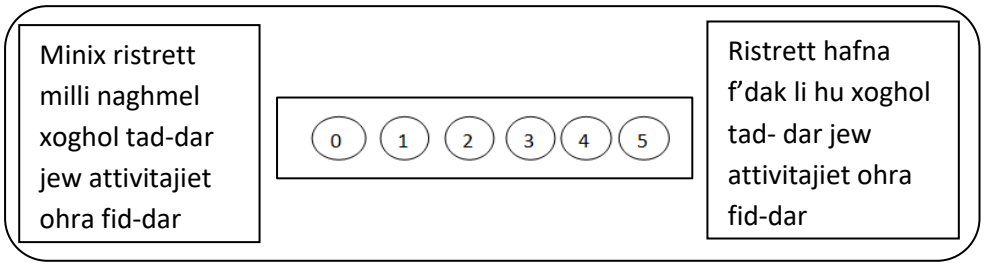
COPD Assessment Test

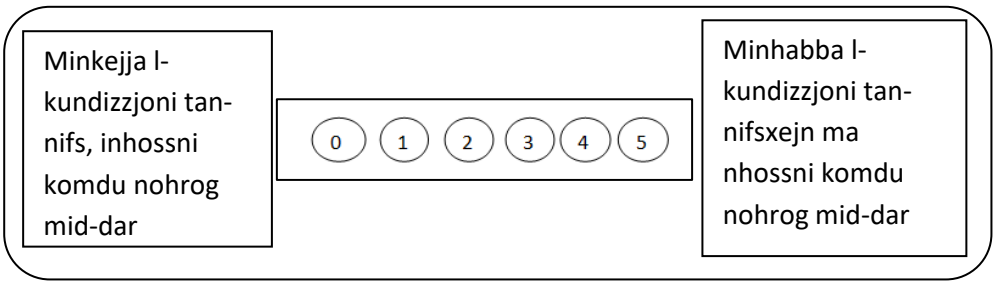
Dan il-kwestjonarju ser jghin kemm lilek kif ukoll lill-ispecjalisti tas-sahha sabiex jitkejjel l-impatt li is-COPD ghandu fuq il-hajja ta' kuljum. It-twegibiet tieghek, kif ukoll il-marka finali jistghu jintuzaw biex flimkien ma' l-ispecjalisti tas-sahha intjebu l-kura tas-COPD.

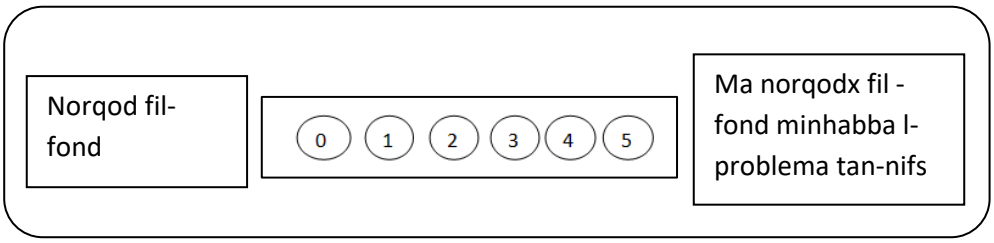
Ghal kul frazi, immarka b'ittra (X) fil-kaxxa li l-aktar tiddeskrivi tajjeb l-istat tieghek. Qis li timmarka riposta wahda biss ghal kul domanda.

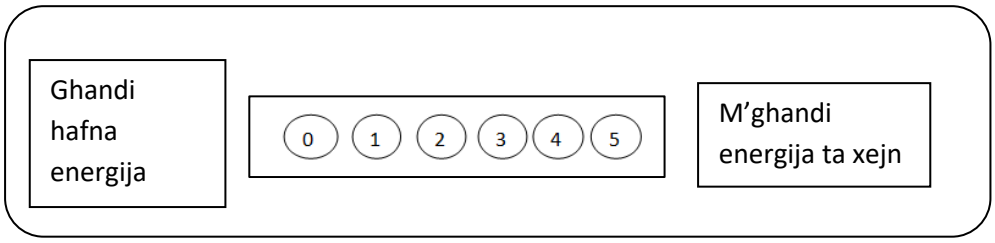
Ezempju: Kuntent hafna 0 1 2 3 4 5 Imdejjaq hafna

Qatt ma nisghol	0 1 2 3 4 5	Nisghol il-hin kollu
M'ghandix katarru (bili)	0 1 2 3 4 5	Sidri mimli katarru
Ma nhossx sidri jissikka	0 1 2 3 4 5	Inhoss li sidri jissikka hafna
Meta nitla' telgha jew sular tarag, ma jkollix qtugh ta' nifs	0 1 2 3 4 5	Meta nitla' telgha jew sular tarag, ikun bla nifs









Puntegg Totali: _____

EQ-5D-3L

Jekk jogħġbok, indika liema dikjarazzjoni l-aħjar tiddiskrivi l-istat tas-saħħa tiegħek illum, billi tagħmel marka f'kaxxa waħda minn grupp hawn isfel.

Mobilità

Jien m'għandix problemi fil-mixi ❑

Għandi problemi biex nimxi ❑

Jien obbligat noqgħod fis-sodda ❑

Kapaċità li tieħu ħsieb lilek innfsek

Jien m'għandix problemi nieħu ħsieb lili nnifsi ❑

Jien għandi xi problemi biex ninħasel jew nilbes ❑

M'hinix kapaċi ninħasel jew nlibbes lili nnifsi ❑

Attivitajiet tas-soltu (eż. xogħol, studju, xogħol tad-dar, attivitajiet tal-familja jew passatempi)

M' għandix problemi biex nagħmel/inwettaq l-attivitajiet tas-soltu tiegħi ❑

Jien għandi xi problemi biex neżegwixxi (nagħmel/inwettaq) l-attivitajiet tas- ❑

Jien m'iniex kapaċi neżegwixxi (nagħmel/inwettaq) l-attivitajiet normali tiegħi ❑

Uġigħ / Skumdità

M'għandix uġigħ jew skumdità ❑

Għandi uġigħ jew skumdità moderata ❑

Inħossni muġugħ ħafna jew skumdità estrema ❑

Ansjetà / Diprexxin

Jien m'hinix ansjuż/ansjuża jew depress/depressa ❑

Inħossni moderatament ansjuż/ansjuża jew moderatament depress/depressa ❑

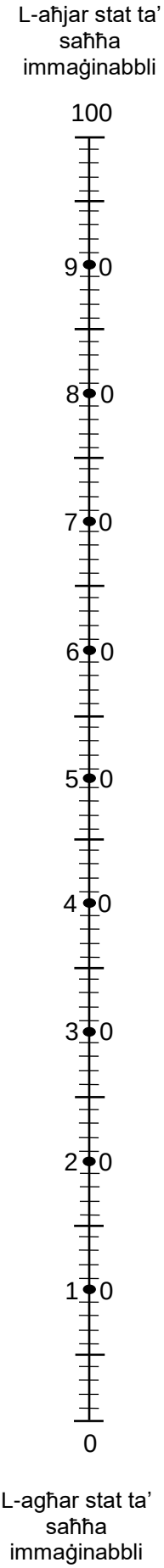
Jien estremament ansjuż/ansjuża jew estremament depress/depressa ❑

EQ VAS (Visual Analog Scale)

Sabiex ngħinu l-persuni jgħidu kemm hu tajjeb jew ħażin l-istat ta' saħħa tagħhom, ħloqna skala (pjuttost bħal termometru) li fuqha l-aħjar stat li int tista' timmaġina jiġi mmarkat b'100 u l-agħar stat li int tista' timmaġina huwa markat b'0.

Nixtiequk li tindika f'din l-iskala, il-fehma tiegħek ta' kemm hi tajba jew ħażina saħħtek illum. Jekk jogħġbok agħmel dan billi tpinġi linja mill-kaxxa li qegħda hawn taħt sa kwalunkwe punt fuq l-iskala, kemm l-istat ta' saħħtek huwiex tajjeb jew ħażin.

L-istat ta' saħħtek illum



Inhaler Adherence Scale

1. Gieli kont traskurat fl-uzu ta' l-inhaler jew nebulizer, f'dawn l-ahhar tlett xhur?
   Iva Le
2. Gieli nsejt tuza' l-inhaler jew in-'nebuliser', f'dawn l-ahhar tlett xhur?
   Iva Le
3. Qatt waqaft tuza' l-inhaler ghax hassejtek ahjar f'dawn l-ahhar tlett xhur?
   Iva Le
4. Qatt uzajt l-inhaler jew in-'nebuliser' anqas minn kemm ordnalek it-tabib ghax hassejtek ahjar, f'dawn l-ahhar tlett xhur?
   Iva Le

Le = punt wiehed

Puntegg Totali (mas. 4): _____

It-Teknika ta' l-Inhaler

Metered Dose Inhaler

1. Caqlaq l-inhaler u nehhi l-ghatu
2. Zomm l-inhaler wieqaf
3. Hu nifs twil 'il barra
4. Poggi l-'mouthpiece' fil-halq
5. Waqt li tikkarga l-inhaler, hu nifs 'il gewwa u bil-mod
6 Kompli hu nifs qawwi u bil-mod
7. Zomm in-nifs ghal 5–10 s
8. Nehhi l-inhaler minn ma halqek u zomm in-nifs ghal 5-10 s

Puntegg (mas. 8): _____

Dry Powder Inhaler

1. Ipprepara l-inhaler qabel l-uzu
2. Zomm l-inhaler mindud
3. Hu nifs twil 'il barra
4. Poggi l- 'mouthpiece' fil-halq
5. Hu nifs fil-fond u qawwi 'l gewwa
6. Nehhi l-inhaler minn ma' halqek
7. Zomm in-nifs ghal 5 s

Puntegg (mas. 7): _____

Approval to use EQ-5D-3L Tool

L-Università ta' Malta

Jessica Spiteri <jessica.spiteri.08@um.edu.mt>

EQ-5D registration

Bianca Smit <smit@euroqol.org> 26 January 2017 at 17:01
To: "jessica.spiteri.08@um.edu.mt" <jessica.spiteri.08@um.edu.mt>

Dear Ms. / Mr. Jessica Spiteri,

Thank you for registering your research at the EuroQol Research Foundation's website.

As the study / project "COPD Exacerbations - Cost, Risk Factors, and Impact of LAMAs" you registered involves low patient numbers (100) you may use the EQ-5D-3L Paper version free of charge.

Please note that separate permission is required if any of the following is applicable:

- The registered study / project is funded by a pharmaceutical company, medical device manufacturer or other profit-making stakeholder;
- Using EQ-5D in a Routine Outcome Measurement or Registry setting;
- Using EQ-5D in languages other than the ones indicated in this email;
- Using digital representations (e.g. PDA, Tablet or Web) of the EQ-5D

I'm attaching the English (Malta), Maltese (Malta) EQ-5D-3L Paper version (in MS Word format). Requests to use digital representations of EQ-5D (e.g. web, tablet, PDA) should be made separately to userinformationservice@euroqol.org attaching your initial registration. The corresponding user guide can be downloaded from our website: http://www.euroqol.org/eq-5d-publications/user-guides.html.

Kind regards,

Bianca Smit
Communications Officer
EuroQol Research Foundation
T: +31 884400190
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W: www.euroqol.org

2 attachments

Effective_Malta (English) EQ-5D-3L Paper Self complete v1.0 (ID 23976).docx
101K

Effective_Malta (Maltese) EQ-5D-3L Paper Self complete v1.0 (ID 24200).docx
104K

Approval to use CAT Tool

L-Università ta' Malta

Jessica Spiteri <jessica.spiteri.08@um.edu.mt>

FW: cat test
1 message

Veronica Azzopardi <veronica.m.azzopardi@gsk.com> 3 January 2018 at 08:13
To: Jessica Spiteri <jessica.spiteri.08@um.edu.mt>

Dear Jessica,

Please find the terms and conditions for CAT test use, below.

Kind regards,

Veronica AzzoPardi

Therapy Area Lead Respiratory & Pharma: Cyprus, Malta & Gibraltar

Pharma Europe

http://www.catestonline.org/images/UserGuides/CAT_HCP%20User%20Guide.pdf

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Appendix 3

Data collection proforma validation

COPD Exacerbations: Cost, Risk Factors, and Impact of LAMAs

Thank you for accepting to be part of the expert panel for validation of the Data Collection Proforma. Below please find a validation form, which is required in order to complete the validation process.

i.) Is the data collection proforma a valid one?

Yes ❑ No ❑

ii.) Did the data collection proforma create a positive impression?

Yes ❑ No ❑

iii.) Is the data collection proforma adequate to reach the study objectives?

Yes ❑ No ❑

iv.) Is the data collection proforma a good measurement for estimating the costs of COPD exacerbations leading to hospitalisations?

Yes ❑ No ❑

v.) Is the data collection proforma a good measurement for comparing the risk factors leading to hospitalisations?

Yes ❑ No ❑

vi.) Are there any parameters you would add or omit?

---

vii.) Are the COPD Assessment Test and EQ-5D-5L tools simple and viable to carry out in a hospital setting?

Yes ❑ No ❑

viii.) Is the Maltese version of the COPD Assessment Test reliable and precise?

Yes ❑ No ❑

ix.) By the end of the study, do you think that the data collection proforma will fulfill its aims?

Yes ❑ No ❑

Further comments and recommendation which you wish to suggest regarding the data collection proforma.

_____

_____

Validation results of data collection proforma

Recommendation	**Reason(s)**
Changes in font, sentence structure and correction of typographical errors	To create the appearance of sections and to ensure better understanding.
Change in measuring Socioeconomic Status from British Registrar's General Social Classes to Level of Education and Occupation as surrogates for socioeconomic status	The British Registrar's General Social Classes is not practical.
Omission of Arterial Blood Gases (ABGs)	Parameter not relevant for the scope of the study. It may also be cumbersome to collect this parameter since the ABG results are published in little printouts (which easily get mislaid) and there is often inconsistent reference to the results in the case notes.
Omission of serum eosinophil count	Irrelevant parameter for the scope of the study, and it does not always help to differentiate COPD from asthma – it can be normal in asthmatics too.
Exclusion of patients with consolidation on Chest X-ray, implying pneumonia	To increase the accuracy of measuring the hospital admissions which are purely due to COPD exacerbations and not due to pneumonia which can be easily mistaken for or overlap with COPD exacerbations.

Appendix 4

Ethics approval and consent forms

Ethics Approval

L-UNIVERSITÀ TA' MALTA

Msida – Malta
Skola Medika
Sptar Mater Dei

UNIVERSITY OF MALTA

Msida – Malta
Medical School
Mater Dei Hospital

Ref No: **93/2016**

Monday 20th February 2017

Ms. Jessica Spiteri
66, Amourelle
Triq il-Ghajn
Swieqi
SWQ3126

Dear Ms. Jessica Spiteri,

Please refer to your application submitted to the Research Ethics Committee in connection with your research entitled:

COPD Hospitalisations – Cost, Risk Factors and the Impact of LAMAs

The University Research Ethics Committee granted ethical approval for the above mentioned protocol.

Yours sincerely,

Dr. Mario Vassallo
Chairman
Research Ethics Committee

Patient Information Sheet

COPD Hospitalisations – Cost, Risk Factors and the Impact of LAMAs

January 2017

Dear Sir /Madam,

I am currently reading for a Doctoral Degree in Pharmacy and as part of this course I am carrying out research on patients who have Chronic Obstructive Pulmonary Disease (COPD).

The purpose of this research is to study the patients admitted to hospital as a result of worsening of their COPD condition and to study the cost and risk factors for COPD hospitalisation.

I will need your consent to participate in this study. I will then access data from your cases notes and take a few minutes of your time in order to complete a questionnaire.

All data will remain confidential.

Regards,

Jessica Spiteri

Bsc. Pharm. Sci, M.Pharm

Ittra ta' Informazzjoni ghall-Pazjent

COPD Hospitalisations – Cost, Risk Factors and the Impact of LAMAs

Jannar 2017

Ghaziz Sinjur/a,

Bhalissa qieghda nistudja ghal dottorat fil-farmacija u parti mill-kors jikkonsisti f'ricerka. Jiena ghazilt li nirricerka l-marda tas-COPD, maghrufa wkoll bhala Chronic Obstructive Pulmonary Disease, jew bronkite kronika tas-sigaretti.

L-iskop ta' din ir-ricerka hija li nara l-ammont ta'nies li jinzammu l-isptar minhabba l-attakki tas-COPD u l-impatt finanzjarju minhabba dawn l-attakki. Se nkun qed inhares ukoll lejn xi fatturi u riskji tal-pazjenti b'din il-kundizzjoni.

Sabiex inwettaq dan l-istudju, ghandi bzonn il-kunsens tieghek. Wara dan ser ikolli bzonn naghmillek kwestjonarju f'forma ta' intervista, kif ukoll access ghan-noti tat-tobba.

Nassigurak li kull informazzjoni se tibqa' kunfidenzjali.

Grazzi bil-quddiem,

Jessica Spiteri

Bsc. Pharm. Sci, M.Pharm

Patient Consent Form

COPD Hospitalisations – Cost, Risk Factors and the Impact of LAMAs

I am a Maltese citizen and am over eighteen (18) years of age.

I have been asked to participate in a research study entitled: COPD Hospitalisations – Cost, Risk Factors and the Impact of LAMAs

The purpose and details of the study have been explained to me by Ms. Jessica Spiteri and any difficulties which I raised have been adequately clarified.

I give my consent to the Chief Investigator and his delegate either to make the appropriate observations.

I understand that the results of this study may be used for medical or scientific purposes and that the results achieved from the study in which I am participating may be reported or published: however, I shall not be personally identified in any way, either individually or collectively, without my express written permission.

I am under no obligation to participate in this study and am doing so voluntarily.

I may withdraw from the study at any time, without giving any reason. This will not influence in any way the care and attention and treatment normally given to me.

I am not receiving any remuneration for participating in this study.

In case of queries during the study I may contact Ms. Jessica Spiteri on 79372406

Signature of participant _____

Name of participant _____

ID number of participant _____

Signature of Chief Investigator _____

Name of Chief Investigator _____

ID number of Chief Investigator _____

Date _____

Formola ta' Kunsens tal-Pazjent

COPD Hospitalisations – Cost, Risk Factors and the Impact of LAMAs

Jien/a ċittadin/a Malti/ja u għalaqt tmintax (18)-il sena.

Talbuni biex nieħu sehem fi studju riċerka bl-isem ta': COPD Hospitalisations – Cost, Risk Factors and the Impact of LAMAs

Il-għan u d-dettalji ta' l-istudju spejgathomli Ms. Jessica Spiteri li wkoll iċċaratli xi mistoqsijiet li għamilt.

Nagħti l-kunsens tiegħi lill-persuna responsabbli għal-din ir-riċerka u l-assistenti tagħha biex jagħmlu l-osservazjonijiet li hemm bżonn.

Jiena nifhem li r-riżultati ta' dan l-istudju jistgħu jintużaw għal skopijiet xjentifiċi u jista' jiġi ppubblikat rapport bil-miktub: jekk isir hekk b'ebda mod ma nista' nkun identifikat/a, individwalment jew bħala parti minn grupp, mingħajr il-kunsens tiehħi bil-miktub.

Jiena ma għandi l-ebda dmir li niehu sehem f'dan l-istudju u dan qed nagħmlu minn rajja.

Jiena nista', meta rrid, ma nkomplix niehu sehem fl-istudju, u mingħajr ma' nagħti raġuni. Jekk nagħmel hekk xorta nibqa' nieħu l-kura li ssoltu tingħatali.

Jiena mhux qed nitħallas biex nieħu sehem f'dan l-istudju.

Jekk ikolli xi diffikulta' waqt l-istudju, nista' nistaqsi għal Ms. Jessica Spiteri fuq 79372406

Firma tal-parteċipant _____

Isem tal-parteċipant _____

Numru ta' l-identita _____

Firma tal-persuna responsabbli għal din ir-riċerka _____

Isem tal-persuna responsabbli għal din ir-riċerka _____

Numru ta' l-identita _____

Data _____

Appendix 5

Summary of admission costs and bed-night costs

Summary of admission costs and bed-night costs[11]

Department	Cost per admission (Euro)	Cost per day (Euro)
Medical Ward	105	226
HDU	190	1046
ITU	190	1046

[11] Personal communication. Mr. John Abela. Financial Consultant: Crowe Horwath; September 2017.

Appendix 6

Sample size margin of error calculation

Margin of error calculation for case-control study sample size

Margin of Error $= z\sigma_{\bar{p}}$

For a 95% degree of confidence, $z = 1.96$
σ_p is the standard error (Standard deviation of the sampling distribution of proportion), which is given by:

$$\sigma_p = \sqrt{\frac{p(1-p)}{n}\left(\frac{N-n}{N-1}\right)}$$

p is an unknown population proportion and σ_p is maximized when p = 0.5. Given that the sample size is $n = 162$ respondents and the population size is $N = 350000$ then the maximum value of the standard error σ_p is:

$$\sigma_p = \sqrt{\frac{p(1-p)}{n}\left(\frac{N-n}{N-1}\right)} = \sqrt{\frac{(0.5)(0.5)}{162}\left(\frac{350000-162}{350000-1}\right)} = 0.00393$$

$$\text{Maximum margin of error} = z\sigma_{\bar{p}} = (1.96)(0.0393) = 0.077 = 7.7\%$$

A sample size of 162 participants selected from a population of size 350000 possible participants aged at least 16 years guarantee a maximum margin of error of 7.7% assuming a 95% confidence level.

Appendix 7

Raw data

Univariate analysis for continuous variables

Variable	Group	Mean	Std. Deviation	*p*-value
Number of cigarettes daily	Case	39.63	23.388	0.704
	Control	38.08	23.135	
Age started smoking	Case	15.35	5.904	0.588
	Control	15.85	6.884	
Age stopped smoking	Case	62.32	10.818	0.668
	Control	62.07	8.914	
Pack years smoked	Case	91.92	58.050	0.778
	Control	88.72	56.401	
CAT Score	Case	23.90	7.843	<0.001
	Control	14.28	7.222	
EQ VAS	Case	51.93	22.465	<0.001
	Control	67.81	19.142	
Inhaler adherence scale	Case	2.88	1.344	0.218
	Control	3.20	0.999	
Inhaler technique optimal MDI	Case	6.23	1.414	0.005
	Control	6.77	1.268	
Inhaler technique optimal DPI	Case	5.80	0.810	0.099
	Control	6.05	0.738	
Number of comorbidities	Case	2.79	1.941	0.001
	Control	1.78	1.245	
Number of previous COPD hospitalisations	Case	4.42	6.265	<0.001
	Control	0.74	1.421	
Total COPD exacerbations in the previous year	Case	2.47	3.685	<0.001
	Control	0.85	1.517	
Attendance to general medical outpatients in the previous year	Case	0.23	0.712	0.140
	Control	0.32	0.804	
BMI	Case	27.60	6.131	0.477
	Control	30.60	21.968	
FEV1	Case	45.91	18.518	<0.001
	Control	58.86	17.967	
FVC	Case	62.32	19.446	<0.001
	Control	76.05	19.308	
FEV_1/ FVC	Case	59.55	17.102	0.501
	Control	61.53	15.148	

Univariate analysis for categorical variables relating to medical care

Medical Care		Case	Control	Chi Square	*p*-value
Drug history of inhaled SABA	**Yes**	77	73	1.440	0.230
	No	4	8		
Drug history of inhaled SAMA	**Yes**	63	61	0.138	0.711
	No	18	20		
Drug history of inhaled LABA	**Yes**	41	57	6.612	0.001
	No	40	24		
Drug history of inhaled LAMA	**Yes**	4	3	0.149	0.699
	No	77	78		
Drug history of inhaled LABA / LAMA	**Yes**	13	9	0.842	0.359
	No	68	72		
Drug history of inhaled corticosteroids	**Yes**	52	55	0.248	0.619
	No	29	26		
Drug history of oral methylxanthines	**Yes**	2	0	2.025	0.155
	No	79	81		
Oral corticosteroid use in the last 3-months	**Yes**	38	17	12.140	<0.001
	No	43	64		
Oral antibiotic use during in the last 3-months	**Yes**	45	30	5.586	0.018
	No	36	51		
Intravenous antibiotic use in the last 3-months	**Yes**	28	3	24.932	<0.001
	No	53	78		
Home nebuliser use in the last 3-months	**Yes**	23	6	12.138	<0.001
	No	58	75		
Health centre nebuliser use in the last 3-months	**Yes**	29	14	7.123	0.008
	No	52	67		
Influenza vaccination during the past year	**Yes**	38	50	3.582	0.058
	No	43	31		
Pneumococcal vaccination ever	**Yes**	21	25	0.486	0.486
	No	60	56		
Pulmonary rehabilitation during the past year	**Yes**	15	9	1.761	0.185
	No	66	72		
Domiciliary use of oxygen (short burst cylinder) in the last 3-months	**Yes**	32	6	23.241	<0.001
	No	49	75		
Domiciliary use of oxygen (concentrator) in the last 3-months	**Yes**	22	4	14.844	<0.001
	No	59	77		
Compliance with LTOT (>15hrs/day)	**Yes**	9	1	0.362	0.547
	No	13	3		
Spacer use with MDI	**Yes**	56	63	1.736	0.188
	No	22	15		

Univariate analysis for demographic data

		Group				
		Case	Control	Total	Chi Square Value	*p*-value
Smoking History	**Current**	27	20	47	2.358	0.308
	Ex-smoker	54	60	114		
	Never	0	1	1		

		Group		Chi Square Value	*p*-value
		Case	Control		
Level of Education	**No schooling**	5	1	9.786	0.044
	Primary	29	16		
	Secondary	41	58		
	Post-Secondary	5	4		
	Tertiary	1	2		

Univariate analysis for inhaler adherence scale individual questions

		Group		Chi Square Value	*p*-value
		Case	Control		
Carelessness with using inhalers/nebulisers	**Yes**	24	20	0.502	0.479
	No	56	60		
Forgotten to use inhaler/ nebuliser	**Yes**	26	25	0.029	0.865
	No	54	55		
Stopped using inhaler because felt better	**Yes**	17	9	2.939	0.086
	No	63	71		
Used inhaler/nebuliser less than the doctor prescribed	**Yes**	23	11	5.378	0.020
	No	57	69		

Logistic regression raw data

Variable	-2 Log Likelihood	Chi-Square	df	*p*-value
Inhaled LABA	64.621	4.588	1	0.032
Oral corticosteroid use in the last 3- months	66.080	6.047	1	0.014
Intravenous antibiotic use in the last 3-months	62.107	2.073	1	0.150
Home nebuliser use in the last 3-months	60.176	0.142	1	0.706
Emergency nebuliser use in the last 3-months	69.212	9.179	1	0.002
Domiciliary use of oxygen (short burst cylinder) in the last 3-months	60.179	0.146	1	0.702
Domiciliary use of oxygen (concentrator) in the last 3-months	61.862	1.829	1	0.176
Level of education	67.386	7.353	4	0.118
Used inhaler / nebuliser less than the doctor prescribed	62.984	2.951	1	0.086
CAT Score	68.943	8.910	1	0.003
EQ VAS	63.099	3.066	1	0.080
Inhaler technique optimal MDI	60.298	0.265	1	0.607
Number of comorbidities	64.219	4.186	1	0.041
Number of previous COPD hospitalisations	69.145	9.112	1	0.003
Total COPD exacerbations in the previous year	64.056	4.023	1	0.045
FEV_1	60.608	0.575	1	0.448
FVC	60.120	0.087	1	0.768

Appendix 8

Publications

Abstract submitted to American College of Clinical Pharmacy (ACCP)

13/03/2018 Submission Completed

Your abstract submission for the Original Research has been received

Click here to print this page now.

You have submitted the following abstract to 2018 ACCP Global Conference on Clinical Pharmacy (October 20-23). Receipt of this notice does not guarantee that your submission was complete or free of errors.

Chronic obstructive pulmonary disease exacerbations: a hospital-based study

Jessica Spiteri, B.Sc. Pharm. Sci. (Hons.) M.Pharm.[1], Louise Grech, B.Pharm (Hons), MPhil, Ph.D, MRPharmS[1], Stephen Montefort, M.D., Ph.D.(S'ton.), F.R.C.P.(Lond.), F.R.C.P.(Edin.), F.R.C.P.(Glas.), F.A.C.P., F.E.F.I.M, F.C.C.P.[2] and Lilian M. Azzopardi, BPharm. (Hons.). MPhil., PhD., MRPharmS, FFIP[3]
(1)Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta, Msida, Malta
(2)Department of Medicine, Mater Dei Hospital, Msida, Malta
(3)Department of Pharmacy, University of Malta, Msida, Malta

Abstract Text:

Introduction: Health care resource utilisation data for chronic obstructive pulmonary disease (COPD) exacerbation-related hospitalisations can be used to drive the introduction of long-acting muscarinic antagonists (LAMAs) on local formularies.

Research Question or Hypothesis: This study aimed at identifying COPD exacerbations leading to hospitalisation and the resulting costs.

Study Design: A 3-month observational cohort-study carried out at Mater Dei Hospital. Hospitalisation was defined by an admission to a medical ward or Intensive Therapy Unit (ITU).

Methods: A data collection proforma was designed and validated. This included data pertaining to patient demographics, clinical variables, and use of hospital resources. All the hospital admissions during February-April 2017 were screened and those flagged as COPD exacerbations noted. Exclusion criteria included the presence of consolidations on chest x-ray and instances where the diagnosis on the discharge letter differed from the initial diagnosis of COPD exacerbation. Clinical data was obtained from patients' files whilst economic data was obtained from the hospital's administrative and finance departments. Cost estimates using an activity-based costings approach was computed.

Results: A total of 148 COPD exacerbation-related hospitalisations met the study's inclusion criteria. Out of these only 16.9% were on LAMA therapy, indicating a low number of patients on optimum therapy. The length of hospital stay ranged from 1-44 days with the median being 4 days. Nine patients required non-invasive ventilation and 3 patients required ITU admission. The length of hospital stay showed significantly positive correlation with the number of comorbidities and BAP-65 scores respectively (Pearson correlation 0.198, 0.199; p-value=0.016, 0.015). The estimated total cost for COPD exacerbation-related hospitalisation amounted to €225,000.

Conclusion: The cost estimation of COPD exacerbation-related hospitalisations gives the opportunity of measuring their impact on healthcare resource use. Health care policy-makers may use this information to carry out a cost-benefit analysis for widespread local LAMA use.

Title:
Chronic obstructive pulmonary disease exacerbations: a hospital-based study

Submitter's E-mail Address:
jessica.spiteri.08@um.edu.mt

Preferred Presentation Format:
Poster

Field of Application:
Pulmonary

IRB Approval:
My research has been approved by my institution's IRB

Commercial Sponsorship:
No

Acceptance for Publication at the ACCP

L-Università ta' Malta

Jessica Spiteri <jessica.spiteri.08@um.edu.mt>

2018 ACCP Global Conference (Early Decision) - Abstract Notification

abstracts@accp.com <abstracts@accp.com> 16 April 2018 at 22:45
Reply-To: abstracts@accp.com
To: jessica.spiteri.08@um.edu.mt, jessica.spiteri@gov.mt

Dear Jessica Spiteri,

Congratulations! Your abstract, titled "Chronic obstructive pulmonary disease exacerbations: a hospital-based study", is ACCEPTED as a POSTER PRESENTATION at the 2018 ACCP Global Conference on Clinical Pharmacy. The meeting will take place October 20-23, 2018, at the Washington State Conference Center, Seattle, Washington, USA.

IMPORTANT PRESENTATION/PUBLICATION REQUIREMENTS:

- Posters *must* be presented to have the abstract published in an official journal of ACCP.
- The poster presenter *must* be an author listed on the abstract (including encore posters).
- All poster presenters *must* be registered* for the Global Conference to present their poster.
- You will receive a second e-mail today providing a link to confirm your understanding of these requirements.

Poster notes and specifications:

- Your poster presentation day and time will be emailed in late August.
- All poster boards are 4 feet high by 8 feet wide; your poster must fit within these dimensions.
- All relevant conflicts of interest must be disclosed on each poster.
- All forms of financial support for projects must be displayed on the poster.
- Encore abstracts are included full-text in the meeting app, but only the title, authors, and original place of presentation/publication are published.

Reviewers' scores and comments may be reviewed at http://accp.confex.com/accp/2018am/authorratingview.cgi?username=45557&password=961535. This feature is not available for Encore abstracts.

*All poster presenters *must* be registered for the meeting in order to present their poster. Presenters must either be registered for the full meeting or have a one day registration for the day of their presentation. For registration information and details on the 2018 ACCP Global Conference on Clinical Pharmacy, go to https://www.accp.com/meetings/gc18/index.aspx.

We look forward to your presentation. If you have any questions in the upcoming months please contact ACCP at abstracts@accp.com.

Sincerely,

Shelly J. Enders, Pharm.D.
Consultant Pharmacist
American College of Clinical Pharmacy
13000 W. 87th St. Parkway
Lenexa, KS 66215
Phone: (913) 492-3311
Fax: (913) 492-0088

Abstract submitted to the European Respiratory Society Congress

01.12 - Clinical Problems - COPD

12041
Predictors for COPD hospitalisations in Malta: a case-control analysis

Public health, Health policy

J. Spiteri[1], L. Grech[1], S. Montefort[2], L. Azzopardi[1]

[1]Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta - Msida (Malta), [2]Department of Medicine, Mater Dei Hospital - Msida (Malta)

Introduction

An understanding of the predictors of COPD exacerbations leading to hospitalisation may contribute to improved care.

Aims and objectives

To determine the predictors for COPD-related hospitalisations.

Method

Cases were recruited by convenience from COPD-related hospitalisations at Mater Dei Hospital, during the months of February-April 2017. A data collection sheet was designed de novo and validated. This included data pertaining to patient demographics, medical care, clinical parameters, and adherence to inhaled medication. Data was gathered from patients' medical records and via patient self-report. Pre-validated tools (CAT and EQ-5D-3L) were completed through a semi-structured interview. Control patients, who were clinically stable without a COPD-related hospitalisation in the previous year, were recruited from respiratory outpatients during the same time frame. Cases and controls were matched for age and gender.

Results

A total of 81 cases and 81 control subjects were recruited. Logistic regression identified six significant predictors. CAT scores above 18.9 (OR 1.193; 95% CI 1.096-1.299), a history of at least 2 past COPD hospitalisations (OR 1.702; 95% CI 1.238-2.339), and at least 2 comorbidities (OR 1.593; 95% CI 1.025-2.474), were positively associated with the occurrence of a hospitalisation. Inhaled LABA, IV antibiotic use during the last 3-months and emergency nebuliser use during the last 3-months were similarly associated.

Conclusion

The predictors for COPD-related hospitalisation in Malta have been identified. These may have important implications both at the clinical level and for implementing healthcare policies.