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Polypharmacy is Associated with Co-morbidity and Predicts outcome in Patients undergoing Index Pulmonary Hypertension Assessment

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Abstract

Aims: We sought to evaluate the incidence of polypharmacy in patients referred for pulmonary hypertension assessment, assess the relationship of polypharmacy to the presence of co-morbidity and document the influence of polypharmacy and co-morbidity on unplanned readmissions and mortality in this cohort.

Methods: We performed an audit of outpatient clinical medical records for 215 consecutive patients referred to a tertiary referral centre for pulmonary hypertension assessment between March 2009 and April 2016. Data on number and class of medications were recorded, as well as past medical history and investigations relevant to assessment of pulmonary hypertension.

Results: At the time of pulmonary hypertension evaluation, patients were prescribed a mean of 8 ± 4 medications with 83.2% of patients being on 5 or more regularly prescribed medications. Taking 8 or more medications was associated with co-morbidity, as assessed by the Charlson Co-morbidity Index, and reduced exercise capacity. The presence of co-morbidity resulted in a significantly higher risk of unplanned admission. The presence of polypharmacy is a marker of important co-morbidity, identifying a group at high risk.

Conclusion: Patients referred for assessment of pulmonary hypertension had high rates of polypharmacy reflecting extensive comorbidity, which in turn predicts adverse outcome in this patient population. The presence of polypharmacy should be considered a simple clinical marker of co-morbidity, increased risk and adverse outcome.

Keywords: Co-morbidity; Medications; Polypharmacy; Pulmonary hypertension; Unplanned admissions

Introduction

It is well established that polypharmacy, defined as 5 or more regularly prescribed medications, is now a significant cause of morbidity and mortality in older adults with a linear correlation between the total number of medications and risk of harm [1,2]. Pulmonary arterial hypertension (PAH) is a disease characterised by progressive increase in pulmonary vascular resistance, typically with a prolonged latent phase before the development of symptoms. The insidious and non-specific nature of the presenting symptoms may result in significant delay between onset of symptoms, definitive diagnosis and commencement of specific PAH treatment [3]. Due to the protracted nature of the diagnosis of PAH, and that patients presenting to dedicated pulmonary hypertension clinics may have received previous specialist treatment, there may be an important incidence of polypharmacy in patients referred for dedicated pulmonary hypertension assessment.

We sought to evaluate the incidence of polypharmacy and assess the relationship with regards to the presence of pulmonary hypertension, co-morbidities, unplanned readmissions and mortality.

Materials and Methods

We performed a retrospective audit of outpatient clinical medical records for 215 consecutive patients referred to our centre for diagnosis and consideration of advanced PAH therapies, if applicable, between March 2009 and April 2016.

The study was conducted at a tertiary outpatient multi-disciplinary PAH Clinic at the John Hunter hospital, Newcastle, New South Wales. The clinic has specialist input and consultation from the cardiology, respiratory, rheumatology and immunology departments combined with specialist nursing support. The PAH Clinic includes a comprehensive medical history, physical examination and review of investigations in association with specialist assessment for patients referred for both diagnostic evaluation and for initiation of PAH specific therapy. Medication history, including all prescription and over the counter medication, was obtained at the time of presentation to the multi-disciplinary clinic and recorded electronically. Clinical data was extracted from the medical records, a locally maintained PAH clinic database, and referral information. The presence and severity of co-morbidity was assessed using the Charlson Co-morbidity index [4]. The number and class of medications were recorded. Classes of medications were defined as anti-hypertensive, diuretics, heart rate controlling agents (including beta and calcium channel blocking agents, digoxin and additional anti-arrhythmic therapies), respiratory, lipid lowering, immuno-modulating, gastrointestinal, mental health, analgesic, PAH agents, anti-coagulants, anti-platelet treatment or other. Polypharmacy was defined as use of 5 or more regular medications.

Mortality and unplanned admission data was provided by the Hunter New England Local Health District (HNELHD) Cardiac Stroke Outcome Unit (CSOU). The CSOU provides mortality data through linkage to the New South Wales (NSW) Registry of Births, Deaths & Marriages. Unplanned admission data was available for all patients presenting to a HNELHD hospital within the study period.

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Continuous variables are displayed with mean and standard deviation or median and interquartile range (IQR) if not normally distributed. Comparisons between continuous variables were made using two sided t-tests. Categorical variables are displayed as count (percentage). Categorical variables were compared using chi-square test or Fisher's exact test. We used logarithmic regression analysis to assess the individual relationship between covariates and unplanned readmission and death. We used Kaplan-Meier survival estimates and Cox proportional hazards regression to assess the relationship between polypharmacy and survival and unplanned readmission adjusting for important covariates. All data analysis was performed using STATA Version 14 (STATA Corp).

This study was approved by the Hunter New England Research Ethics Committee.

Results

Patient demographics

A total of 215 consecutive patients presenting to the PAH clinic were included in the study. There were 151 females (70.2%) and 64 males (29.8%). The mean age of the patients reviewed was 65.6 ± 13.6 years. The median age was 68 years (IQR 57-75 years). Most patients were assessed as having WHO Class II (41.4%) or Class III (39.1%) symptoms. Additional clinical characteristics are outlined in Table 1. Following assessment in the multidisciplinary clinic, 76 patients (38.6%) were determined to have pulmonary arterial hypertension (Group 1), with the majority of other patients having pulmonary hypertension secondary to left heart disease (47 patients, 23.9%) or chronic lung disease (55 patients, 27.9%). The follow up period ranged from 0.4 to 7.4 years.

Medication use

At index presentation patients were prescribed a mean of 8 ± 4 medications with 83.2% of patients being on 5 or more regularly prescribed medications. The absolute number of medications is demonstrated in Figure 1. Patients with pulmonary hypertension secondary to left heart disease had a significantly higher number of total medications compared to other classes of pulmonary hypertension (p=0.001). On simple linear regression, there was a significant relationship between older age and the number of medications (Coefficient 0.062; p<0.001) and the Charleston comorbidity index and total number of medications (Coefficient 0.7499; p<0.001). There was also a significant inverse relationship between six-minute walk test distance and the number of medications (Coefficient – 0.0125; p<0.001).

Medications were categorised according to various drug classes, as outlined in Figure 2. Anti-hypertensive agents were used by 72% of patients, 54% were on diuretic therapy, 27% were on an inhaled respiratory agent and 22% were on PAH specific agents.

Outcome measures

During the study period there were a total of 743 unplanned admissions, with a median time from clinic assessment to unplanned admission of 345 days (IQR 145-659 days). Those patients taking 8

Age (Mean ± SD)	65.6 ± 13.6
Gender (female)	70.2%
NYHA Functional class (%)	
I	12.6
II	41.4
III	39.1
IV	7
Average regular medications (Mean ± SD)	7.96 ± 3.91
Patients on 5 or more medications (%)	83.26
Charlson Co-morbidity index score (Mean ± SD)	2.3 ± 1.5
Follow up period (years)	0.4 – 7.4
Medication class (%)	
Anti-hypertensive	71
Cardiac rate control	41
Respiratory	27
Lipid lowering	39
Anti-platelets	27
Anti-coagulants	32
Diuretic	54
Gastrointestinal	59
Immuno-modulating	26
Mental health (depression or anxiety)	41
Pain	33
PAH specific therapy	22

Table 1: Characters are shown for the cohort at time of initial clinic assessment. NYHA = New Year Heart Association. PAH = Pulmonary artery hypertension.

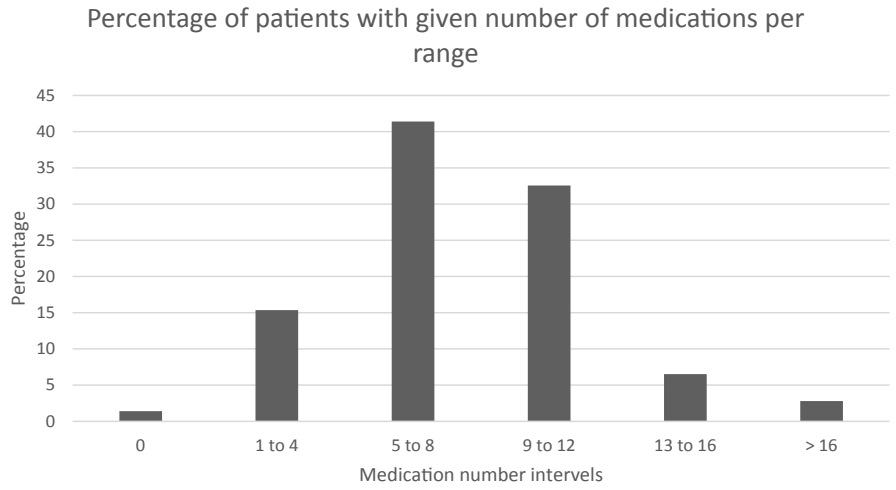

Figure 1: Number of patients in a medication range at index presentation to clinic, 0, 1 to 4, 5 to 8, 9 to 12, 13 to 6 or more than 16 as a percentage of the total cohort (215 patients).

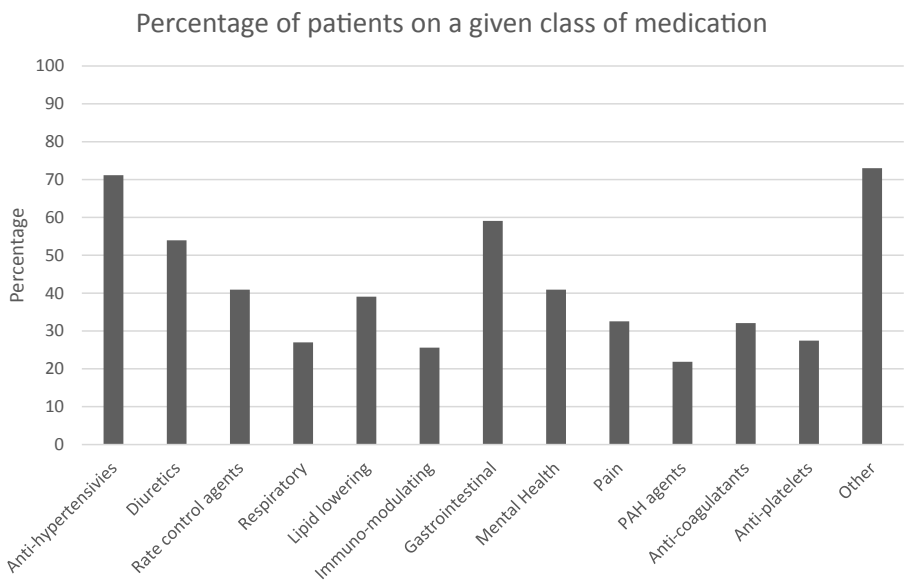

Figure 2: Percentage of patients on a given class of medications at their index presentation to the Pulmonary Hypertension multidisciplinary clinic.

or more medications had a significantly higher risk of unplanned admission (OR 2.77; p=0.01; Figure 3). Patients aged over 68 had a higher risk of readmission compared to those aged under 68 (OR 2.25; p=0.006). Patients with WHO Class II (OR 3.01; p=0.015), III (OR 4.10; p=0.002) and IV (OR 5.81; p=0.02) had a higher risk of readmission compared to WHO Class I patients. We analysed the relationship between the number of medications and unplanned admission, by grouping patients into two categories (1-7 medications, 8 or greater medications). Using Cox proportional hazards regression adjusting for age, sex, WHO Class and Charleston Comorbidity Index, there was no significant relationship between polypharmacy and unplanned admission (HR 1.19; 95% CI 0.83-1.71; p=0.347). After adjustment for age, sex, WHO Class and Charleston Comorbidity Index, there was similarly no significant relationship between polypharmacy alone and death (HR 0.82, 95% CI 0.46-1.44; p=0.489). There was a significant relationship between the Charleston Comorbidity Index score and risk of readmission (OR 1.75; p<0.001). There was no relationship between aetiology of pulmonary hypertension and risk of readmission.

During the study period there were 64 deaths (30%) in the cohort. Fifty-four patients (84%) who died were aged 65 years or older. We again used Cox Regression to assess the relationship between the number of medications and death. There was a trend towards higher mortality with an increasing number of medications, however, this was not statistically significant (Figure 4).

Discussion

We have described the prevalence of polypharmacy in a cohort of patients referred to a specialist pulmonary hypertension clinic. In a cohort with a mean age 65 years, polypharmacy was noted in more than 83% of referred patients. Our data suggests that polypharmacy is a surrogate for other co-morbid conditions that may impact the risk of readmission or death. The high rates of polypharmacy were not limited to older patients, reflecting the diagnostic and therapeutic difficulties in patients of all ages with unexplained dyspnoea. Polypharmacy was noted particularly in those with pulmonary hypertension complicating left heart disease, which may reflect appropriate utilisation of guideline based therapy including the use of beta-blockade agents, mineralocorticoid antagonists, ACE inhibitors and diuretics.

Previous studies have documented the difficulty in diagnosis of pulmonary arterial hypertension and consequently the delay in commencing appropriate therapy leading to adverse patient outcomes [3]. We had hypothesised that this protracted diagnostic course may result in polypharmacy; while we did identify high rates of polypharmacy, we noted co-morbidity was more closely linked to readmission. This study is reassuring, suggesting that polypharmacy itself, while prevalent in patients assessed with pulmonary hypertension, does not contribute directly to adverse outcome in referred for consideration of advanced PAH therapies. This supports previous cohort data, which has not noted polypharmacy to be an adverse predictor in patients undergoing therapy for PAH [5], of note, these registries typically only include patients maintained on advanced PAH treatment, with this cohort incorporating a broader, more heterogenous group referred for assessment. Previous registry data has not consistently demonstrated an association of co-morbidity with outcome in cohorts with PAH [6-8]. While in our study, polypharmacy correlated with co-morbidity, which is expected, the use of presumably appropriate medical therapy did not protect against readmission. Pulmonary hypertension when noted complicating left sided heart disease, pulmonary disease and sleep disordered breathing portends a poorer prognosis; it is not surprising that the presence of pulmonary hypertension in patients with comorbid medical conditions are prone to adverse events.

While polypharmacy may be appropriate, there is a recognition that it may be associated with both overtreatment and under-treatment of patients with multiple medical conditions [9]. Polypharmacy has been associated with an increased risk of prolonged hospital stay, mortality and readmission [10]. The poor outcomes seen in polypharmacy may be due to adverse drug effects, drug interaction and non-compliance with required therapies [9]. Previous research has shown that pharmacist involvement can reduce consequences of polypharmacy through systematic deprescribing [11,12], it is unclear if this approach would be appropriate in a cohort with such significant comorbid conditions. Research assessing the role of pharmacist-based interventions in this population may represent an area of future investigation.

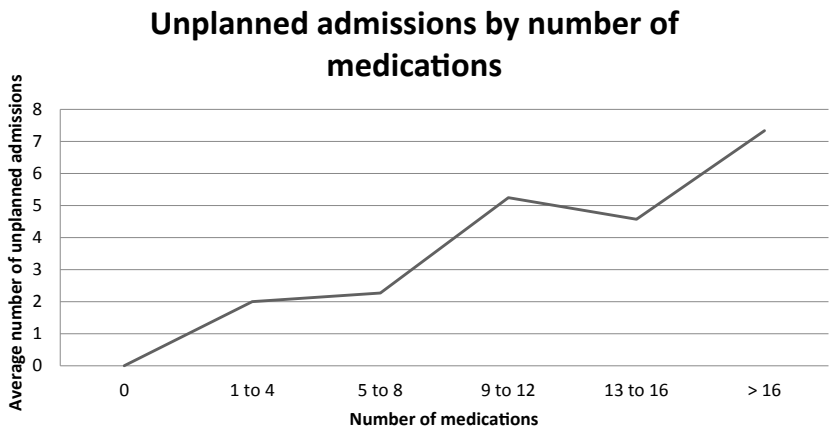

Figure 3: Average number of unplanned readmissions during follow up period relative to total number of medications recorded at Index Assessment.

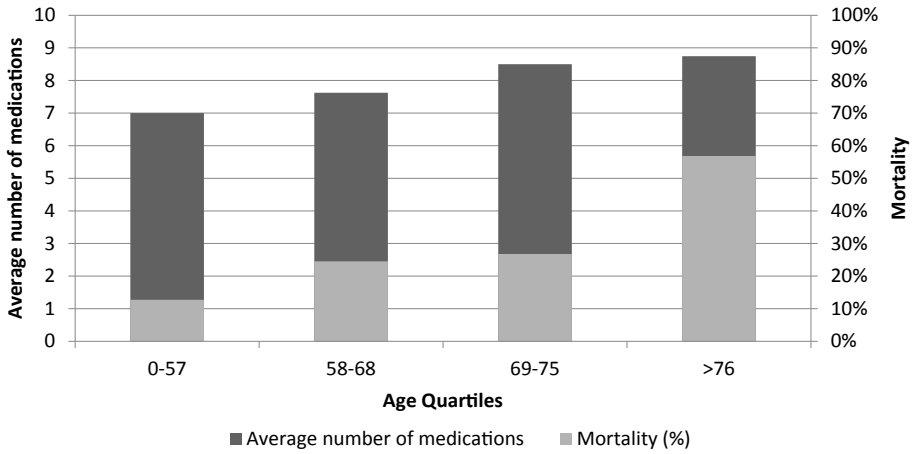

Figure 4: Average number of Medications and Mortality expressed as Age Quartiles.

The group assessed is heterogenous in terms of pulmonary hypertension aetiology, however, reflect the diagnostic challenges in clinical practice and remind the clinician of the need to identify polypharmacy and comorbidity as identifying patients at high risk for adverse outcomes. There are several limitations to this study, primarily being retrospective, lack of information relating to change in medications following clinic assessment and the lack of information from time of symptom onset until diagnosis. A further, prospective study to assess polypharmacy, co-morbidities and evidence-based prescribing in a multidisciplinary setting with regards to patient outcomes would be beneficial. We also hypothesise that a systematic approach to unexplained dyspnoea would not only result in shorter time to diagnosis, but may also lead to a reduction in polypharmacy; a multi-disciplinary approach may also result in a coordinated approach to drug prescription rather than multiple providers with individual prescribing patterns.

Conclusion

In a large cohort of patients referred for assessment of pulmonary hypertension, we noted polypharmacy and extensive comorbidities in majority of patients with a concomitant hazard in terms of need for hospitalisation. Future research should address the influence of delay in diagnosis on polypharmacy and assess potential outcome. A dedicated diagnostic algorithm for unexplained dyspnoea might improve patient outcomes and address the prevalence and associated risks of polypharmacy.

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