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A population-based analysis of attributable hospitalisation costs of invasive fungal diseases in haematological malignancy patients using data linkage of state-wide registry and costing databases: 2009 - 2015

Short running title: Hospitalisation costs of invasive fungal disease

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Abstract

Background: Invasive fungal diseases (IFD) are associated with significant treatment related costs in patients with haematological malignancies (HM).

Objectives: The objectives of this study were to characterise the gross and attributable hospitalisation costs of a variety of IFD in patients with HM by linking state-wide hospital administrative and costing datasets.

Patients/Methods: We linked the Victorian Admitted Episodes Dataset, Victorian Cancer Registry and the Victorian Cost Data Collection from 1st July 2009 to 30th June 2015. IFD-cases and uninfected controls were matched 1:1 based on age within ten-years, same underlying HM and length of stay prior to IFD diagnosis. The cost difference between surviving cases and controls, indexed to 2019 Australian dollars (AUD) calculated twelve-months from IFD diagnosis, was determined using Poisson and negative binomial regression (NBR).

Results: From 334 matched-pairs, the gross hospitalisation cost of cases was AUD\$67,277 compared to AUD\$51,158 among uninfected controls, associated with an excess median hospitalisation cost of AUD\$16,119 ($p<0.001$) attributable to IFD, approximating to USD\$11,362 and €10,154 at purchasing power parity. Median attributable costs were highest for patients with invasive aspergillosis (AUD\$55,642; $p<0.001$) and mucormycosis (AUD\$51,272; $p=0.043$) followed by invasive candidiasis AUD\$24,572 ($p<0.001$). No change in median excess attributable costs was observed over the study period ($p=0.90$). Analyses by NBR revealed a 1.36-fold increase ($p<0.001$) in total hospitalisation costs among cases as compared to controls twelve-months from IFD diagnosis.

Conclusion: Invasive aspergillosis and mucormycosis have high attributable hospitalisation costs but the overall excess IFD cost of AUD\$16,119 is modest, potentially reflecting missed or miscoded fungal episodes arguing for better quality surveillance data at hospital level.

Keywords: *Invasive fungal disease; data linkage; hospitalisation costs; health economics; surveillance*

Introduction

The economic impact of invasive fungal disease (IFD) complicating haematological malignancy (HM) treatment is significant.¹ Inpatient hospitalisation costs of IFD in the United States exceed USD\$4.5 billion, of which *Candida* and *Aspergillus* infections account for the majority at USD\$1.4 billion and USD\$1.2 billion, respectively². In the Australian healthcare setting, the attributable hospitalisation costs of these infections is predominantly limited to institutional¹ or disease-specific reports^{3,4}. A conservative estimate of hospitalisation costs attributable to IFD using median quantile regression from a quaternary Australian transplant centre between 2002 and 2007, indexed to 2009, was AUD\$30,957 (indexed to AUD\$32,111 in 2019), driven primarily by pharmacy costs (64%), of which antifungal drugs comprised 27%¹. A multicentre German analysis estimated the attributable mean IFD-associated hospitalisation cost in acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS) patients to be €21,063 (2012, $p < 0.05$), with total costs dominated by antifungal medication (36%), hospital stay (32%) and the use of blood products (23%)⁵. Heterogeneity in cost determination methods means that estimates have varied from total hospitalisation costs^{6,7} or using assumptions in the absence of real-world data⁸⁻¹⁰.

Data linkage is an efficient means of evaluating the costs and epidemiology of IFD in haematology-oncology patients at a population-level^{7,11}. A population-based analysis of IFD in Australia from 1995 to 1999 showed that invasive candidiasis was more common than invasive aspergillosis, representing 0.36% and 0.03% of all acute hospital discharges, respectively. However, this study excluded the second-most populous state in Australia, namely Victoria, with a population of 6.50 million residents¹². To date, the economic impact of IFD at a state-wide level leveraging linkage of population-based datasets has not been performed in Australia.

Rare infections like IFD inclusive of non-*Aspergillus* moulds like mucormycosis and lomentosporiosis, are challenging to study. Mucormycosis is difficult to manage and costly to treat with a median total hospitalisation cost of USD\$57,324 (2014) in HM and allogeneic-haematopoietic stem cell transplantation (allo-HSCT) patients⁴ with similar estimates reported in Germany (€53,261, 2016)¹³. In contrast, there are few data on the economic burden of non-*Aspergillus* moulds, including mucormycosis and scedosporiosis in Australia^{3,14} partly due to their rarity and lack of surveillance systems in hospitals where IFD are managed¹⁵.

To overcome the challenges of data acquisition for a rare disease, we utilised data linkage of population-based administrative coding and costing datasets with state-based cancer registry data. With linked data, we could for the first time, evaluate the gross and attributable IFD hospitalisation costs adjusted for key clinical covariates and the longitudinal expenditure associated with IFD over a six-year period in Victoria, Australia.

Materials and Methods

Study design, study population, data sources and data linkage

This was a retrospective, matched case-control study of adult inpatients (≥ 16 -years) diagnosed with a HM in Victoria, Australia. We linked the largest inpatient hospital-morbidity database in Australia being the Victorian Admitted Episodes Dataset (VAED), to hospitalisation costs documented in the Victorian Cost Data Collection (VCDC) and new cancer diagnoses recorded in the Victorian Cancer Registry [VCR]. All VAED-derived clinical data are coded according to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification* (ICD-10-AM, Supplementary Tables S1-2 contains HM and IFD codes respectively) for patients admitted to private and public hospitals in Victoria.¹⁶ The VCR captures all cancer diagnoses among Victorian patients, with the exception of squamous and basal cell carcinomas. Data linkage was mediated by the Victorian Data Linkages Unit (VDLU), a state government authority with access to government and health data repositories within Victoria, Australia¹⁷.

We identified HM patients from 1st July 2005 to 30th June 2016 and linked their hospitalisations to the VCR to determine their index (or first) hospitalisation with a new diagnosis of HM. The next hospitalisation with an *Australian Classification of Health Interventions* (ACHI) procedural code for chemotherapy (Supplementary Table S3) was defined as the approximate date of induction chemotherapy noting that all dates were supplied in month and year format. All diagnostic, procedural and complication codes, rather than specific codes, were requested. Linkage with the VCR was only available between the 1st January 2008 and the 31st December 2014 because of delays in the mandatory reporting and collation of cancer diagnoses. All reporting parameters are consistent with the Quality of Health Economic Studies (QHES) instrument¹⁸ (Table S4, Supporting Information).

Only total hospitalisation cost for each recorded hospitalisation was supplied by the VCDC, from 1st July 2009 to 30th June 2015 for Victorian hospitals. These data are an aggregate of direct and indirect (i.e. overhead treatment) costs with no separation of types of costs (e.g. drug acquisition, diagnostics) possible under the VCDC business rules¹⁹. The VDLU utilised a step-wise probabilistic and deterministic linkage to combine individual patient covariates between the databases, assigning statistical linkage keys for each anonymised hospitalisation (Figure 1). Where costing data were not reported to the VCDC, the latter were coded as missing. Non-parametric descriptive statistical analyses were employed using VAED data linked with the VCR only.

INSERT FIGURE 1 HERE

Case-control matching criteria

Clinical data were linked with the VCDC with IFD-episodes matched 1:1 to control episodes using previously published matching criteria¹. Matching criteria included age (in years) within ten years of IFD case, same underlying HM and length of stay (LOS, in days) at least as long as that of case patients prior to the hospitalisation containing the IFD diagnosis in order to disentangle the effect of IFD from underlying HM. The unspecified IFD-category was removed from the costing analysis due to its non-specific description being either other specified mycoses and unspecified mycosis (ICD10-AM code B49 in supplementary TableS2). The VCDC collect costing data from Victorian public hospitals only. As such, costing analyses were limited to the public healthcare sector.

Study definitions

Index hospitalisation was defined as the first ICD-10-AM code denoting a HM at hospitalisation coinciding with the date of HM diagnosis in the VCR (Supplementary Table S1). Where a HM diagnosis preceded 1st January 2008 or proceeded the 31st December 2014, the first hospitalisation reported in the VAED was taken as the index hospitalisation. IFD-episodes were defined as patients assigned an ICD-10-AM code denoting IFD from the date of HM diagnosis while HM patients without ICD-10-AM codes for IFD were controls. Allo- and autologous (auto)-HSCT recipients were defined by an ACHI procedural code denoting a HSCT post-index hospitalisation. Duplicate IFD codes were treated as the same IFD. Exclusion criteria included children (<16-years) and HM patients diagnosed with mycoses including coccidioidomycoses, paracoccidioidomycoses, histoplasmosis and blastoplasmosis that are endemic to parts of North America and superficial fungal infections (Supplementary Table S5).

Economic and statistical analyses

Wilcoxon signed-rank tests were used to compare the statistical significance of non-parametrically distributed covariates between matched cases and controls. The primary cost analysis was performed from the perspective of the public healthcare sector from 1st July 2009 to 30th June 2015 corresponding to the VCDC. The crude unadjusted hospitalisation cost attributable to IFD was the difference between median (inter-quartile range [IQR]) expenditure between IFD cases and uninfected controls. Gross hospitalisation costs were calculated on a per patient level and were stratified by IFD and HM type. The total unadjusted hospitalisation costs were then analysed from the time of HM diagnosis until twelve-months post an IFD episode and was compared to uninfected controls. Twelve-months was selected as the analytic time horizon to account for the cumulative cost increases from the time of IFD diagnosis. Patient-level summation of Charlson Comorbidity Index (CCI) scores were determined ²⁰.

The relationship between LOS and total hospitalisation costs was evaluated using a Poisson regression model. Where the deviance goodness-of-fitness test generated a statistically significant p-value ($p < 0.05$), a subsequent negative binomial regression model was used, indicating over-dispersion in the costs. For each of the categorical independent variables included in the model, an adjusted incidence rate ratio (aIRR), adjusted for underlying malignancy, age (in years), neutropenia and hospital region, and its corresponding p-value were generated. Where polychotomous categorical variables exist, the aIRR was compared to

the group of known lowest economic burden. Costs are reported in Australian dollars (AUD) inflated to 2019 using the healthcare component of the Australian Consumer Price Index ²¹. Final costs were converted to 2019 United States dollars (USD) and Euro (€) using purchasing power parity measures ²². All p-values were two-tailed and a p-value<0.05 was considered statistically significant. All statistical analyses were undertaken using Stata/SE v14.2 software (StataCorp® LLC, College Station, Texas, U.S.A.).

Ethics

Ethics approval was granted by the Alfred Health Human Research Ethics Committee (project number: 93/17) and the need for written informed consent was waived.

Results

Patient characteristics

There were 32,815 HM patients with 619,702 hospitalisations recorded in the VAED from 1st July 2005 to 30th June 2016, with patient characteristics shown in Table 1. Invasive fungal disease was diagnosed in 669 (2.04%) patients in the twelve-months from HM diagnosis. Of 1,765 allo- or auto-HSCT recipients, 111 (6.29%) were diagnosed with an IFD up to twelve-months post-transplantation. Among HM patients only, the prevalence of concurrent neutropenia was significantly higher in IFD cases than uninfected controls (cases: N=549 (82%); controls: N=6,735 (21%); p<0.001). Admission to the intensive care unit (ICU) was higher among IFD cases (N=37 (5.53%)) than uninfected controls (N=585 (1.82%); p<0.001). A significantly greater proportion of IFD cases (N=591 (88%); p<0.001) were treated at a metropolitan-based hospital compared to uninfected control patients (N=25,077 (78%); p<0.001). Among HM patients, the twelve-month overall mortality rates were 43% in IFD cases and 19% in uninfected controls (p<0.001).

From the overall cohort, 334 matched IFD case-control pairs were identified. From this cohort, the median LOS was 12-days greater in IFD cases (52-days) than uninfected controls (40-days; p<0.001), as was the median LOS in ICU (IFD cases, 4.91 days; uninfected controls, 2.75-days; p=0.003). After stratifying by IFD, median [IQR] inpatient LOS was greatest for invasive aspergillosis (IA) (cases: 66 [28-105] days, controls: 45 [14-69] days; p<0.05), followed by mucormycosis (cases: 55 [48-73] days, controls: 52 [23-82]; p=0.564)

and invasive candidiasis (IC) (cases: 35 [16-75] days, controls: 21 [7-36] days; $p=0.002$) (Supplementary Table S6).

INSERT TABLE 1 HERE

Epidemiological features of invasive fungal disease

Absolute numbers of IFD was highest in acute myeloid leukaemia (AML) (N=249), non-Hodgkin lymphoma (N=192), aplastic anaemia (N=101), acute lymphoblastic leukaemia (ALL) (N=75) and chronic lymphocytic leukaemia (N=46) diseases, with rates according to patient numbers shown in Table 2. IFD incidence was greater in allo-HSCT recipients (12.2%) compared to auto-HSCT recipients (4.83%).

IA was the most common IFD among the HM population (N=254; 29%), followed by mucormycosis (N=24; 3.05%). The majority of mucormycosis cases occurred in the AML subgroup (N=12; 0.45%), followed by ALL (N=5; 0.75%). Invasive candidiasis occurred in 23% of all HM cases.

INSERT TABLE 2 HERE

Case-control analysis: total and attributable hospitalisation costs of invasive fungal disease

A total of AUD\$1.72 billion in hospitalisation expenditure accounted for 93% of 151,428 hospitalisations between 1st July 2009 and 30th June 2015 in the VCDC. Costing data was unavailable for 7.15% of hospitalisations in the VAED extract (i.e. 56% from private patient admissions, 51% due to non-coded or incompletely coded admissions rendering them unfundable, 68% from metropolitans hospitals) with no clustering seen. These episodes were excluded from analysis. From analysis of the matched-pairs, the median excess total hospitalisation cost for cases was AUD\$16,119 higher compared to controls ($p<0.001$), approximating USD\$11,362 and €10,154 at purchasing power parity. Costs were unchanged over the study period with a growth rate coefficient of AUD\$59 [95% CI: -\$875 to \$992]; $p=0.90$) per month observed (Figure 2). Subgroup analyses of matched pairs (excluding mucormycosis with very few numbers) revealed non-significant increases in attributable costs per month for IA \$216 [95% CI: -\$698 to \$1130]; $p=0.63$; for “other IFD” \$153 [95% CI: -\$2,038 to \$2,345]; $p=0.88$ and a reduction in invasive candidiasis hospitalization costs of -\$612 [95% CI: -\$1,317 to \$93]; $p=0.080$ per month.

INSERT FIGURE 2 HERE

The HM subgroups associated with the highest crude hospitalisation costs attributable to IFD were ALL (AUD\$210,845; $p=0.387$), chronic myeloid leukaemia (AUD\$73,799; $p=0.049$) and Hodgkin lymphoma (AUD\$35,912; $p=0.423$) IFD case patients (Table 3; Figure 3).

INSERT FIGURE 3 HERE

Figure 4 illustrates that IA was associated with the highest crude IFD attributable cost among HM patients (AUD\$55,642; $p<0.001$) followed by mucormycosis (AUD\$51,272; $p=0.043$) and IC (AUD\$24,572; $p<0.001$). Controls accrued a higher attributable IFD cost for the IFD-other category (cases: AUD\$67,799; controls: AUD\$79,257; $p=0.037$).

INSERT FIGURE 4 HERE

Distribution of costs is illustrated in Supplementary Table S7. Main determinants of attributable IFD costs were admission to ICU (AUD\$69,808; $p=0.3173$), admission to a metropolitan hospital (AUD\$25,670; $p<0.001$) and concurrent neutropenia (AUD\$24,001; $p=0.5283$).

INSERT TABLE 3 HERE

Poisson and negative binomial regression model for total inpatient hospitalisation costs

A negative binomial regression (NBR) model was performed with the Pearson goodness-of-fitness test χ^2 p -value indicating over-dispersion ($p<0.001$), and generated an aIRR of 1.36 for IFD (95% confidence interval [CI]: 1.05–1.74; $p<0.001$). Table 4 shows the aIRR for each independent categorical variable associated with a $p<0.05$ as identified by the manual backward elimination method. Variables associated with high IRRs for HM are ages 55-64 years (1.66) and ALL (2.44). Consistent with the findings from the descriptive costing analysis, the difference in the crude median hospitalisation costs between cases (AUD\$67,277) and controls (AUD\$51,158) of AUD\$16,119 ($p<0.001$) approximates the magnitude of the 1.36 aIRR derived by the NBR model (AUD\$69,575).

INSERT TABLE 4 HERE

Discussion

This study characterises the economic burden of IFD in patients with haematological malignancies by linking state-wide administrative and costing databases. Although single-site analyses are pertinent to the institution in question, population-based economic studies provide a broad overview of the economic burden of disease. Our main findings indicate that, relative to patients without an IFD, a diagnosis of IFD is associated with an excess median LOS of 12-days and excess median total hospitalisation cost of AUD\$16,119. Over the six year study period, total attributable hospitalisation costs were stable ($p=0.90$) with increases in IA ($p=0.63$) and other IFD ($p=0.88$) balanced against a decrease in invasive candidiasis related costs ($p=0.08$) with none reaching statistical significance likely due to small numbers of matched pairs. A 0.28% decrease in IFD incidence in the companion epidemiological study ¹¹ corroborates institutional studies from two major Victorian transplant centres ^{15,23} suggesting that improvements in supportive care like antifungal prophylaxis have affected IFD incidence.

Despite six-years of linked data with the VCDC, only a modest number of case-control matched-pairs were identified (334 matched-pairs). These few matched-pairs reiterate the need to improve IFD surveillance and to develop innovative machine learning solutions ^{15,24,25} for prospective real-time surveillance of IFD in cancer populations. The strengths, however, of our data linkage approach are evidenced in our ability to evaluate the longitudinal economic impact attributable to IFD at a state-wide level, to perform cost regression modelling that adjusted for neutropenia and hospital region not included in the matching criteria and to reaffirm mucormycosis as an established IFD with a significant cost burden.

Our analysis of administrative cost data reveals that IA, followed by mucormycosis, present a significant economic cost among patients with HM. Similar to our high median IA-associated hospitalisation cost (AUD\$55,642; $p<0.001$), Menzin *et al.*, in an analysis of the U.S. Healthcare Cost and Utilization Project National Inpatient Sample, reported a mean IA-attributable cost of USD\$25,128 (indexed to AUD\$36,629 in 2019) ⁷. Our mucormycosis-attributable median hospitalisation cost of AUD\$51,272 ($p=0.043$; approximates

USD\$36,115 and €32,299 at purchasing power parity), and is comparable to a retrospective analysis of the FungiScope™ Global Registry which revealed similar cost estimates in patients with HM (€53,261 ($p<0.001$))¹³. Although methodological differences between our study and others limit these comparisons, the cost estimates for IA and mucormycosis nonetheless reflect the complexity of managing these patients who often require multiple surgeries, high cost antifungal drugs such as liposomal amphotericin B and ICU admission²⁶.

Stratification by HM revealed the highest median cost attributable to IFD was accrued among the ALL population. An Australian multicentre study demonstrated that the median attributable hospitalisation cost for treating IFD in ALL was AUD\$121,520 per patient²⁷ as compared to our cost estimate of AUD\$210,845. The implications of our findings underscore the importance of ALL as a HM subgroup associated with high IFD treatment-related costs. Further, Valentine *et al.*¹¹ demonstrated that the prevalence of IFD in ALL patients is high (11%) as compared to AML (9.42%) and auto-HSCT (4.83%) patients. These data are a compelling argument for better preventative strategies including mould-active antifungal prophylaxis that are as yet unresolved in patients with ALL²⁸.

The non-parametric distribution of the cost data, even after log transformation, motivated our choice of a negative binomial regression. A negative binomial regression accommodates skewness through variance weighting and it is recognised in the literature that a negative binomial regression is an appropriate fit for over-dispersed cost data analyses²⁹. Our negative binomial regression model's aIRR for IFD twelve-months from IFD diagnosis (aIRR=1.36; $p<0.001$) suggests that total hospitalisation costs increase by a magnitude of 1.36 compared to an uninfected control. These findings are consistent with the median cost estimates observed in our matched case-control analysis, where the median cost of cases was approximately 1.36-times greater than controls (AUD\$67,276 versus AUD\$51,158). The implication is that hospitals and the healthcare system can pre-empt the cost burden of IFD to be 1.36-times that of a non-IFD patient in the twelve-months after IFD diagnosis in those patients who survive that interval, keeping in mind that the short-term mortality attributable to IFD ranges from 33% to 64% at six-weeks post IFD diagnosis³⁰.

Our study has several limitations. The higher inpatient attributable IFD costs among controls in the "Other IFD" subgroup of AUD\$11,458 may be due to errors in coding. This "Other IFD" category had non-specific ICD-10-AM codes including B48.7 ('opportunistic

mycoses') and B48.8 ('other specified mycoses') that may reflect culture negative possible cases, emerging fungal pathogens or misclassified IFD cases (e.g. coded as non-specific when microbiology was positive but poorly documented). Conversely, it is possible that some true IFD episodes were miscoded as controls resulting in falsely elevated hospital costs for controls. The high contribution of the other IFD group comprising 101 matched pairs may have resulted in the modest excess overall cost of AUD AUD\$16,119 observed. Unfortunately, without linkage of VAED data to identifiable medical record data as per privacy protections, resolution of the accuracy of IFD coding for disease surveillance is not possible. An older US study described a sensitivity of 32% of coding data for proven/probable invasive aspergillosis but contemporary figures are lacking³¹. A relatively small matched-pair cohort (334 pairs), reflects the constraints of a cohort-matched analysis. This study is biased towards a lower acuity IFD population as we included patients who were alive 12-months post IFD onset, likely contributing to survivor bias and the lower attributable IFD cost (AUD\$16,119) relative to previously published works^{1-3,7}. Total hospitalisation data collected from the VCDC were an aggregate sum of direct and overhead costs, concealing the distribution of specific cost parameters like diagnostics and drug acquisition costs. Finally, 7.15% of hospitalisations were missing costing data with at least half of these due to incomplete or uncoded episodes.

In conclusion, our study has demonstrated the value associated with leveraging routinely available hospital administrative and costing data for an uncommon disease through linkage of several population-based datasets. Our findings can inform future studies evaluating the cost-effectiveness of IFD prevention initiatives while leveraging readily available datasets. Forthcoming research will focus on improving the quality of data acquisition for an uncommon but significant disease from hospitals using machine learning^{15,24,25}.

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Tables

Table 1. Patient Characteristics and Clinical Outcomes of the Study Cohort, 2005 - 2016

Characteristic	Haematological malignancy patients, N=32,815		
	Invasive fungal disease cases, N = 669 (%)	Uninfected controls, N = 32,146 (%)	p-value
Overall incidence	669 (2.04)	32,146 (98)	< 0.001
Age (years: median [IQR])	63 [62 – 72]	71 [58 – 81]	< 0.001
15 – 25	38 (5.7)	899 (2.8)	< 0.001
26 – 55	187 (28)	6,407 (20)	
56 – 70	189 (29)	7,095 (22)	
71+	179 (27)	15,042 (47)	
Male gender	406 (60)	18,364 (57)	0.065
Neutropenia (absolute neutrophil count $\leq$ 500 cells/μL blood)			
	549 (82)	6,735 (21)	< 0.001
Inpatient length of stay (LOS; days)			
Median [IQR] hospital LOS	21 [8 – 36]	1 [1 – 1]	< 0.001
Intensive care unit			
ICU admission	37 (5.5)	585 (1.8)	< 0.001
Median [IQR] ICU LOS (days)	6.1 [2.8 – 16]	2.5 [1.1 – 5.3]	< 0.001
Mechanical ventilation (yes)	29 (4.3)	286 (0.9)	< 0.001

Median [IQR] ICU mechanical ventilation (days)	6.8 [2.7 – 17]	2.0 [0.6 – 6.0]	< 0.001
Haemodialysis			
	68 (10)	478 (1.5)	< 0.001
All-cause mortality			
One-month	43 (6.4)	1,983 (6.2)	0.783
Three-month	110 (16)	3,223 (10)	< 0.001
Six-month	167 (25)	4,353 (14)	< 0.001
Twelve-month	290 (43)	6,004 (19)	< 0.001
Hospital region			
Metropolitan Victoria	591 (88)	25,077 (78)	< 0.001
Regional Victoria	78 (12)	7,069 (22)	
Charlson Comorbidity Index score ≥ 4			
	192 (27)	3,808 (12)	< 0.001

Abbreviations: ICU, intensive care unit; IQR, inter-quartile range; LOS, length of stay

Table 2. Invasive Fungal Disease Incidence Stratified by Haematological Malignancy and Haematopoietic Stem Cell Transplantation from Index Hospitalisation, 2005 – 2016

Invasive fungal disease; incidence (%)	
Haematopoietic stem cell transplantation status in patients	
Allogeneic (N = 335)	41 (12.2)
Autologous (N = 1,449)	70 (4.83)
Haematological malignancy in patients	
Acute lymphoblastic leukaemia (N = 664)	75 (11)
Acute myeloid leukaemia (N = 2,644)	249 (9.42)
Aplastic anaemia (N = 7,121)	101 (1.42)
Chronic lymphocytic leukaemia (N = 3,459)	46 (1.33)
Non-Hodgkin lymphoma (N = 15,267)	192 (1.26)
Multiple myeloma (N = 5,614)	58 (1.03)

Hodgkin lymphoma (N = 2,030)	17 (0.84)
Chronic myeloid leukaemia (N = 1,240)	10 (0.81)
Other haematological malignancies (N = 1,897) †	22 (1.16)

† As defined
by coding

definitions in Supplementary Table S1

Table 3. Total Median Excess Inpatient Hospitalisation Costs (AUD) Among Cases and Controls Stratified by Haematological Malignancy and Invasive Fungal Disease

Haematological malignancy (matched-pairs¹, n=334)	Cases: median [IQR]	Controls: median [IQR]	IFD attributable cost	p-value
Acute lymphoblastic leukaemia (4)	\$325,843 [\$214,624 – \$359,526]	\$114,998 [\$87,788 – \$270,811]	\$210,845	0.387
Acute myeloid leukaemia (106)	\$90,618 [\$45,228 – \$157,543]	\$66,106 [\$25,618 – \$116,245]	\$24,512	< 0.001
Chronic lymphoblastic leukaemia (23)	\$48,350 [\$11,025 – \$153,855]	\$48,369 [\$27,934 – \$85,594]	-\$19.00	0.784
Chronic myeloid leukaemia (3)	\$89,127 [\$66,755 – \$111,499]	\$15,328 [\$7,429 – \$23,227]	\$73,799	0.049
Hodgkin lymphoma (6)	\$49,242 [\$37,864 – \$76,606]	\$13,329 [\$7,808 – \$63,942]	\$35,912	0.423
Multiple myeloma (70)	\$68,191 [\$16,613 – \$174,594]	\$51,901 [\$22,162 – \$83,962]	\$16,290	0.057
Non-Hodgkin lymphoma (122)	\$58,501 [\$40,618 – \$117,556]	\$51,101 [\$23,957 – \$90,039]	\$7,400	0.001
Invasive fungal disease (matched-pairs, n=334)	Cases: median [IQR]	Controls: median [IQR]	IFD attributable cost	p-value
Invasive aspergillosis (137)	\$105,810 [\$50,202 – \$199,027]	\$50,167 [\$18,541 – \$92,940]	\$55,642	< 0.001
Invasive candidiasis (92)	\$58,738 [\$29,089 – \$123,884]	\$34,164 [\$9,634 – \$68,995]	\$24,572	< 0.001
Mucormycosis (4)	\$133,436 [\$71,074 – \$206,348]	\$82,164 [\$40,691 – \$144,118]	\$51,272	0.043
Other invasive fungal disease (101)	\$67,799 [\$38,961 – \$135,544]	\$79,257 [\$36,128 – \$139,467]	-\$11,458	0.037

Abbreviations: IFD, invasive fungal disease; IQR, inter-quartile range; ¹Matching criteria included age (in years) within ten years of IFD case, same underlying HM; length of stay (in days) at least as long as that of case patients prior to the hospitalisation containing the IFD diagnosis.

Table 4. Negative Binomial Regression Output for Gross Inpatient Hospitalisation Costs (AUD) Twelve-Months from Invasive Fungal Disease Diagnosis Compared to Uninfected Controls

Covariate	Adjusted incidence rate ratio	Standard error	95% confidence interval	p-value
Invasive fungal disease	1.36	0.18	1.05 – 1.74	< 0.001
Hospital region				
Metropolitan	1.39	0.20	1.06 – 1.84	0.018
Haematological malignancy^{†, ‡}				
ALL	2.44	1.39	0.80 – 7.45	0.117
AML	1.23	0.35	0.71 – 2.14	0.453
NHL	1.11	0.30	0.66 – 1.88	0.697
CML	1.02	0.60	0.32 – 3.25	0.983
MM	0.87	0.26	0.49 – 1.56	0.639
HL	0.78	0.31	0.36 – 1.72	0.542
Neutropenia	1.78	0.24	1.38 – 2.30	< 0.001
Age (ten years)[†]				
25 – 34	1.50	0.81	0.52 – 4.32	0.458
35 – 44	1.53	0.78	0.57 – 4.12	0.397
45 – 54	1.62	0.79	0.62 – 4.21	0.325
55 – 64	1.66	0.91	0.57 – 4.84	0.354
65 – 74	1.37	0.75	0.47 – 4.00	0.562
75 – 84	1.39	0.77	0.47 – 4.10	0.549
85 +	1.19	0.73	0.36 – 3.94	0.777

[†] Reference category: haematological malignancy, CLL; age (ten years), 15 – 24 years.

Reference categories were chosen as the lowest risk-burden for invasive fungal disease

[‡] Myelodysplastic syndrome patients excluded due to a small overall sample size (N=61)

Abbreviations: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CML, chronic myeloid leukaemia; HL, Hodgkin lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma

Note: Incidence rate ratio is a measure of comparative risk for an event between cases- and control groups.

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Figure Legends

Figure 1: Consort diagram of the probabilistic and stepwise deterministic linkage across administrative and costing datasets held by the State Government of Victoria, and the 1:1 case-control match. HM, haematological malignancy; IFD, invasive fungal disease; LOS, length of stay; VAED, Victorian Admitted Episodes Dataset; VCDC, Victorian Cost Data Collection.

Figure 2: The total inpatient crude hospitalisation costs (AUD) of invasive fungal disease (IFD) stratified by haematological malignancy (HM) (334 matched-pairs).

Figure 3: Median attributable IFD hospitalisation costs from 1 July 2009 to 30 June 2015

Figure 4: Total inpatient crude hospitalisation costs (AUD) of invasive fungal disease (IFD) stratified by IFD among haematological malignancy patients (334 matched-pairs).

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Figure 2. The total inpatient crude hospitalisation costs (AUD) of invasive fungal disease (IFD) stratified by haematological malignancy (HM) (334 matched-pairs).

Abbreviations: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphoblastic leukaemia; CML, chronic myeloid leukaemia; HL, Hodgkin lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma. Figures in parentheses denote the number of matched-pairs.

Figure 3. Median attributable IFD hospitalisation costs from 1 July 2009 to 30 June 2015

Dashed line denotes the pooled median IFD attributable cost (AUD\$16,119; $p < 0.001$)

Figure 4. Total inpatient crude hospitalisation costs (AUD) of invasive fungal disease (IFD) stratified by IFD among haematological malignancy patients (334 matched-pairs).

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